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MULTIPLE CONGENITAL ARTICULAR RIGIDITIES

A Review of the Literature with Reports of Two Cases

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Part I

The admission of two infants with the condition of multiple congenital articular rigidities, to the Duchess of York Hospital for Babies within six months of each other, provoked this review of the literature and an enquiry into its pathogenesis. The condition has been described under such names as: amyoplasia congenita (Sheldon), arthrogryposis multiplex congenita (Stern, who apologised for its inadequacy), myophagism congenita (Dalmain), multiple congenital articular rigidities (Nové-Josserand), multiple congenital contractures with muscle defects (Magnus), multiple congenital contractures (Wunsch), congenital contractures of the upper extremities (Rosenkranz), the syndrome of congenital arthromyodysplasia (Rossi), myodystrophia fœtalis deformans (Middleton) and dystrophia muscularis congenita (Howard).

Of all these names for the condition, that of multiple congenital articular rigidities, introduced by Nové-Josserand, is, in the state of our present knowledge of the etio-pathogenesis of the syndrome, to be preferred until such time as more conclusive evidence of its origin becomes available and enables a more exact term to be applied to what is a well-recognised and not uncommon entity. There is little doubt left, after this review of the cases which have appeared in the literature, that the articular defects are the result of an embryonic mesenchymal dysplasia which has its beginning in the first month or two of intra-uterine life. The name given by Nové-Josserand, more than any other, very appropriately describes the condition as it presents itself clinically, whereas other names which imply a sure knowledge of the origin of the deformities have not as yet sufficient factual support for their indisputable acceptance.

The syndrome may be defined as one of developmental, prenatal contractural deformities of usually more than one articulation of the extremities, in which both active and passive movement are limited to a less or greater degree and which may be associated with other developmental anomalies.

Symptomatology

The clinical picture may be exaggerated to one of two extremes of postural fixation of the joints. The first report to appear in the literature was that of Otto (1841). In his case all the joints of the extremities were in a position of complete flexion (the feet being in plantar flexion), the compact fœtal position. The other extreme is one so aptly described by Redard (1893) as that of " poupée en bois, sans articulations." In this attitude the joints of the extremities are held in full extension, except, perhaps, the wrists which are usually volar flexed. There is adduction and extreme internal rotation of the upper limbs, and abduction, external rotation and usually pes equinus, equino-varus or a variant of this deformity, of the lower. The upper limbs press close to the sides with the elbows pointing laterally or even anteriorly, the cubital fossæ opening towards the trunk. The external rotation of the lower extremities is in embryonic correspondence with the internally rotated upper extremities. The lack of muscle volume about the shoulders is often pronounced and much of this is due to a deficiency of the deltoid and pectoral muscles.

Between these two typical extremes lie all degrees of flexion and extension contractures of a variable number of joints. The affected limb is more or less rigid and there is a marked hypoplasia or even aplasia of muscle groups, usually symmetrically disposed. The joints may be absolutely immobile or a degree of active and/or passive movement may be possible. The fixation strongly suggests a fibrous ankylosis. The affected muscle groups are always those responsible for the functional deficiency. The lower limbs when affected are characterised by the absence of sharp definition from the trunk. The possible combinations and degrees of contracture beggar classification. Rocher (1913) attempted a division into three types: (i) fixation of the four limbs in extension. (ii) knees fixed in flexion with, perhaps, hips in abduction and flexion. (iii) fixation of one elbow in extension, the other in flexion and the legs, perhaps, in extension. However, as the case reports accumulated they showed this division to be inadequate.

Some authors have not realised that it is not the muscles of the girdles and extremities only, that may be affected. The cervical or thoraco-dorsal or lumbar groups or combinations of these may be involved, to produce corresponding deformities, and there is a case recorded of a compensating hypertrophy of the platysma muscle (Schanz, 1898).

There is frequently an associated though less prominent abnormality. Rigidity of the temporo-mandibular joint, the mouth being difficult or impossible to close and so making a feeding difficulty, has been observed by several authors. There may be a subluxation of one or more joints and very often the hip-joint is dislocated on one or both sides. A rudimentary, impalpable or absent patella is quite common, whether the knees be in flexion or extension. There is frequently also, a creaking or crackling in the affected joint on passive movement,

which indicates an abnormal joint surface. There may be disproportion of the limbs or segments thereof. The bone and joint configuration and contours are not uncommonly abnormal, and even the vertebral and pelvic bones may be faulty (Rocher and Ouary, 1929). An unusual state of the subcutaneous tissue of the limb has been remarked upon many times but the observations made differ widely from case to case, although others, again, have been in agreement. The subcutaneous tissue may feel rather thick, doughy, and even gelatinous to the touch, and obliterate the normal bony outlines as in a case of Rocher, or, on the other hand, be practically completely absent as it was in a case reported by Magnus (1903) in which also, the muscle hypoplasia was so severe that the child seemed to be no more than skin and bone. Yet the abnormal subcutaneous tissue may be so excessive that the joint and limb outlines are completely obscured and the extremity have the appearance of a " stuffed sausage," and little or no muscle be palpable.

The peripheral circulation is often poor and the limbs cold and, as in the case of Altman and Davidson (1939), the skin be like scleroderma, unable to be picked up in folds between the fingers. " Compression dimples " are common about the patella, elbows and condyles. Cryptorchidism, inguinal hernia, hypospadias, and cleft palate (but not hare lip) have been associated. Unilateral and bilateral palpebral ptosis have been reported. Micrognathia also occurs and was present in both cases which I have described in this paper. Mental deficiency has not been uncommon.

