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ARTHROGRYPOSIS MULTIPLEX CONGENITA (a.m.c.)

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## ARTHROGRYPOSIS MULTIPLEX CONGENTIA (a.m.c.)

This paper will review the history and nomenclature, incidence, pathology, etiology, and treatment of a bizarre and uncommon- but not rare disorder. In doing this, more explicit diagnostic criteria will be presented and also an attempt will be made to arrive at a unified concept of etiology and etiological factors.

The first written description of this condition was given by Otto (1841) who described the condition in a female fetus of seven or eight months as 'Monstrum humanum trunco nimis brevi et extremitatibus incurvatis!' (cit 19). Redard presented four cases of the children as resembling 'a wooden doll without joints' (28). It is interesting that Otto's case represented one end of a spectrum<sup>um</sup> with all joints of extremities in flexion, while that of Redard (case #1) represented almost the other end of a spectra with most joints in extension<sup>s</sup>.

Wunch (1901) described a case and termed the condition "Multiple Congenital Contractures". Nove<sup>s</sup>-Josserand in his *Precis d'Orthopedic* coined the term "Multiple Congenital Articular Rigidities" (28). Magnus (1903) described a case as "Multiple Congenital Contractures Accompanied by Muscle Aplasia".

Howard (16) who did the first adequate post-mortem study of the condition- those done previously e.g. Otto were quite cursory -, described it as "Dystrophia Muscularis Congenita".

Stern (30) (1923) first used "Arthrogryposis Multiplex Congenita". Names coined since then are Sheldon (1932) (29)- "Amyoplasia Congenita", Middleton (1934) (26)- "Myodystrophia Fetalis Deformans", Rossi (1947) (19)- "Congenital Arthromyodysplasia", among others.

There has been much debate among authors as to which name is most appropriate e.g. whether to use a descriptive name or one which supposedly has an etiological basis. Stern's name has been widely criticized for mixing Greek and Latin words, plus its intimation of primary joint disease. However, since it is the term most widely accepted, it probably should be used if only to give uniformity in reporting.

Arthrogryposis Multiplex Congenita (a.m.c.) is extremely variable in its clinical manifestation. Some authors such as Rocher (28) have attempted- without much success- to outline categorical clinical types of involvement, with regard to the position of, and the joints involved. Other authors (3) have attempted to match a clinical type with a pathological type.

This condition is characterized by:

- 1.) Extreme limitation of motion (both active and passive) about two or more joints.
- 2.) This limitation of motion is not resolved under anesthesia or after death- vs. Little's Syndrome.
- 3.) The manifestations must be bilateral and usually symmetrical, although in any combination both in regard to the number of joints involved and the position.
- 4.) The condition is present before birth and is non-progressive after birth.
- 5.) Other articular abnormalities such as congenital hip dislocation, or kypho-scoliosis tend to strengthen the diagnosis although they are not essential (9).

- 6.) Decrease in absolute and relative volume of voluntary musculature, (18) which may evidence itself not only in the extremities but also in the trunk, neck and head (8)- with the probable exception of the diaphragm (6) (3) (12).

The variability in clinical manifestations may be illustrated by some of the cases which the author has examined:

Case #1

A twenty-three year old male who has two normal siblings. There is no available history of neurological or myopathic disease in the ancestors. The obstetrical history, as given, was contributory only to the fact of a difficult breech delivery.

P.E. The joints of all four extremities are involved. Shoulders, slight adduction; elbows, 85° flexion; knees, 90° flexion; ankles, equino-varus; spine, slight thoracic kypho-scoliosis.

There is no loss of special senses and he is above average intelligence (at present, is full-time college student) and performs many activities using mouth and neck which are not clinically involved. The main problem, besides immobility, has been recurrent bouts of pneumonia.

Case #2

A seven year old female with one brother who also has a.m.c. The obstetrical and family history is unreliable, however, the mother and father are first cousins.

P.E. Hips, externally rotated, flexed, and abducted, bilateral dislocation; knees, 120° flexion; feet in talipes equino-varus; minimal flexion deformity of wrists and fingers. The legs are of very small diameter and she appears as if she were squashed down upon legs which are folded under her. She also appears mentally retarded.

Case #3

A twelve year old male- a brother of case #2-has 110° flexion deformity of knees and talipes equino-varus. There is no apparent involvement of other muscle groups or special senses and he is of normal intelligence.

