Current Concepts Review

Etiology of Idiopathic Scoliosis: Current Trends in Research*

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- Current population studies characterize idiopathic scoliosis as a single-gene disorder that follows the patterns of mendelian genetics, including variable penetrance and heterogeneity.
- The role of melatonin and calmodulin in the development of idiopathic scoliosis is likely secondary, with indirect effects on growth mechanisms.
- Reported abnormalities of connective tissue, skeletal muscle, platelets, the spinal column, and the rib cage are all thought to be secondary to the deformity itself.
- Although no consistent neurological abnormalities have been identified in patients with idiopathic scoliosis, it is possible that a defect in processing by the central nervous system affects the growing spine.
- The true etiology of idiopathic scoliosis remains unknown; however, it appears to be multifactorial.

Idiopathic scoliosis is a pathological entity of unknown etiology. Although the entity was first described by Hippocrates, the term idiopathic scoliosis was probably introduced in the middle of the nineteenth century by Bauer[39]; it was used by Nathan in 1909[67], defined by Whitman in 1922[93], included by Cobb in his classification[19], and popularized by the Scoliosis Research Society[40]. Although most physicians who treat spinal deformities understand the term idiopathic scoliosis, the important questions concerning its etiology remain unanswered.

The objectives of this paper are to provide an update on a number of aspects of the etiology of idiopathic scoliosis, to present an inventory of current investigational work, and to suggest directions for future research. The identification of etiological factors will depend on continued research in each of the areas discussed in this review. Further understanding of this disorder will enable the clinician to better predict prognosis and to aid in the development of more effective treatment modalities. This work represents an effort on the part of the Scoliosis Research Society Etiology Committee to promote an awareness of the research in this field.

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Genetic Factors

The role of hereditary or genetic factors in the development of idiopathic scoliosis has been widely accepted[9,20,26,45,97]. Clinical observations as well as population studies have documented scoliosis within families, with the prevalence higher among relatives than within the general population[24,34,37,77,79,97].

Harrington[45] studied women with a scoliotic curve that exceeded 15 degrees and found a 27 percent prevalence of scoliosis among their daughters. Population studies involving index patients and their families have indicated that 11 percent of first-degree relatives are affected, as are 2.4 and 1.4 percent of second and third-degree relatives, respectively[77].

Studies of twins have consistently shown that monozygous twins maintain a high concordance rate for the condition of approximately 73 percent, whereas dizygous twins have a concordance rate of 36 percent[31,35,50,55,64]. These values are higher than those reported for first-degree relatives from studies of populations of families identified through an affected individual in which the affection status of the first-degree relatives was determined primarily through an initial examination[77,95]. This may be related to the high rate of radiographic confirmation of the presence of this condition in studies of twins com-

pared with that in large population studies of families. Radiographic confirmation of the disease potentially lowers the false-negative rate, as small scoliotic curves undetectable by clinical examination are identified.

Despite documentation of the familial nature of this condition, the mode of inheritance has been debated. Studies based on a wide variety of populations have suggested an autosomal dominant, X-linked, or multifactorial inheritance pattern[15,22,37,61] (Fig. 1). Wynne-Davies[95] reported on a series of 2000 individuals in which all first-degree relatives of an identified affected individual (the proband) were clinically examined. Radiographs were made only if a positive diagnosis was suspected clinically. The results suggested a dominant mode of inheritance. In a series of 2869 individuals reported on by Riseborough and Wynne-Davies[77], all first-degree relatives were examined clinically and radiographically and 81 percent of second and third-degree relatives were evaluated radiographically. That series showed a multifactorial pattern of inheritance.

In 1972, Cowell et al.[20], noting the paucity of reports of male-to-male transmission, selected seventeen families (192 individuals) for physical and radiographic examination and reported a pattern consistent with an X-linked inheritance. With the advent of statistical analysis directed to the potential linkage of genes to known disorders (genetic linkage analysis), Miller et al.[61] investigated X-linkage in fourteen families (136 individuals). This analysis calculates the odds (LOD score) that the genetic loci are linked to an observed trait compared with the odds that a given segregation pattern of genetic loci occurs by chance alone. Overall results did not support X-linkage within the entire population; however, when each family was considered independently, the LOD scores suggested that at least two loci (one autosomal and one X-linked) may have been involved in the expression of scoliosis within these families.