The variations in the overall clinical picture are numerous as the foregoing resumé of symptomatology only indicates. While the grosser manifestations suggest the syndrome at once, it is true to say that minor degrees of the condition have been left undiagnosed by even the orthopædic surgeon. The nature of the disability from which these patients suffer, an interference with locomotion, is the reason for the very large majority of the case reports having been published in the surgical journals, and usually by orthopædic surgeons. The ages of the reported cases have ranged from prematurity (Otto) to 61 years (Herson, 1947, cit. Parkes Weber, 1947).

Case Reports

Case 1.—J. K., No. 24443. When the patient, a male infant, was 6 weeks old, it was referred to the Duchess of York Hospital for Babies as a feeding problem. It had been nursed unsuccessfully at the breast where it sucked very poorly, but the mother had not managed any better by feeding her baby from a bottle.

Family History.—The father was well, aged 30 years. The mother was well, aged 24 years but she had had, in the past before the birth of the patient, a nervous breakdown. There was an elder female sibling, aged 18 months, who appeared normal in all respects. There had been no other pregnancies. There was no history of congenital or other deformities in the family.

Past History.—The mother had not contracted any infectious or communicable disease during pregnancy which she brought to term. She had experienced " quickening " about the fifth month and she had not become aware of any fading away of the embryo's activity, but she had observed a rather unusual abdominal girth and when her waters broke at the time of confinement, there was an excess of the amniotic fluid. The patient's birth weight was 7 pounds and 6 ounces (3·3 kg.). The delivery was not difficult, the presentation being a normal vertex. The infant breathed and cried spontaneously immediately after birth which was conducted without anæsthesia. The appearance of the genitalia raised some doubt about its sex but eventually the babe was discharged from the nursing home as a male.

Physical Examination.—This showed a pale, thin but not dehydrated, miserable infant who whined persistently but seemed unable to cry with vigour. The eyes were " sticky," there was a slight nasal discharge. There was slight asymmetry of the skull which was very sparsely covered with hair. The anterior fontanelle was level, under no tension and measured 1·8 cm. across. The head circumference was 34·5 cm., the chest 34 cm., and the abdomen 37·5 cm. in circumference. The crown-rump length was 39·5 cm. The eyes were microphthalmic with a very short visual axis (it took a plus 17 D lens of the ophthalmoscope to bring the fundus into focus for normal vision). The palpebral fissure was correspondingly narrow but the lids were otherwise normal. The disks and fundi also were normal. The upper margin of the pinna of the right ear was level with the outer canthus of the eye, and the upper margin of the left pinna was just below this level. There was hypoplasia of the mandible resulting in an obvious micrognathia, but full passive movement was not restricted although the sucking reflex was very poor. The symphysis mentis was palpable as a groove. The palate was normal except for a bifid uvula. The neck was thin, but not short, passive movement was full but little attempt was made to move the neck actively. The chest was of normal shape, heart and lungs normal to percussion and auscultation, and the abdomen to palpation. However the genitalia were grossly abnormal. The penis was of a size compatible with age, but the meatal orifice was exposed by the prepuce which did not have the usual phimosis normal for this age. There was no scrotum, only a wrinkle or two of the skin below the penis to suggest scrotal skin. The testes were not present in the inguinal canals but on one occasion only, when the infant did make an effort at crying the right testis was palpated momentarily in the canal. The mother was sure that she had on more than one occasion seen the left testis in the canal, but at this or subsequent examinations it did not put in an appearance. See Fig. 1.

Upper Extremities.—The skin was smooth and of good texture but the subcutaneous tissue here, as generally, was very poor, rendering the underlying structures readily palpable. There was full passive range of movement of the shoulders, elbows and wrists. Only the left shoulder showed signs of any active movement and they were slight. The right index and middle fingers were flexed into the palm. Attempted extension prominently displayed the flexor tendons and some tightness of the overlying skin. Neither of the thumbs was adducted or opposed and both could be moved through a full range of passive movement. See Fig. 2.

The left fifth finger was completely flexed into the palm and the ring-finger only slightly so.

Lower Extremities.—These were not externally rotated but on the contrary

the hips were completely flexed with the thighs against the abdomen, but both hip-joints could be passively extended 90°. The knees also were held in complete flexion and they also were extensible to 90°. In none of these joints, hips and knees, was there any sudden locking of movement at the end of the arc of movement possible, just a rapid deceleration of the ease of passive movement. It was not possible to detect the presence of the patellæ. The sulcus between the femoral condyles could be defined readily. The proximal half of the bellies of the quadriceps muscles could be palpated but it was not possible to determine where these muscles had their insertion. See Fig. 3. There was a moderate bilateral talipes equino-varus which was not manually correctible. The configuration of the feet, except for this, was normal. The only active movement in the lower extremities was a return to a position of flexion after passive extension. Over the lateral condyle of the left tibia was a " petite fossette " of Rocher, *i.e.* a dimpling of the skin without deep attachment. Similar dimples lay over right and left fibular heads.

The Spine.—The erector spinæ muscles were poorly developed but there was no clinical restriction of mobility of the vertebral column. There was, nevertheless, an unusual prominence of the spines of the first and second lumbar vertebræ.

Roentgen studies did not show any abnormalities of the bones or joints except for almost complete absence of the angle of the mandible.

Laboratory Data.—Hæmoglobin 120 per cent., erythrocytes 5·2 million, polymorphonuclear leukocytes, 46 per cent., lymphocytes 53 per cent., eosinophils 1 per cent. Urinalysis, essentially normal. 17-ketosteroids, 6·6 mg. per litre of urine per 24 hours.