Case #4

A twelve year old male with no siblings and no family history of neurological or myopathic disorders. The obstetrical history as given is non-contributory.

P.E. An obese male child with bilateral cryptorchism and involvement of most of the joints of the extremities. Shoulders, internal rotation; elbows, 45° of flexion; forearm, severe pro-nation; wrist, flexed; fingers, slight flexion; thumbs adducted; knees, flexed; feet, talipes

equino-varus; hips not involved. He has normal <sup>5</sup>senorium and intelligence.

These cases illustrate some of the common features of a.m.c.-  
for example:

- 1.) The variability in the number of joints affected and the position of the joints.
- 2.) The familial incidence.
- 3.) The frequency of sex of 3:1 male to female.
- 4.) The secondary complications such as: pneumonia, dislocations.
- 5.) The difficulty at parturition due to immobility of the limbs.

Even with the bizarre presenting symptoms, the grosser manifestations suggest the condition at once. It is true, however, that minor degrees of the disorder have been left undiagnosed by even orthopedic surgeons (19).

Howard (16) was the first author to remark on the more minimal involvement which may be present. He thought that arthrogryposis was merely an advanced stage of the condition found in talipes equino-varus.

Adams et al (1) were impressed by the similarity of club-foot and a.m.c., while Jacobson et al (19) were so impressed by this relationship that they suggested that the presence of club-foot or a congenitally dislocated hip in the new-born should bring to mind a.m.c. and initiate a search for contractures. It has been only recently, however, that minimal degrees of the condition, such as involvement of only fingers and wrists has been reported in the literature (13) (23) (25). Reports of head and neck involvement are also now more common (6) (8).

The reported incidence of this disease varies widely- from those who describe it as a 'once in a lifetime diagnosis', to a

report of examining fifty-four cases with quite severe involvement i.e. one case born every eight months for thirty years (22).

The incidence by sex has been reported as five times more frequent in males (11), although the most commonly reported frequency is 2:1 in males (22) (28).

The life span of children with this disease is probably shorter than normal. There are many reports of children dying during, or shortly after a difficult delivery (3) (12). The difficulties during parturition are brought to light by the frequent reports of multiple bone fractures during birth, and also by Ealing's (8) description of the great difficulty found in maintaining a position favorable for delivery. In his case, the fetus, during the ninth month, was many times maneuvered into position, only to have it shift into a transverse lie or breech position.

These children also seem prone to develop respiratory infections. This is probably secondary to impairment of the accessory muscles of respiration, rather than involvement of the diaphragm which has appeared normal in the cases studied (3) (6). However, with better treatment of secondary complications, these children are now living longer, and instances of ages like case #1 or cases such as the forty year old male and the sixty-one year old female by Ellman and Weber (10) are becoming more common.

There has been vehement defense of etiological backgrounds for this condition with little in the way of adequate pathological study either by biopsy or necropsy. The primary site of the disease process has been questioned repeatedly;- that is, whether the primary

lesion is in the muscle, nervous system or even in the joint.

The first controversy as to whether the primary site of the disease process is in the joints began when Howard (16) found that the joints could not be straightened after the muscles had been stripped. In the knee, he found that this was due to shortening of the ligaments on the flexor aspect and 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 located. He concluded that any joint changes were those of inadequate coverage or size of articular cartilage, corresponding to areas of bone contact and were probably secondary to muscle changes.

Stern (30) thought that the contractures were due to primary disease of the joint membranes- i.e. an intrauterine peri-arthritis and that the condition was unrelated to what he thought were imagined contractures of muscle and tendon. Price (27) counters with the observation that it would be very difficult to account for the distribution of the changes in the muscle if the condition is primary in the joints. This is enforced by the finding of no microscopic changes in the joint tissues (1) (12). The current thought is summed by Badgley (2) who decided that the fixation of the joints is not a result of the architecture of the joints, but of a failure of fetal motion secondary to muscle paralysis i.e. the joints form intrinsically, but require motion even in embryonic life to maintain mobility. Yet even to-day, arthrogyrosis is most often indexed under joint diseases.

Another change related to lack of motion namely osteoporosis has been a fairly constant finding- Jacobson et al (18) found it in all the cases he studied. However, he also found the change most marked in the lower extremities and absent in the skull, while Katzeff (21) found porosis absent in the new-born but present in older children, and they therefore took their findings to indicate that porosis is merely secondary to inactivity.

