Severe Achondroplasia
Demonstration of Probable Heterogeneity within this Clinical Syndrome

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True achondroplasia is a well-delineated and distinct entity as familiar to the layman as it is to the members of the medical profession (Maroteaux and Lamy, 1964). In the past the designation was often assigned to a hodgepodge of entities such as Morquio's disease and spondylo-epiphysial dysplasia (McKusick, 1966; Maroteaux and Lamy, 1959; Jacobsen, 1939). It is considered to be due in all instances to a dominant allele, and is usually the result of a new mutation, as the reproductive fitness of sufferers is much lower than normal (Mørch, 1941). Certainly there is little reason to suppose that there is any genetic heterogeneity among the sufferers from the more commonly seen form of this disorder. The question of whether there might be a different variety of the disease, presenting in a more severe form and with recessive inheritance, arose when there was born to a young Brisbane couple a second child afflicted, like the earlier sib, with a very severe form of chondrodystrophy associated with multiple congenital defects.

The Family

The immediate family tree is shown in Fig. 1. Mother and father were both young and both apparently in excellent health. The mother, aged 19 at the date of birth of the second affected child, had had two male children by different fathers before she married. These children had been adopted, and in consequence could not be studied, but the information that they were perfectly normal healthy infants is reliable since any defect would have prevented their legal adoption. The mother was the youngest of a family of seven, and had grown up in difficult circumstances, her mother dying by suicide when she was young, and she herself having been brought up in institutional care. She had one brother, the fourth of the sibship, who was said to have died at the age of 5 days from renal agenesis, but the report, depending as it does only on the mother's impression of what she had been told, is unreliable. Apart from this the immediate family are living and have no skeletal abnormality.

The father is aged 20, and his mother was of Maori descent. He is the eldest of three normal boys. The mother lost stillborn twins, sex unknown, between the second and third boys. The more distant family as far as can be ascertained on both sides is normal.

The two older boys were born on 27 October 1964 and 21 November 1966, at 40 and 41 weeks' gestation and weighed 2665 g. and 2863 g., respectively. Delivery was normal. Both had a normal neonatal period and both were adopted as soon as they were free to leave hospital.

Case 1 (first abnormal child). This child was born on 26 February 1968, at 36 weeks' gestation, a phenotypic female. Pregnancy was complicated by some degree of hydramnios and premature rupture of the membranes. Delivery was normal, and on delivery the baby was noted to have multiple deformities. A weak heart beat was detected, but efforts at establishing respiration were unsuccessful. The placenta was normal with a bledore insertion of the cord, weight 737 g.

At necropsy the child was noted to have a weight of 1814 g., crown–rump length of 32 cm., rump heel length of 11 cm., and head circumference of 33 cm. Arms and legs were grossly shortened and the rib cage was as grossly deformed, with the costochondral junction being much posterior in position. The appearances

![Fig. 1. Immediate family tree of the propositi. Black symbols indicate the affected individuals. Slashed symbol indicates death in infancy. Small circles indicate stillbirth.](http://jmg.bmj.com/)

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were those of classical achondroplasia (Fig. 2). There was a total cleft palate and a centrally situated defect in the upper lip of differing appearance to the common harelip. Internally the larynx was normal with a small epiglottis. The trachea and main bronchi were small but otherwise normal. The pleural cavities were very small and the lungs small, pale, and hypoplastic. The pulmonary vessels were normal in anatomy. Most of the thoracic cavity was taken up by heart and thymus. The diaphragm was displaced downwards to a considerable degree, so that the liver and spleen were totally below the costal margin and the abdomen was consequently quite distended. The heart and great blood vessels were normal. The brain showed dilatation of the lateral and third ventricles which was quite conspicuous and which was the result of stenosis of the cerebral aqueduct through which a probe could not be passed. The fourth ventricle was also dilated. Microscopical examination confirmed the presence of pulmonary hypoplasia. The costochondral junction (Fig. 3) showed the typical abnormality of achondroplasia, with failure of palisade formation of cartilage cells and irregular ingrowth of capillaries into cartilage. There was a rough, uneven plane between cartilage and osseous tissue. Bony trabeculae were large, and solid masses abutted onto cartilage.

Case 2 (second abnormal child). This child, also a phenotypic female, was born on 22 March 1969, at 34 weeks' gestation. Pregnancy on this occasion was complicated by some pyelonephritis and renal pain.
requiring a short period in hospital at six months' gestation, but there was no hydramnios. Delivery was normal, and on delivery the baby, like its sib, was noted to have multiple congenital deformities, and died three-quarters of an hour later. Birthweight was 1680 g., crown-rump length 28·5 cm., crown heel length 38·5 cm., head circumference 31·5 cm. The placental weight was 708 g. and it was of normal appearance.

At necropsy the child showed very much the same appearance as the earlier infant (Fig. 4 and 5). There was gross shortening of arms and legs and deformity of the rib cage. There was a partial central cleft lip, and also a defect of the soft palate, with a high arched hard palate. There was a considerable degree of hydrocephalus with diastasis of the cranial sutures. The lungs showed the same hypoplasia as before, but on this occasion there was a congenital heart lesion as well. The pericardium and pericardial cavity were normal. The heart showed a poorly developed right ventricle, and a conspicuous hypoplastic pulmonary artery, with no pulmonary valve, arose from it. The ductus arteriosus was widely patent. The mitral, tricuspid, and aortic valves were normal. There were large atrial and ventricular septal defects. The myocardium was normal. It was considered that the liver and thymus were both larger than might have been expected. There was a gross hydrocephalus, with enlargement of the lateral and fourth ventricles. The other organs were normal.