Electrical Reactions.—The following muscles responded to galvanism and faradism :—adductors of thighs ; gastrocnemius bilaterally, but weaker on left ; hip flexors ; all gluteus muscles ; hip extensors ; abductors of thighs ; quadriceps, weakly, and right better than left ; anticus and posticus muscles bilaterally ; the peroneii ; the long extensors of the toes including great toes. The responses varied considerably in their briskness of reaction, the quadriceps especially was weak. With galvanism the A.C.C. was on the whole, brisker. Upper extremities : there were fairly brisk responses to stimulation of the biceps, triceps, external and internal rotators, extensors and flexors of wrists and fingers.

Spinal muscles showed similar responses. Nowhere was there evidence of degeneration. In the quadriceps it was observed that the " motor point " appeared to have shifted more distally from the point where it is normally situate.

Case 2.—J. E., No. 25709. A female infant, age 6 weeks, was transferred to the Duchess of York Hospital for Babies, as a feeding problem associated with multiple deformities.

Past History.—The mother had carried the child to term. Delivery was by vertex presentation with extended legs. The birth weight was 5 pounds and 9 ounces (2·5 kg.). The mother stated there was little amniotic fluid.

Family History.—Parents were both well. There were 3 normal elder siblings and no family history of deformities.

Physical Examination.—A small pale weak infant with a constant whine and much upper respiratory mucous catarrh producing a noisy respiration. There was obvious micrognathia. The palate was intact. The eyes were small, but other than this there was nothing abnormal about the head. Weight was 6 pounds (2·7 kg.).

Upper Extremities.—There was no fixation of the shoulders and no internal rotation, there was a full range of passive movement. The elbows could be extended to 170° without difficulty. The wrists, however, were in acute volar flexion, with poorly developed fingers in marked metacarpo-phalangeal flexion. Opposed and adducted thumbs. There was some active movement of the fingers.

Lower Extremities.—There was a very severe degree of bilateral talipes equino-varus. The knees were held in incomplete extension of 140°, further extension was not possible. Further flexion of a few degrees was possible. There was extension of the hips and some external rotation of the hips, the left being more marked than the right. The left hip was also dislocated anteriorly. The Wassermann reaction was negative.

Discussion

This review has made possible the collection of at least 240 reports and mentions of cases of m.c.a.r. which have appeared in the literature since the first report in 1841. To this number I have been able to add two more. It is not unlikely that there are others which have escaped me. However this may be, the evidence goes to show that the syndrome in all its vagaries is not uncommon and that much of the interest paid to it, centres about the etiopathogenesis which still remains obscure. A number of hypotheses have been proposed from time to time but no one hypothesis has been adequate enough to explain new factual evidence which has come to light from further study which has been applied to new cases at intervals. Even now more facts are necessary, and also confirmatory investigations of the pathology which may be present in the central nervous system. Such investigation is possible by post-mortem study only, and the natural history of the condition provides little opportunity for this.

We do know that the physical features are congenital, that is, prenatal in origin and with this fact to begin with, the cause should be looked for among the following factors of which one, or more in combination, may be responsible. These factors are :—mechanical, genetic, nutritional, infectious, endocrine, actinic, and chemical. Observation and experimental biology have shown these capable of producing congenital abnormalities in mammals and man.

Many authors have expressed their belief in the intra-uterine compression hypothesis and Rocher regarded the " cicetricielle " often seen over bony prominences, in the regions of the knees and elbows, as a " stigma of compression " : due to the " surcharge intrauterine." The compression, sui generis, is the mechanical factor stated by some, to be the inevitable accompaniment of oligohydramnios and hydramnios. Sheldon discounted compression as being of etiologic significance and Roberts, in his remarks on the cause of the comparable condition of stiff-jointed lambs also discounts this as a factor, in that the position assumed by the fœtus is most unlikely to be that producible by intra-uterine pressure upon the developing fœtus from the uterus or its surrounding organs. This observation applies equally well to the

deformities as they appear in the new-born babe. The position with extended extremities is most unlikely to be the result of a centripetal compression force. Whereas it may be said that the position with the limbs in acute flexion could be attributable to such a force, the fact that two such opposite types of the same condition do occur, weighs heavily against compression being the etiologic factor in m.c.a.r., irrespective of what part it may play in the production of other kinds of congenital malformations. Rocher used the evidence of Lefour and Apert in an attempt to support his thesis and Wunsch quoted Heusner (1898) and his theory on the development of the limbs but neither of these authors could draw any convincing evidence to bolster up the hypothesis of mechanical compression. Schanz likewise, believed in compression as the responsible agent and ascribed the deformities of the extremities to an " inaction atrophy " following the restriction of fœtal activity by the force of compression. Stern submitted three possible causes, either a maldevelopment of ovum and fœtus, or an intra-uterine peri-arthritis, or intra-uterine compression with forced intra-uterine position, and he was inclined to believe in intra-uterine pressure plus peri-arthritis, that the condition was due to peri-articular contracture and not to any muscle or tendon contracture *per se*.