The other common associated condition is congenital hip dislocations. In cases with hip affection, Katzeff (21) found approximately 40% to have dislocation, while Kite (22) found that approximately 50% of all his cases to have dislocations. It is found so commonly that Badgley (2) has set up the characteristic signs, i.e.- it is for all practical purposes an irreducible (reduction and maintainance is extremely difficult and functional results are very poor (22)) anterior displacement of the head with formation of a secondary acetabulum; the fetal limb position is retained; and there is no evidence of anteversion of the head and neck of the femur. Bechtol and Mossman (4) accepted this in part and went further in postulating a mechanism for the dislocation,- theorizing that it was due to a combination of retained fetal posture and fibrosis or shortening of muscle. With the hip flexed  $90^{\circ}$  and externally rotated  $90^{\circ}$ , the greater trochanter lies close to the obturator foramen, and there is shortening of the obturator muscle. At birth, extension of the leg in the presence of a shortened obturator externa, acting as a fulcrum, could lever the femoral head out of the acetabulum.

The great and as yet not completely resolved question is whether the primary lesion is in the muscle or the C.N.S. The main difficulty in answering this question is found in the paucity of exacting necropsy studies. The first person to present evidence of a primary muscle lesion was Howard (16) who in 1908 did a post-mortem exam of a seven day old male infant, who had a twin brother who was still born and had some joint deformity but was not studied. His case had flexion contractures of elbow, wrist, hips, knees and talipes equino-varus. Howard remarked on the smallness of muscle on the opposite side of the deformities and also mentioned changes in trunk musculature. He outlined the muscles involved but his report of microscopic findings of muscle is quite sketchy, i.e.- much fatty infiltration with some larger than normal and some smaller than normal fibres with abundant nuclei. The C.N.S. was too decomposed to allow for microscopic study, but he did make sections of the spinal and cranial nerves and could find nothing abnormal. Likewise he could find no abnormalities in the nerves, blood vessels, or lymphatics of the affected muscles, nor did he find any perivascular or perilymphatic infiltration. He was not able to postulate a condition with lesions of the anterior horn cell without change of the peripheral nerves. Also not thinking it likely that cerebral degeneration would give neither macroscopic changes nor peripheral nerve changes, he concluded that the primary lesion must of necessity be located in the muscle.

Two other pathological studies have been done since then which tended to give credence to this view (3). However, it was not until

1957 that an adequate necropsy study was reported which agreed with Howard's concept. Banker et al (3) published a study of a five and a half month old male infant who clinically resembled Howard's case and who died of bronchopneumonia. They found no macro- or microscopic abnormalities in the cerebrum, brain stem, or the spinal cord (cells in the anterior and posterior horn were normal in number, size and appearance). There was no glial reaction nor any inflammatory or cellular reaction. The meninges and spinal roots were normal.

The only pathological changes were found in the muscles.

Where the fibres ranged in size from 5 micra (resembling fetal fibres with centrally placed nuclei and small numbers of myofibrils) to 87 micra (resembling the B fibres of Wolfhart but larger and more numerous than normal). In the most severely involved muscles there were a few fibres as small as 2-3 micra with some striate fibrils while others resembled primitive myotubes. There were rare degenerated fibres with evidence of phagocytosis, but there was not a significant degree of cellular infiltrate and no evidence of regeneration. There was also an increase in the endomysial and perimysial connective tissue and numerous fat cells.

It was also noted that the changes were more marked in the proximal muscles, and, in individual muscles, the peripheral fasciculi and those near the origin and insertion were more markedly affected, also, the changes appeared to be of different stages within the same muscle.

In another case which again resembled clinically that of Howard,

Bechtol and Mossman (4) (employing silver stains) found no abnormalities of nerves or motor and plates of any muscle studied. They also found microscopic sections of viscera, spinal cord, eye and brain to be normal.

Banker et al (3) were so impressed with their findings that they attempted to align the pathological findings with a definite position of the limbs as seen clinically (flexion of hips and knees and adduction of the legs).

These findings tend to indict the muscle cell; however, findings of changes in the C.N.S. are not lacking.