Microscopical findings were not greatly different from the previous infant. Cartilage structure itself appeared within normal limits, but the formation of bone from cartilage was disordered, as in the earlier child. The sections of brain showed heavy focal mononuclear aggregations, particularly subependymally (probably remnants of embryonic tissue) some perivascular cuffing, and a mild increase in glial tissue.

Discussion

There appears little doubt that these infants were suffering from the same condition and that its expression, though lethal in both, was more severe in the second child. The gross anatomical changes, together with the microscopical appearance of the endochondral ossification as shown in the first child, make it difficult to describe this condition by any other title than achondroplasia. This disorder in the adult gives rise to a highly characteristic clinical picture. In these infants, where this picture has not had time to develop one must beware of mistaking the diagnosis, but there is no other well-delineated condition which can be confused with this. Morquio's disease, fragilitas ossium, Hurler's syndrome, and the other forms of dwarfism each have their own highly characteristic clinical and histological picture, and in none of them is the disorder of ossification of the type shown here manifest. The condition of diastrophic dwarfism (le nanisme diastrophique) described by Lamy and Maroteaux (1960) is probably the same condition as seen here.
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In their paper they described the radiological and clinical appearances of three surviving cases, and put forward cogent reasons for considering the condition as being distinct from classical achondroplasia, but the paper contained no description of the histological appearances of cartilaginous ossification which in our cases so much resembled that of true achondroplasia, that we are content to use this term to describe the condition.

Achondroplasia is inherited as an autosomal dominant, though as noted already, owing to the low reproductive fitness of those afflicted with the disease, a large proportion of cases represents new mutations. The occurrence of the disease in two sibs makes the likelihood of recurrent mutation in this case so remote as to be well-nigh impossible. The fact that the mother had already given birth to two perfectly normal infants, and the fact that she was seen to have had uneventful pregnancies, makes the possibility of a common intrauterine environmental factor almost as remote. No material was available for attempting to karyotype the infants, but as the parents each had a normal karyotype, the possibility of a chromosomal abnormality being the cause of the condition is extremely unlikely. The most probable explanation is that one is observing the expression of a rare recessive allele in the homozygous state.

Potter in her textbook (Potter, 1961) states that, of 10 achondroplastic infants in her experience among more than 100,000 births in Chicago, all but one child died shortly after birth. She has given reference (Potter and Coverstone, 1948) to a family with a normal mother and father and five affected children, but the documentation is poor and the family was reported on hearsay evidence only. She postulates a mutant clone of cells giving rise to ovarian tissue containing the abnormal allele in an otherwise normal individual who can then give birth to multiple affected children. The concept is feasible in theory, but we are aware of no documented example of such abnormal gonadal tissue in genetic literature.

Achondroplasia has been the subject of analysis in regard to mutation rates (Mörch, 1941; Popham, 1953) and the rates estimated of $4 \times 10^{-5}$ per gamete are very high. It has been suggested (Stern, 1960) that this is a falsely high estimate owing to the disease consisting of several distinct genetic entities. The distinction of syndromes such as the one described here gives strong support to such suggestions.

The matter was discussed at some length by Maroteaux and Lamy. They noted that in 1964 though the existence of an autosomal recessive mode of transmission in achondroplasia had been the subject of numerous discussions, not a single published observation was adequate to prove such a claim. They remarked that the examples offered in support of such a claim concerned not achondroplasia, but similar affections. The matter is probably one of semantics. If one accepts the term achondroplasia as referring to the disease caused by the dominantly effective allele, then obviously the disease in these two children, being due to a different allele, quite possibly at a different locus, is not achondroplasia. However, if one uses the term to describe a specific defect of endochondral ossification, then these children do indeed suffer from achondroplasia of a demonstrably different form, with a high probability of being due to recessive inheritance.

The separation of distinct genetic entities with different patterns of inheritance, and the later demonstration of different clinical appearances in these diseases, has been shown for several groups of disease such as ichthyosis and ovalocytosis (Wells and Kerr, 1965; Morton, 1956).

There are several diseases in animals which lead to lethal effects from skeletal disorders similar to achondroplasia and which are the effect of a homozygous recessive allele. Such are the 'bulldog calves' obtained by cross-breeding 'Dexter' cattle and also the achondroplastic condition in rabbits. The presence of hydrocephaly and hydropulsion of the lungs in the two infants under discussion as well as the harelip and cleft palate could be explained as secondary results of development of the skeleton. The congenital heart lesion in the second case may well have had a similar cause. One speculates whether some of the cases of grave achondroplasia, such as those described by Thurner (Thurner, Mignani, and Huss, 1959), might be due to mutations at the same locus as has possibly given rise to the condition seen in the cases described here.

We conclude that the balance of the evidence favours the action of a genetic entity distinct from classical achondroplasia in this family. There are good clinical grounds for differentiating the conditions because of the presence of the additional manifestations of harelip, hydrocephalus, and in one of the infants, congenital heart disease. Equally well, there is evidence from the population genetics of achondroplasia for doubting whether it has a single genetic cause. The only alternative hypothesis which occurs to us, that of a mutant clone of cells giving rise to abnormal gonadal tissue from which ovum or sperm may have been derived, seems in consequence to be a less likely explanation of the phenomena reported here.
Summary

A description is given of two severely affected achondroplastic sibs, with multiple additional congenital abnormalities including harelip, hypoplastic lungs, and hydrocephaly. The parents were phenotypically normal and unrelated. The mother had had two normal children by previous unions. Grounds are given for suspecting that this is an example of recessive inheritance and that achondroplasia may consist of more than one genetic entity. 

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