There is little to support the hypothesis that m.c.a.r. is the outcome of a hereditary genetic influence. It is well, however, to keep in mind the fact that a recessive pathologic characteristic may depend upon 4 pairs of genes located in different chromosomes and they have one chance in 256 of combining. The probability that the characteristic will appear in a small family is, therefore, rather remote (Macklin, 1935). So it is possible for m.c.a.r. to be the manifestation of such a recessive genetic factor. It must be added, however, that some of the families which threw up a case, were quite large, but as Warkany (1947) puts it, lack of familial occurrence of a pathologic character does not exclude its genetic origin. In no family has there appeared a second case, nor a case with some other congenital abnormality. We may place within the domain of genetic influence the hypothesis proposed by Sheldon (1932) and by B. H. V. Mayer (no reference) cited by Wunsch (1901) that the cause lies primarily in a hypoplasia and even aplasia of muscle and that the joint contractures are secondary to the muscle deficiency.

The first recorded post-mortem examination was that of Otto (1841) but Howard was the first to make a very thorough examination by dissection and he found : the diaphragm normal and thymus normal in size and position. Sympathetic nervous system, and spinal nerves were normal to the naked eye. The veins, arteries and lymphatics also were normal. The brain was too decomposed for section cutting but macroscopically was normal. The intra-cranial membranes, cranial nerves and spinal cord were normal to the naked eye. The muscles of the face and neck were normal. The subcutaneous tissue of upper extremities was normal with a fair amount of fat. The subcutaneous

nerves and vessels occupied usual positions. The deep fascia was not thickened and readily dissected from muscle but lines of fat were found running between and into muscles, so accurate dissection of muscles was not possible. The muscles were in various stages of fatty degeneration and all were small and some almost absent. Others showed less fatty infiltration. It was especially difficult to follow the muscle to its origins and insertions of tendons. The ext. dig. comm. muscle was very small, *e.g.* could not be traced along backs of fingers. The atrophy and fatty degeneration did not follow any nerve distribution, it was quite capricious but there was no muscle normal in size and colour. The vessels were small but had the usual branches and relationships. The brachial plexus and nerves in arm and forearms were normal, but perhaps smaller than usual. The rectus abdominis muscles were pale and atrophied, thin, and badly developed, but not infiltrated with fat to the naked eye. All layers of fascia were normal. The latissimus dorsi muscle was practically absent and not to be differentiated from fat. The serratus magnus muscle of the chest was atrophied and infiltrated with fat as were the costal parts of the pectoralis major muscle. The attachment of the abdominal muscle to the ribs was indefinite. The muscles of the buttock were almost absent and dissection quite impossible. The hamstrings were thin and fatty. The great sciatic nerve was normal. The anterior thigh muscles were atrophied and the leg muscles small. All blood vessels of lower extremities were small but had the usual branches which were arranged in the usual way. The superior articular surface of the humerus was smaller than usual, and the shaft of the humerus twisted so that the inferior articular surface looked laterally and the olecranon process of ulna articulated on the internal aspect instead of the posterior. *The hip-joint could not be extended after all the muscles had been removed.* The head of the femur was somewhat flattened—there were two abnormal facets on the neck of femur and acetabulum where position brought the bones in contact. Coxa vara was marked.

After all the muscles had been removed from the knee joint and only ligaments left, it was still impossible to straighten the joint, this was attributed to two causes :—

(i) Shortening of ligaments on the flexor aspect, and
(ii) the shape and position of the articular surfaces. The bones were covered with articular cartilage only where they came in contact and these articular facets were abnormally situated.

The inward twist of the feet was due to similar changes in the talus and talo-navicular joints—all the ligaments were slightly contracted.

Section of muscle for microscopy showed large amounts of areolar tissue with fat and section of nerves, vessels and lymphatics appeared normal. Here and there, only the muscle sheath remained, or sarco-

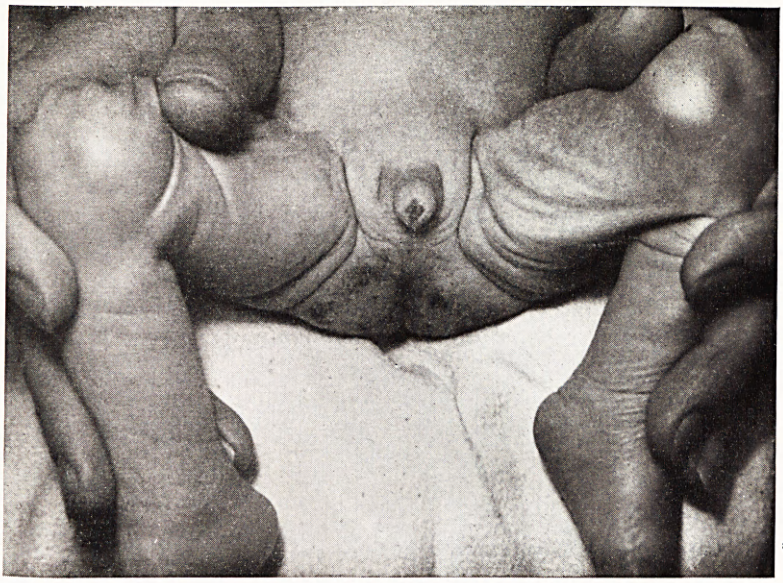

FIG. 1.—Case 1, showing absent scrotum and scanty subcutaneous tissue of lower limbs.

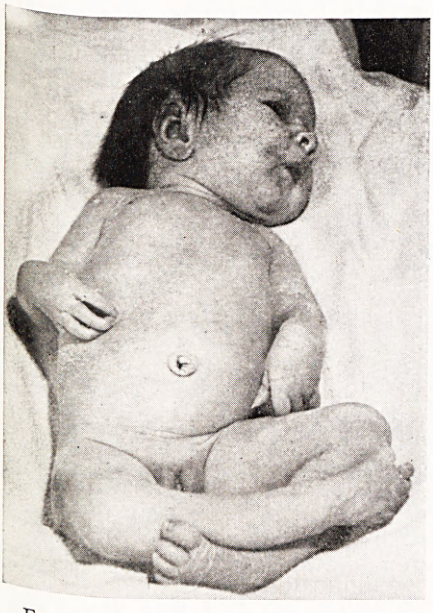

FIG. 2.—Case 1, showing the degree of micrognathia.