An alternative statistical method directed at the clarification of a genetic model and the penetrance of a familial disease is complex segregation analysis. This methodology is applied to an unscreened population and can confirm clinical observations that a genetic determination exists for a specific disorder. Aksenovich et al.[2] used complex segregation analysis to study a population of ninety families (283 individuals). While their results confirmed the clinical observation of a genetic determination of the disorder, the best-fitting genetic model proves to be equivocal.

Collectively, these studies characterize idiopathic scoliosis as a single-gene disorder that follows the simple patterns of mendelian genetics. This concept defines the gene as the inherited unit transmitted from parent to offspring, which is responsible for the observable trait. Traits can be dominant in expression, meaning that the presence of one gene is sufficient to express the condition, or they can be recessive, meaning that the condition is expressed only in the absence of the dominant factor. Careful descriptions of a study population are essential to determine the expression of a specific gene and hence the transmission pattern of an observable trait. For example, Marfan syndrome is a dominant trait in which the gene is responsible for the condition transmitted from each affected parent to half of his or her offspring. However, simple gene disorders are susceptible to the genetic principles of variable penetrance and heterogeneity. Variable penetrance occurs when a certain percentage of individuals carrying the gene of interest do not express the observable trait. Genetic heterogeneity exists when two or more genes within a study population act independently and each leads to

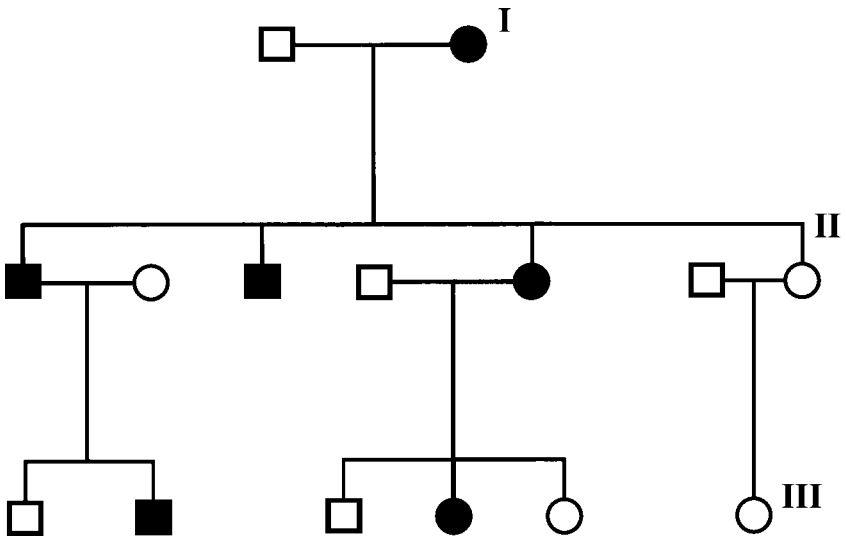

FIG. 1

A representative pedigree of a family with multiple members affected with idiopathic scoliosis. Individuals affected with the disorder occur in every generation (I, II, and III), suggesting a dominant mode of inheritance, and within each gender. Squares represent males, circles represent females, closed symbols represent affected individuals, and open symbols represent unaffected individuals.

the observable trait. Thus, clinically identical subgroups are the result of distinct genetic etiologies. Common disorders among the population, such as scoliosis, that present clinically in different ways and are believed to have a genetic basis are potentially the result of these complex genetic interactions. Consequently, it is difficult to conduct isolated studies of a family or a small sample population in an effort to yield positive results for genetic linkage.

Role of Melatonin

In 1983, Dubousset et al.[27] found that scoliosis routinely developed in pinealectomized chickens, and they attributed this effect to decreased melatonin production. This led Dubousset and Machida[28] to measure the levels of melatonin in thirty adolescents with idiopathic scoliosis and in fifteen age-matched controls. The patients had severe scoliosis ranging from 57 to 75 degrees; the curves were divided into those that had progressed more than 10 degrees in the preceding year and those that had not. Patients with progressive scoliosis had a 35 percent decrease in melatonin levels throughout the night compared with those with stable scoliosis or the control subjects[28].

Bagnall et al.[7] suggested that the action of melatonin may be mediated by growth hormone. Sporadic cases of a rapid increase in scoliotic curvature have been reported in patients undergoing growth-hormone therapy[48]. In a study of side effects of growth-hormone treatment, Allen[3] noted scoliosis in fewer than 1 percent of patients, but progression sometimes occurred during treatment. However, the pharmacological relationship of growth hormone to melatonin is still unclear.