The first case which tended to substantiate changes in the nervous system was reported by Price in 1933 (27). In the text of her article, the microscopic findings of muscle tissue are not well outlined. Mention is made of considerable shrinkage of nerve cells, and cells of both the anterior and posterior horns were shrunken and degenerated. The white and grey matter of the posterior horns appeared broken up and to consist chiefly of what appeared to be neuroglial fibres. The spinal roots evidenced partial or complete demyelination. A large 'U' shaped space filled with homogeneous substance and with blood vessels was found in the central grey matter and other smaller spaces and fissures were present in both the grey and white matter. Also the central canal was very slightly increased in size. The dura appeared thickened and the pia appeared both thickened and increased in vascularity.

However, in the discussion, it is revealed that the spinal cord which was examined from C4 - T4 had been previously stored in formalin

for some months. The pathological findings are summarily dismissed with the statement that the anterior horn cells appeared normal in both size and number, and there was no evidence of hydrocephalus or meningeal irritation during life. The only changes cited were the demyelination of both anterior and posterior roots and a degeneration of nerve fibres.

In a paper written by Kanof et al (20), a case of a one year old severely retarded child is presented. They thought the most striking feature of the microscopic picture of muscle was the irregularity of involvement i.e. it was not unusual to find within the same field both normally appearing fibres and fibres with typical embryonal appearance. At first blush, the findings in the C.N.S. and P.N.S. appear most significant. They found the brain normal in contour, volume and symmetry and the ventricles were normal. Myelination appeared normal in the cerebrum, cerebellum and brain stem. There did appear to be a decrease in the number of anterior horn cells in the rostral portion of the cord although there was no evidence of inflammatory cell infiltrate or gliosis. In addition, the pyramidal tract (caudal to the brain stem) and the anterior roots were often demyelinated. Likewise, the femoral nerves and brachial plexus showed severe demyelination and active degeneration of axons- exemplified by club-formation, zones of basophilic discoloration and a mild degree of Schwann cell hyperplasia, the motor end plates were normal by Ranvier stain. However although they describe, in the discussion, the case to be typical with marked flexion and adduction contracture of the hips,

the text of the article does not substantiate this. The authors also admit that the changes seen are difficult to interpret, for the assessment of such changes is clouded by the frequent observation of such changes in many agonal states.

Ek (9) did a clinical study of eight cases with varied position types and extent of involvement (although in most cases he did not explicitly specify the positions assumed), one of his cases with brain damage resembles Banker et al (3) <sup>the described by</sup> child. In four of the cases he demonstrates, by pneumo-encephalogram, objective evidence of organic cerebral lesions. In two other cases he presents subjective evidence for cerebral involvement. However, he could not substantiate his statements with necropsy study of the two cases who died (one was refused and other was restricted) or biopsies of any of the cases, and therefore begs the question as to whether the C.N.S. defects may be associated but unrelated to the arthrogyrosis

A female still-born at thirty weeks was studied by Gilmour (12) who found the most conspicuous abnormality to be the smallness of skeletal muscle due to the deficiency in the number of fibres. Within the muscle, there was an absolute increase in adipose tissue and a slight increase in endomysial and perimysial connective tissue. The muscle fibres varied from 3-24 micra and even some of the largest fibres had centrally placed nuclei. In some of the smallest fibres there was an absolute increase in the number of nuclei which were arranged in chains. There was very scant evidence of degeneration and phagocytosis. He emphasized that no muscle can

be assumed to be absent, even if appearing so macroscopically, in view of the fact that he found the Erector Spinae to be represented by only a few fibres in transverse action.

In his sections of the spinal cord, he found what appeared to be a decrease in the number of cells in the anterior horns of the thoracic cord and a decrease in size of the cells in the cervical cord.

In a case reported by Adams et al (1), with involvement of all four extremities, there were few or no cells in the anterior horn of the "lumbo-sacral" cord. In the rest of the cord, there was a decrease in number of anterior horn cells, and those remaining were small and darkly stained. There were no inflammatory cells or neuroglial reaction. The posterior and lateral horns, Clark's Column and the dorsal root ganglia cells were normal. The brain was small and underdeveloped with incomplete fissuration and large lateral ventricles. In a second case with only involvement of the legs, there was a significant decrease in the number and size of the anterior horn cells in the "lumbo-sacral" cord segments.