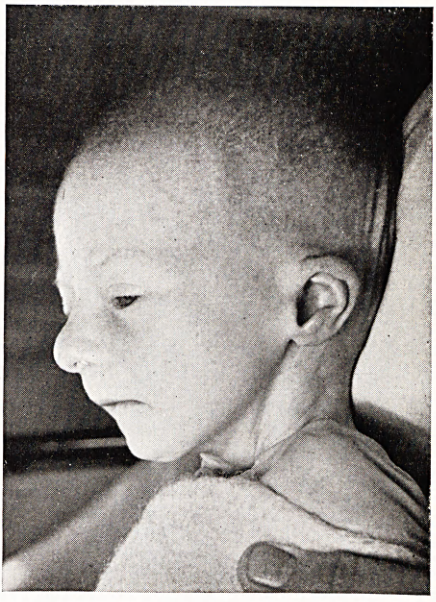

FIG. 4.—Case 2, showing the multiple contractural rigidities.

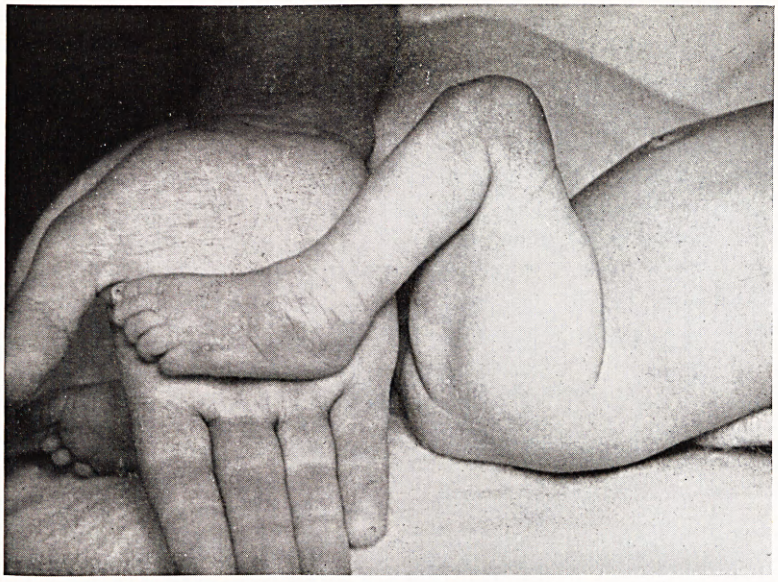

FIG. 3.—Case 1, showing the degree of contractural deformity of the lower limbs.

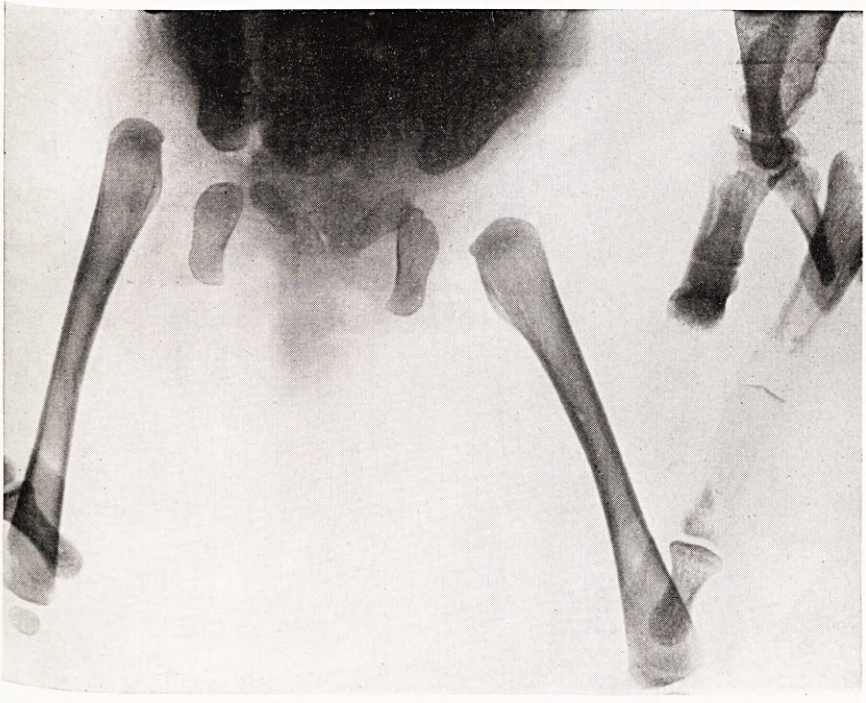

FIG. 5.—Case 2. Skiagraph showing the congenital dislocation of the right hip-joint.

lemma with a little brown pigment; elsewhere the muscle elements were broken up and the nuclei abundant, or the muscle fibres were pale and lacked clarity of outline and resembled greatly the muscle fibres of pseudohypertrophic muscular paralysis but nerve endings were normal.

There was nothing to suggest inflammation; in every section there were fibres with definite transverse striation and only slight signs of degeneration and all the important nerves were normal.

Howard regarded it as difficult to imagine lesions of the motor cells in the cord with such unchanged peripheral nerves and unlikely that a cerebral degeneration would have neither naked-eye changes nor degenerative changes in the peripheral nerves.