The diurnal variation in melatonin levels seems to be important in determining the effect of this factor on the development of idiopathic scoliosis. However, this rhythm is obliterated in several diseases and does not have an obvious effect on the development of scoliosis. Moreover, patients with idiopathic scoliosis do not have documented difficulties with sleep or immune function, which might be expected with a substantial decrease in melatonin. There is no evidence that patients with idiopathic scoliosis have an inability to form melatonin. Thus, if a lack of melatonin is a factor in the development of scoliosis, it must be due to an alteration of its synthesis. On the basis of the available data, it is possible that melatonin plays a secondary role in the development of idiopathic scoliosis. However, it seems unlikely that scoliosis results from a simple absence of melatonin. Rather, it could result from alterations in the control of melatonin production, with either direct or indirect consequences on growth mechanisms.

Effects of Connective Tissue

Collagen and elastic fibers are principal elements in the supporting structures of the spinal column and have been the focus of many studies dealing with the pathophysiology of idiopathic scoliosis. Because scoliosis is a phenotypic characteristic of many connective-tissue disorders, such as Marfan syndrome, the hypothesis that a defect within the connective tissue is the causative factor of idiopathic scoliosis is plausible.

Work focusing on the quality and quantity of the proteoglycan and collagen contents of the intervertebral discs has produced conflicting results. Pedrini et al.[74] demonstrated an abnormal proportion of glycosaminoglycans and collagen content of the nucleus pulposus of intervertebral discs in patients who had idiopathic scoliosis. This finding was supported by Taylor et al.[90] but not by Oegema et al.[73]. Using specimens obtained at autopsy as controls, Roberts et al.[78] performed a histological and biochemical study of vertebrae and intervertebral discs in adolescents with idiopathic scoliosis. While changes in the distribution of collagen compared with that in normal subjects were evident, they were not consistent among the subjects who had scoliosis. Those authors suggested that the changes may be secondary to the abnormal mechanical forces applied to the discs rather than being the primary cause of the scoliotic deformity itself.

The elastic fiber system, the second major component of the extracellular matrix, has been studied in individuals with idiopathic scoliosis by two groups of investigators. Echenne et al.[29] examined the skin of patients who had idiopathic scoliosis and found substantial differences within the middle and deep dermis compared with those of normal subjects. However, type-I muscle abnormalities also were observed in seventeen (50 percent) of the thirty-four scoliotic patients. In 1994, Hadley-Miller et al.[43] reported elastic fiber abnormalities in the spinal ligaments of a substantial number of patients with idiopathic scoliosis compared with those of normal individuals. Analysis of harvested fibroblasts cultured *in vitro* indicated a potential failure of matrix incorporation of elastic fiber components in several patients with scoliosis.

Carr et al.[15] and Miller et al.[60] focused on the genes responsible for the structural components of the extracellular matrix system. Both groups of investigators selected families in which scoliosis was expressed in an autosomal dominant pattern and analyzed genetic linkage within the families through a candidate-gene approach. With this approach, genes are selected for study on the basis of scientific data, physiological rationale, and clinical understanding of the disease. Genetic linkage is established if the disease phenotype (that is, scoliosis) segregates with a particular allele of the gene. Conversely, if the gene is inherited independent of the disease, it cannot be responsible for the disorder. The structural genes of collagen types I and II, fibrillin 15 (FBN), and elastin were excluded as potential causative factors for idiopathic scoliosis within the study populations. While this information may be regarded as definitive, the studies were limited to a selected number

of families with idiopathic scoliosis. The dilemma of whether the changes observed within the connective tissues of individuals with idiopathic scoliosis might be the consequence of scoliosis rather than the causative factor is still ongoing. However, most researchers concede that abnormalities reported within these elements of the majority of individuals affected with idiopathic scoliosis are probably secondary to the structural forces of the scoliotic deformity itself[30,45].

Skeletal Muscle Abnormalities

The idea that an abnormality of the paraspinous muscles might be the cause of idiopathic scoliosis has been entertained for many years. Spencer and Eccles[87] were apparently the first to describe the two types of muscle fibers in paravertebral muscles in patients with adolescent idiopathic scoliosis. They differentiated between type-I (slow-twitch) and type-II (fast-twitch) fibers and noted that the number of type-II fibers was decreased in their patients, suggesting a myopathic process. Sahgal et al.[79] noted similar findings in the gluteus medius muscle. Bylund et al.[13] described a normal distribution of type-I and type-II fibers on the convexity of the curve but a lower frequency of type-I fibers on the concavity. Slager and Hsu[85] biopsied paravertebral muscle in thirty-one patients with adolescent idiopathic scoliosis and noted a decrease in the number and size of type-II fibers in twenty-one and seventeen patients, respectively, with no preference for either the convex or the concave side. Yarom et al.[99,103] noted similar findings in muscles from distant sites (the deltoid, trapezius, gluteus, and quadriceps) and concluded that this represented a myopathic process.