Thus, it appears at first glance as if there are two separate disease processes to be dealt with- or is there a possibility that the two pathological pictures may in reality be varied expressions of a similar process? It would be foolhardy to argue in a vein which would dismiss the work which has already been done- rather there may be value in light of this work, hypothesizing that some factor has been over-looked- or examined with too little care. That factor was first seriously considered by Gilmour- namely the intramuscular neural apparatus.

Coërs and Woolf (5) are quite vehement in pointing out the failure to adequately demonstrate the intramuscular neural apparatus. They blame this lack on two factors. First, the misconception that the motor <sup>e</sup> and plates are distributed randomly throughout muscle, and secondly the relative crudity of nerve impregnation techniques which failed to demonstrate most of the changes which they now consider to be diagnostically valuable. Coërs has now done a series of biopsy studies of muscle, employing a technique, by which the aneural portions of the muscle can be excised. He has also developed and modified histological techniques with which he has been able to demonstrate nerve endings with exquisite delicacy and completeness. Through his techniques of vital staining with methylene blue, for the first time, the synaptic surface of the motor end plate was made visible, and by employing Couteaux's modification of the Koelle-Friedenwald technique (utilizing the cholinesterase of the post-synaptic surface and receptors) it is possible to demonstrate with precision the sub-neural and sub-sarcolemmal portions of the end plate. It has therefore become possible to demonstrate accurately and with regularity the intramuscular nerve endings. Although they have published their findings of biopsy of many diseases, they have not as yet published any work on a.m.c. If there are changes in the motor end plate in a.m.c. which until this time have not been recognized, it would of course tend to again unite the variant theories exemplified by Banker et al (3) and Adams et al (1).

In reviewing the literature, there seems to appear a very

interesting correlation between the positioning of the limbs as clinically evidenced in a.m.c. and the positions of the limbs at varied stages of gestation.

Therefore one finds, as in the fifth case presented by Rocher (28), internal rotation of the shoulders- the antecubital fossa opening postero-laterally; non-flexion of the elbow with the arms pointing caudally, hips externally rotated with abduction and slight flexion; and knees in extension- a picture very reminiscent of early fetal limb posture i.e. before the limbs have undergone torsion about long axis. At the other end of the spectrum, the child reported by Otto (19) resembles the position assumed by the mature fetus after torsion of the limbs has occurred. Other cases are described which seem to represent stages of changes in limb position between these two extremes. It seems that the cases with histological evidence of C.N.S. involvement tend to resemble in clinical appearance the case of Rocher, while those cases with evidence of no C.N.S. involvement tend to resemble clinically the case of Otto.

Another phenomenon apparent in reviewing cases, reported in the literature and also in the cases reported in this paper is the seeming progression of involvement. That is, when the four extremities are involved, it often appears that the more distal portion of any extremity is more severely involved. Again if only two extremities are involved it seems to involve the legs more commonly, and within the legs themselves if all joints are not affected, the distal joints seem more prone to involvement than those proximally. Therefore, it would appear that the extent of involvement seems to

follow to some degree the cephalocaudal growth pattern of the fetus.<sup>1.e</sup>  
(That is) the arms developing earlier than the legs and the development proceeding from the proximal to the distal portions.

Considering the foregoing observations and facts, the question may be raised as to whether some noxious agent could affect some portion of the voluntary neuro-muscular system at different stages of its fetal development and thereby produce the different histopathological patterns which are seen i.e. the stage of development being a critical factor. This critical time factor may be as follows:

It appears that some spontaneous fetal movement occurs before neuro-muscular union has occurred (7). Moreover, it appears that normally by the sixteenth week, the voluntary muscle has all the fundamental structures which are necessary for the maintenance of relatively strong contractions- which are manifested as "quickenings" in the sixteenth week with subsequent diminution (22), would tend to point toward the abnormality manifesting itself during or before the sixteenth week. It has been generally agreed that the process is fully manifest, at least by the seventh month of gestation. The case of Gilmour (12) of the premature infant and the x-ray of the fetus in utero by Sheldon (29) would substantiate this fact.

If the apparent correlation between clinical posture and fetal posture is an actuality and if it is accepted that torsion of the limbs occurs some time before the fifteenth week of gestation, and that muscle and nervous tissue differentiate after the sixth week then it would appear that a time factor is important, or at least that the process leading to histologically apparent C.N.S.

involvement probably occurs between the sixth and fifteenth week. As a corollary to this, the process leading to no histological evidence of C.N.S. involvement would probably occur after the fifteenth week.