He put forward three possible causes :—

(*a*) A degeneration of muscle following acute inflammation or chronic myositis.
(*b*) A non-development of the muscular system.
(*c*) A degeneration of the muscular system. There were no inflammatory changes and it was impossible to distinguish the muscle condition from pseudohypertrophic muscular dystrophy.

He regarded it as a case of " Primary degeneration of muscle occurring before birth."

This autopsy is given in some detail in that it is the first and only detailed dissection of the anatomical structure of the soft tissues affected to have been carried out.

Phocas (1899) carried out an autopsy but it was much less detailed than that of Howard. He found the posterior muscle of the thigh tense and contracted and very short. The muscles of the leg were normal except for the extensors which were short and extended the toes. The patellæ were normal. After the soft tissues were removed from the joint, but not the ligaments, it was still impossible to correct the knee to a normal position and he considered therefore, *that the muscles are not the principal cause of persistence of the deformity.*

The articular surface of the proximal end of the tibia was structurally abnormal and extension of knee joint produced a genu valgum from abnormal articular facets in the knee joint and it was this abnormality of joint surfaces in their number and disposition that prevented reduction of the deformity even after removal of the soft tissues.

He referred to the condition as a complex deformity with a number of elements, osseous, muscular, articular, ligamentous and for treatment all these have to be treated.

Only biopsy examinations were made up to the autopsy examination into the condition by Price in 1933, but these biopsies served only to elucidate the local histo-pathology of the muscle and related tissues in one particular case and little or nothing to suggest the cause of the muscle defect. If anything else, they at times confused the issue (Katzeff, Altman and Davidson, Roberts, Middleton). The more

usual findings were a fatty-fibrous tissue with remnants of recognisable muscle-fibre which in places was normal to all appearances.

Within the purview of genetic influence falls Badgely's theory of embryonic arrest which he propounded in a presidential address in 1943. He considered the condition to be a true embryonic malformation. He referred to the characteristic posture of the limbs as definitely akin to an arrest in development with failure of normal rotation of the limb buds, an arrest of posture analogous to that seen in the third month of fœtal life. The striking similarity of the fœtal attitude in the third month of life to the syndrome under review, he believed to be of great significance. He added that the difficulty encountered in reducing the dislocation of the hip and the club-foot is to be explained by the malformations being embryological developmental defects. Rarely is it possible to reduce the dislocation and club-foot by manipulation as can be done with the more common congenital dislocation and club-foot. The hip is usually dislocated anteriorly with an associated hypoplasia of the anterior margin of the ilium. The abduction and external rotation of the femur is also a characteristic of embryonic dislocation. Nevertheless, it appears from Badgely's remarks that it is the limb posture like that of Redard's " wooden doll " that focuses his attention and has led him to evolve so very plausible a theory. His theory does not account for the numerous varieties of the syndrome which have been reviewed in this paper but it does allow for its expansion. Badgely summarised his theory of the pathogenesis by stating that it could best be explained by a primary pathologic change of the muscle which has been proved inherent in lambs but of unknown etiology in man and which could be the causative factor of the arrest of embryonic development, the causative factor affecting a loss of muscle function which results in the feature of the characteristic rotation of the human limb buds.

Middleton, when he investigated the comparative pathology in sheep, found no abnormalities in the brain, cord, meninges or peripheral nerves. He believed the facts pointed to a primary muscle degeneration arising fairly late in intra-uterine life after the muscle fibres have differentiated, and progresses rapidly to cease at birth. Roberts was able to show that in the sheep the condition depends upon the homozygous state of an autosomal recessive factor. He used selective breeding. Middleton was of opinion that the anomaly of muscle development is the result of the muscle cells being deprived of factors which normally enable them to maintain themselves in a highly differentiated condition.

Brandt, however, in 1947, with good evidence, placed the fault primarily in the central nervous system where Price had placed it before him, in 1933. He found the pathogenesis to be different from Price's. Microscopy of the quadriceps muscle showed a great increase of interfascicular connective tissue and extensive atrophy of the muscle cells. These appeared rich in nuclei. Narrow threads of muscle fibres with preserved striations were found in a few places where

atrophy was not so marked—bundles of narrow muscle fibres with well-preserved striations were to be seen with numerous hypolemmal nuclei where they were cut transversely. There was a suggestion of spinal muscle-atrophy, a mingling of atrophic and normal muscle fibre. On the whole the muscle was not the site of degenerative muscle change. There was no inflammatory infiltration and no vascular changes. In the central nervous system there was pronounced degeneration in the peripheral motor neurone. In the spinal cord he found throughout, that the anterior horns showed changes corresponding with Nissl's " profound cell change " with granular, finely or coarsely, vacuolar degeneration, leading to a total disappearance of the motor cells of the anterior horns and leaving empty spaces in the tissue. Added to this there was extreme chromophilia and cell sclerosis with vacuolation. All degrees of pathological change were present. In all the cell groups there remained scattered normal cells, especially in the antero-medial cell groups, those innervating the dorsal muscles. Practically, only the motor cells of the anterior horns were involved, cells of the lateral horns and Clarke's column were relatively well preserved. Lipoid lysis was nowhere demonstrable and there was no demyelination of the white matter of the spinal cord. A few of the other tracts were still incompletely myelinated, according to age. The medulla oblongata, mesencephalon, nucleus spinalis, nervi accessorii were involved and the nucleus of the left facial nerve was severely affected, the right less so. The nucleus lenticularis had normal and slightly degenerate cells, there was vacuolation, hyperchromesia and nuclear pyknosis, especially in the globus pallidus.