Yarom and Robin[100] studied paraspinous muscles as well as other muscle sites with use of light microscopy; they found fiber-splitting, tubular bodies, and contraction bands and confirmed the presence of central core formation in many fibers. Myofilament disarray and Z-line streaming also were found both in paraspinous muscle (to a greater extent on the concave side) and at distant sites (the gluteus maximus). The sarcomere was shortened primarily on the concave side; the A-band also was shortened, but equally on both sides. In a similar study, Low et al.[53] noted that lipid, glycogen, and membranous bodies in the muscle fibers were increased and the sarcoplasmic reticulum was slightly dilated. Both groups of investigators postulated a myopathic process.

Ford et al.[36] noted a marked decrease in muscle spindles in all paraspinous muscles that were tested in patients with adolescent idiopathic scoliosis. Using biochemical analysis of the paraspinous muscles with x-ray fluorescence spectrometry in patients with adolescent idiopathic scoliosis, Yarom and Robin[100] demonstrated a markedly increased calcium content. The authors thought that patients with adolescent idiopathic scoliosis might have a generalized membrane defect — namely, an impaired calcium pump.

Using the stable isotope-labeled L-leucine, Gibson et al.[38] analyzed muscle protein synthesis in paravertebral muscle biopsy specimens obtained bilaterally from the top, bottom, and apex of the curve in nine children with idiopathic scoliosis. No differences were noted between the two sides of the spine; however, at the apex of the curve, synthesis was higher on the convexity than on the concavity in all patients. Muscle ribonucleic acid activity at the curve apex was lower on the concave side than on the convex side. Gibson et al. believed that these results were consistent with effects on muscle protein turnover secondary to increased muscle contractile activity and functional immobilization of the muscle on the curve concavity.

In summary, no definite conclusions can be reached with regard to the etiological involvement of skeletal muscle abnormalities. Most of the abnormalities that have been noted are likely secondary to the deformity itself; however, the histochemical changes that have been described might indicate a defect of the cell membrane.

Thrombocyte Abnormalities

Abnormalities in the structure and the function of thrombocytes have been noted in patients with adolescent idiopathic scoliosis by many investigators[51,63,101,102]. Because the protein contractile systems (actin and myosin) of platelets and skeletal muscle resemble each other, it follows that both of these elements would be affected if there is an underlying systemic disorder involving either the structure or the function of the protein contractile system. The platelet is an attractive model to study because its contractile system, which controls its shape, is independent of the axial skeleton, making it independent of the secondary effects in skeletal muscle that potentially are produced by the scoliotic deformity.

Yarom et al.[102] first noted that calcium and phosphorus levels in skeletal muscle were elevated in several diseases; they subsequently observed that intracellular calcium and phosphorus levels also were elevated in the platelets of the same patients. Increased calcium levels also were found within the intracellular dense bodies. Some of the platelets were larger than normal. A calcium transport defect in connection with the cell membrane or contractile protein metabolism was suggested as an explanation. Muhlrad and Yarom[63] noted decreased activity of the intracellular contractile proteins as well as myosin adenosine triphosphatase activity within the platelets. They also noted decreased platelet aggregation with adenosine diphosphate and epinephrine in patients with idiopathic scoliosis. Using electron microscopy and a metal impregnation technique, they demonstrated three distinct platelet types: reticular, metallophilic, and pale cells. The metallophilic platelet was seen most commonly in patients with idiopathic scoliosis, especially those with larger curves, whereas the reticular type was found in controls. This difference was thought to be related to differences in membrane permeability. In a different

study[102], the authors analyzed platelets from forty-nine patients with mild scoliosis (less than 15 degrees) and twenty patients with curves greater than 20 degrees, and they compared these groups with twenty-five normal adults and thirty normal adolescents. The number of dense bodies was increased in patients with idiopathic scoliosis, especially in those with curves of greater than 20 degrees. Those authors noted a distinct difference in the surface electrical charge, with the patients with idiopathic scoliosis, especially those who had larger curves, having more negatively charged metallophilic platelets than the controls.