It is well to remember that voluntary muscle may differentiate and develop into bundles, in the complete absence of nerve influence (7). It would therefore be possible to have muscle present, which had had no previous neuro-muscular contact. However, since nerves do have a trophic, if not a morphogenic effect on muscle development, (17) unless a satisfactory neuro-muscular contact was made, the muscle fibres would be expected to remain in a histologically embryonal state (5).

With this in mind a review of the histological findings in the leg muscle in the Banker et al study resemble closely those found by Cuajunco (7) in the Biceps Brachii during the fourteenth week of gestation. The muscle nuclei were beginning to move toward the periphery of the cell and this migration was completed in all cells (large and small) by the fifteenth week, and at this time the cells varied from 2-11 micra. Allowing for the time-growth differential, the picture found by Banker et al should occur at approximately the sixteenth week.

Therefore two possibilities arise:

- 1.) The noxious agent which at one stage of maturation may affect the central and peripheral nervous system, may at a later stage of maturation affect the motor end plate in a manner which until recently would not be detectable and thereby give the appearance of no neurological involvement.

- 2.) That there are actually two separate forms of condition, i.e. a neuropathic and a myopathic which merely present similar clinical symptoms.

Numerous authors, considering the latter possibility, have outlined their ideas of the basic processes leading to what they thought was a myopathic condition. Howard (16), among other authors, considered the basic changes to resemble those seen in Infantile Muscular Dystrophy. However, none has set forth a histological picture which agrees with the classical picture as given by Greenfield et al (14) which consisted of an excess of endomysial collagen and adipose tissue; disappearance of small fibres leaving large and medium sized fibres in a sea of collagen or adipose tissue; structural changes in the larger fibres which undergo fragmentation and phagocytosis; and finally, areas of inflammation and regeneration.

Other authors (3) (26) thought the basic process to consist primarily of an atrophy or degeneration. If this were true, one would expect to find evidence of vigorous sprouting of the distal portion of the subterminal fibres, with frequent anastomoses. Since the number of sprouts far outnumber the dwindling muscle fibres, one would expect to see multiple end plates on a single fibre with an increase in the 'actual terminal innervation ratio' and a decrease in the 'functional terminal innervation ratio'. In addition with the multiplicity of end plates and anastomosing fibres one would expect the veritable tangle of nerve fibres ~~a condition~~ ~~a degenerating nerve fibre~~ known as neurocladism (5).

Badgley (2) cit (18) theorized a degeneration secondary to anoxia, caused by the improper timing of the appearance of vessels

in the limb bud or because of interference with proper vascularization, - he reasoned a.m.c. to resemble Volkman's ischemic contracture. However, no other worker has found the changes which Badgley expected to find in the blood vessels.

Stern (30) tried to incriminate forced intra-uterine positions secondary to increased intra-uterine pressure. However, no one has been able to show that there is an increase in intra-uterine pressure in this condition, and secondly, it is most unlikely that the position of extension would occur as the result of a centripetal compressing force (19).

If there is confusion concerning the primary site of the condition, the situation of incrimination an etiologic agent is bedlam - for example, a low grade amniotic infection (27), maldevelopment of the ovum, intra-uterine peri-arthritis (30), increased intra-uterine pressure (28) (30). Perhaps the best way of reviewing these theories is in light of the types of etiologic agents which most commonly cited as leading to congenital anomalies i.e. mechanical, genetic, nutritional, infectious, endocrine, chemical and actinic.

In this condition, actinic effects can be ruled out with a fair amount of certainty by failure of reports of above normal exposure.

Some authors have attempted to indict trauma in the form of the mother falling during the latter part of pregnancy. However since the onset of a.m.c. is most likely much earlier in gestation, the trauma would most likely be incidental.

Belief in the intra-uterine compression theory has been expressed by some authors (28 (30)). Rocher (28) regarded the depressions often seen over the bony prominences of the knees and elbows as the stigma of compression due to increased intra-uterine pressure. Other authors have cited compression as being the inevitable accompaniment of oligo-amnios and hydraninios<sup>a.m.c.</sup> (19). However, it has not been demonstrated that a.m.c. is more common with either of these conditions (15), and as stated previously, it would be difficult to correlate extention deformities with a centripetal compression force.