Brandt's histologic diagnosis was a muscle atrophy due to degenerative changes in the spinal cord. Pathogenetically he thought the picture closely resembled that of Werdnig-Hoffmann's disease but that it was clinically entirely different. He thought the clinical picture might depend upon the time when the degeneration of the peripheral neurones begins and this might not be until the apparatus of motion has developed to a normal degree and then the more familiar m.c.a.r. may result.

Brandt quotes Scarzella who found a disappearance and atrophy of motor cells of the anterior horns of the spinal cord (as in his case) and because of this called it fœtal muscle dystrophy. Brandt was also very much of the opinion that Price's photomicrograph which Middleton interpreted as a dystrophy was " the most beautiful example to be imagined of neurogenic atrophy."

Many hereditary defects are explained by the embryo developing in a normal environment at first but at a certain time some parts may have abnormally high demands and if these demands are not met the growth rate of the parts with high requirements will be diminished and arrested development and malformation follow (Warkany, 1947). A number of teratologists have pointed out that the time when the injurious agent acts is more important in the production of a malformation than the agent itself.

A maternal dietary deficiency may be such an injurious agent. The mother may be in a critical nutritional state, in no sense of being starved or undernourished quantitatively but rather deficient in a specific mineral or vitamin. This specific deficiency may be the cause of abnormal progeny. Not less than adequate nutrition for the embryo is essential for its normal development. Anything less at a critical stage may result in its death. Warkany uses the term nutritional disturbance to include faulty implantation of the ovum, diseases of the placenta, interference with the umbilical blood flow and dietary deficiencies, and transmission of a toxic substance to the embryo. In mammalian experimental biology a borderline state of nutrition is requisite for the induction of malformations and a slight improvement may result in the offspring being normal, a worsening, in embryonic death. How a single element can influence embryonic development is shown by the condition of " swayback " occurring in lambs born of ewes fed on a copper-deficient diet. In this the lesions are limited to the central nervous system in which there is widespread symmetrical degeneration in the white matter which contains cavities filled with a transparent, gelatinous substance, or with fluid. Superficially this disease might be suspected to be a hereditary one because of the same ewe repeatedly producing lambs with the identical syndrome.

Another example is cretinism resulting from iodine deficiency and a vitamin A deficiency can produce abnormalities in pig litters. A most forceful argument for nutritional deficiency states being made responsible for prenatal malformations is made by Warkany and Nelson (1941) who proved that a deficiency of Riboflavin in the diet of rats produces a constant type of abnormality in the young and that repair of the diet results in normal progeny again. There appears to be a critical stage when the presence or absence of sufficient Riboflavin determines normal or abnormal embryonic development. Warkany (1947) states that Riboflavin deficiency interferes with embryonic differentiation but not with embryonic growth and he assumes that a higher Riboflavin level is necessary for differentiation than for growth. It is well within the bounds of possibility that factors similar if not identical with the foregoing may play a similar role in producing m.c.a.r.

There was no evidence until recently, apart from congenital syphilis, that prenatal infection played any part in the production of congenital deformities, but since Gregg's original investigation (1942) which has received world-wide confirmation, that Rubella infection of the mother during the first trimester of pregnancy disturbs normal development of the embryo, much more attention is being paid to this possibility in the determination and prevention of congenital abnormalities. The cases of m.c.a.r. reported before 1942, naturally have no reference made to prenatal infection (other than syphilis) and especially a virus infection, of the mother, but it should now be a routine question in any case which is being investigated. In the more recent literature there are a few references to this possibility and in

the two cases reported here, no history of the mother contracting a communicable disease of any kind during pregnancy, was obtained.

Unlike the comparable condition in sheep as reported by Roberts (1929) which almost always results in a still-born lamb or one that dies immediately after birth, a similar lethal factor does not act in the human and despite the awkward postures which the fœtus may adopt, no cases other than those reported by Otto, and Bouvier, which were prematurely born, came to autopsy until 1908 when Howard made his exemplary detailed dissection, although Phocas in 1899 had made a rather limited post-mortem examination.

In 1933 Dorothy Price published her very interesting case report with post-mortem findings which cast much doubt on the more plausible hypotheses which were finding favour at the time. Price found the thymus enlarged (*cf.* Otto's), an abundance of the superficial fascia of the arms, and the muscle almost wholly replaced by fibro-fatty material. There was an abnormal articular surface to the distal end of the humerus. Microscopically there was the appearance of degeneration of the muscle fibre, and degeneration also in the spinal cord. The white columns were degenerate and the outlines of the nerve fibres were almost indistinguishable, and a similar state of affairs applied to the spinal nerve roots. Still the muscle defects could not be explained. Price, like Brandt, compared the histology with that of the Werdnig-Hoffman and Oppenheim types of muscle dystrophies. It was for this reason that she felt constrained to include the syndrome of m.c.a.r. with the infantile myopathies, despite the marked differences in the clinical features. She was able to find signs of chronic inflammatory changes in the meninges. She thought the primary fault lay in the cord and that the muscle changes were secondary. The cord defects were chiefly in the cervical and lumbar enlargements and it was the muscles supplied from these levels that were affected in her case. The non-involvement of other muscles seemed to confirm her hypothesis that the etiology was of central origin. The presence of inflammatory changes in the cord and the absence of myoblasts in the muscle were inconsistent with any theory of abiotrophy. Most of the cord injury was in the region of VI, VII, and VIII cervical segments and in the lower lumbar region. Price inclined to the hypothesis of amniotic infection in the 4th or 5th weeks of intra-uterine life, as the way in which the infection reached the central nervous system.