Reports of familial incidence are increasing in the literature. Middleton (26) mentioned his work and that of Roberts on a similar condition in sheep in which recessive genetic transmission was quite well proven - both by tracing breeding lines and by selective in-breeding.

Kite (22) found a familial history of the condition in 11% of his patients. He also mentions cases in a brother and sister whose parents were first cousins - the same situation as found in two of the cases outlined in this paper. Ek (9) found two siblings with a.m.c. whose parents were second cousins. He also reported that a sibling of one of his patients had a similar condition which, however, he himself did not examine. Moreover, a lack of familial occurrence of a pathological characteristic does not exclude its genetic origin, for, as James (19) pointed out, a recessive pathological characteristic may depend upon four genes located on different chromosomes and they have but one chance in two hundred and fifty -six of combining.

The fact that genetics is not, however, the only factor, is brought out by the findings of Kite (22) and Hillman and Johnson (15) - the latter with two well documented instances of monozygotic twins, one of which had a.m.c. while the other had no clinical evidence of the condition. The same findings have been reported in two cases of dizygotic twins by Kite (22) and one case by Oleaga and Muguruza (cit 24).

Considering the fact that environmental factors can enhance the variable expressivity or penetrance of a genetic trait (24). One might infer that the same genetic factors of the twins were not similarly enhanced i.e. the identical hereditary pattern was not given clinical expression in the non-affected twin. In this respect, it is interesting that one of Hillman and Johnson's twins was less developed and weighed approximately one kilo less than his normal brother. That variable genetic penetrance does occur in a.m.c. would seem to be borne out by the finding by Lipton and Morgenstern (24) of two identical twins both of which were afflicted.

The above evidence would tend, therefore, to point toward some factor, in addition to genetic, which could preferentially strike one fetus in utero. The most obvious factor would then be nutritional. This factor would, of necessity in the case of twins be secondary to some impairment of transfer of nutrients from the maternal circulation to the fetus - such as decreased placental circulation to one fetus. If this impaired fetal circulation did not exist then perhaps infectious, endocrine and chemical factors could be incriminated.

The treatment of this condition is mainly symptomatic e.g. physio-therapy - which if practised diligently in cases with moderate involvement can produce fairly good results. Other procedures have been attempted in the more seriously involved cases - such as manipulation under anesthesia with temporary fixation in an over-corrected position. Also in the more severely involved cases, surgery has been attempted - such as fasciotomy, capsulotomy, tenotomy, and open reduction of hip joints (21). However, the condition of the muscles tends to make these cases resistant and tends to cause recurrences with further growth (4).

Functional results have, in general, been quite poor, as is illustrated by the five patients with hip dislocation (22) who had successful reduction and maintenance of reduction after surgery. However, they had generally poorer functional results than the patients on whom reduction had not been attempted. The futility of treatment is also shown by the strong consideration of bilateral mid-thigh amputations in case #3 of this paper - to allow him to be fitted with prostheses.

Conclusions:

- 1.) Arthrogryposis Multiplex Congenita is an uncommon condition. It is, however, more common than generally recognized.
- 2.) The condition probably becomes manifest between the sixth and fifteenth week of gestation.
- 3.) The limitation of motion around joints is caused by muscular involvement.
- 4.) The condition may involve almost every voluntary muscle in the body, including those innervated by the cranial nerves - on the other hand, only a few muscles may be involved.

- 5.) This is most likely a neuropathic disorder and what has been considered the myopathic form, may actually be affection of the motor end plate.
- 6.) The condition may be an abiotrophy of muscles secondary to the neurological disorder.
- 7.) Arthrogryposis is probably based on a sex linked recessive genetic trait.
- 8.) This is a possibility of enhancement of the penetrance of the genetic trait, by nutritional factors.
- 9.) The treatment of this disorder has given unsatisfactory results.

**Summary:**

The history and synonyms of Arthrogryposis Multiplex Congenita has been reviewed. Some of symptoms which are frequently encountered have been illustrated by four previously unreported cases, and more stringent diagnostic criteria have been outlined. The numerous proposed etiologies of the condition have been considered and an attempt was made to formulate a unitarian concept of etiology - in doing this an age of onset of the condition has been proposed. Finally, the treatment of the disease was mentioned.

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