There is no hint that chemical, endocrine or actinic roentgen influences have any connection with m.c.a.r.

It is regrettable that the autopsy studies which have been carried out should appear so contradictory and so leave the pathogenesis uncertain. The strong evidence of Price and Brandt puts the origin of the condition without hesitation in the central nervous system, the muscle changes being secondary to this, yet, in every case where the electrical reactions of the muscles have been carried out there has been no suggestion of the reaction of degeneration. Rocher was one of the first to use this fact to exclude without equivocation the

nervous system as a factor. Moncrieff and Wiles (1934) who knew of Price's work, still found it difficult to accept a neuropathic origin for the disease. Middleton, who examined the nervous system of a sheep which died of the like malady, found it normal. An observation made by Roberts, but which is not supported by Howard's autopsy findings with regard to the human material, was that the arterial and venous systems of the affected sheep were grossly imperfect, and in some specimens it was impossible to discover other than the merest vascular twigs ramifying from the arterial supply, and Roberts wondered whether the failure of the autonomic nervous system was a factor in the production of the disease which resulted, perhaps, from incompetence of the vaso-dilator nerves.

Hydrops amnii in the pregnant ewe was a constant omen that the unborn lamb was affected and knowledgeable shepherds knew of it. While there persists a popular understanding with regard to m.c.a.r. that it is very commonly associated with either oligohydramnios or hydramnios, this review reveals little evidence in support of this contention. A comparable feature, however, is the state of the subcutaneous tissue. Roberts described in his lambs the subcutaneous tissue to be of large amount and gelatinous in nature. He thought this was produced in connection with the accompanying hydrops amnii; frequently in the human studies a very similar state of the subcutaneous tissue has been remarked upon. Rocher gives quite a vivid description of this particular anomaly. Another point of comparison, for what it is worth, is the enlarged thymus in Roberts' sheep and the large thymus as found in the cases of Otto and Price.

The fact that the syndrome of m.c.a.r. is so often accompanied by other obvious developmental abnormalities such as hypoplasia of the mandible, cleft palate, hypospadias, cryptorchidism, absent scrotum and undeveloped genitalia, etc., points very strongly towards an early arrest of embryonic development and differentiation of structure, the predominating clinical manifestations being in the osseous musculature of the extremities, which may be deficient to a greater or less degree. As far as our knowledge goes the absence of the electrical reaction of degeneration proves that the amyoplasia is not neurogenic. It is possible that when the central nervous system is involved it is not antecedent to the muscle defect, but concomitant like the other associated malformations which may be present. Whether the basic etiologic factor is an abnormal and wayward recessive gene carrying a pathologic trait, or whether the condition begins to manifest later at a critical stage in the development of the fœtus and is determined by a nutritional deficiency of a particular element or necessary food factor, still remains without supporting facts from human teratologic study, although we have approached a little nearer to its solution since the influence of virus infection on the unborn offspring was shown by Gregg to be capable in the first few weeks of pregnancy of distorting the normal development of the human fœtus. An entirely new theoretical concept of the causative factors in this condition of multiple congenital articular

rigidities is that there are centres or organs which control certain body functions, such as the pancreas and carbohydrate metabolism and by analogy a centre for the regulation of morphogenesis. Bearán quotes Marañon who proposes a eutrophic centre in the embryo and who attributes congenital deformities to this centre. Marañon places this centre in the hypothalamus and talks of " a centre in intimate relationship with the four extremities." Consideration is given to the possibility that such a centre may be affected during gestation by intoxication (chronic alcoholism, etc.) or trauma or infections and that glands of internal secretion intervene in the lesion of the embryonic " eutrophic centre," or lesions of the " eutrophic centre " may cause an endocrine alteration of the hypophysis (*cf.* acromegaly). Collen (cit. Marañon, cit. Bearán) attributes " hormonoids " the precursors of the different glandular hormones—to the embryo and compares these with the " trophogenic impulses."

Bearán divides the condition into two types, the hypo- and hyperplastic, the hyperplastic type having subcutaneous fibro-fatty tissue infiltrating in all directions and the volume of the limb is not determined by muscle volume but by subcutaneous tissue. The hypoplastic type is characterised by an asthenic constitution with skin covering the bones and total absence of subcutaneous cellular tissue and marked muscular atrophy.

Of considerable interest are the three recorded instances of the syndrome occurring in one of twins (Howard, Bearán, and Oleaga and Muguruza). Only Oleaga and Muguruza state the specific twin-status which was bivitelline in their case. The fact that three such instances have been recorded goes a long way to exclude certain of the postulated etiologic factors such as intra-uterine compression including oligohydramnios and hydramnios, which has for so long been influencing thought on the pathogenesis of m.c.a.r., intra-uterine infection, systemic infection of the mother, etc., and at the same time goes far towards placing the etio-pathogenesis in the genetic make-up of the embryo.

Summary

An abstract of each case-report on multiple congenital articular rigidities which has appeared in the literature since 1841, with some few exceptions, has been made in an endeavour to cover all the diverse clinical manifestations of which the syndrome is capable.

Case-reports of two more cases, one with a clinical feature not previously noted, have been added.

The possible and probable pathogeneses of the syndrome with supporting evidence taken from the literature, are discussed.

The two cases reported in this paper were admitted to the Duchess of York Hospital for Babies, Manchester, under the care of Dr S. K. Guthrie. The photographs are by Mr G. Ward, photographer to the hospital.

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