Calmodulin, a calcium-binding receptor protein, is a critical mediator of eukaryotic cellular calcium function and a regulator of many important enzymatic systems. As mentioned, because the contractile protein systems (actin and myosin) of platelets and skeletal muscle resemble each other, it follows that an underlying systemic disorder affecting the contractile system of skeletal muscle would also affect the contractile system of platelets. Calmodulin regulates the contractile properties of muscles and platelets through its interaction with actin and myosin and its regulation of calcium fluxes from the sarcoplasmic reticulum. Increased calmodulin levels in platelets have been shown to be associated with the progression of adolescent idiopathic scoliosis. Kindsfater et al.[51] compared seventeen patients who had adolescent idiopathic scoliosis of varying severity with ten age and gender-matched controls and found that platelet calmodulin levels in skeletally immature patients with curves progressing more than 10 degrees per year were considerably higher than the levels in patients with stable curves (3.8 compared with 0.7 nanogram per microgram of protein); the levels in the patients with the stable curves and those in the control group were similar. This data is particularly important when compared with the recent findings of Dubousset and Machida[28], who noted decreased levels of melatonin in patients with adolescent idiopathic scoliosis that had progressed more than 10 degrees and normal melatonin levels in patients with stable curves. Recent evidence suggests that melatonin may act by modulating calcium-activated calmodulin[28]. Melatonin binds to calmodulin with high affinity and has been shown to act as a calmodulin antagonist; as such, it may modulate diurnally many cellular functions involving calcium transport.

Multiple pathological biochemical and histological changes have been noted in the platelets of patients with adolescent idiopathic scoliosis. As previously discussed, these changes are similar to those in paraspinous muscle and suggest a primary defect in cells with a contractile system. Some of these abnormalities appear to be related to a defect in the cell membrane and include elevation of intracellular calcium and phosphorus levels, decreased activity of intracellular contractile proteins, decreased platelet aggregation, increased numbers of intracellular dense bodies, a greater number of metallophilic cells, a higher negative surface charge of platelets, increased calmodulin activity, abnormal peptide structure of the myosin chains, and a decreased number of alpha-2 adrenergic receptor sites on platelets. A small percentage of thrombocytes in patients with idiopathic scoliosis are larger than normal. This has not been described in controls. These changes in platelet morphology and physiology suggest a cell-membrane defect in patients with idiopathic scoliosis.

Neurological Mechanisms

Over the last twenty years, sophisticated neurological investigations have been used to compare patients who have idiopathic scoliosis with controls and to compare patients who have progressive curves with those who have nonprogressive scoliosis[41,49,54,80]; however, many of the results have been inconsistent[103]. No clear-cut neurological tests either for diagnosing idiopathic scoliosis or for predicting its progression have so far been established.

Evaluation of vibration sense by means of a biothesiometer has been used to investigate dorsal column dysfunction, but the results have varied from study to study and the biothesiometer has now been deemed unreliable[54]. Similarly, impaired peripheral proprioception is not a constant finding[49]. Interestingly, patients with idiopathic scoliosis have responded poorly compared with controls when tests for visual and proprioceptive function have been combined[103] or when spatial orientation has been evaluated[46].

It may be difficult to distinguish cause from effect when a neurological abnormality is found in association with idiopathic scoliosis. For example, an abnormal sway pattern (measured with stabilometry) is one area of proprioception that was originally thought to be a primary abnormality (that is, an abnormality that was causal to the scoliosis)[65]. Increased sway is now considered to be secondary to scoliosis of any cause (that is, it is an effect of the spinal deformity)[98]. It tends to be more marked when the central nervous system is still immature[80]. When growth ceases, the enhanced-sway phenomenon apparently reverts to normal despite the scoliosis[98].

A number of studies have shown an abnormal nystagmus response to caloric testing in patients with idiopathic scoliosis, suggesting an oculovestibular abnormality[72,80,98]. Herman et al.[46] proposed that a dysfunction of the motor cortex that controls axial posture results from a sensory input deficiency concerning spatial orientation and that this effect probably results from central proprioceptive sources involving visual and vestibular function. Other reports have supported this concept[12,49,72]. The clinical syndrome of symmetrical horizontal or lateral gaze palsy is associated with a high prevalence of scoliosis of the idiopathic type[44]. The site of neurological abnormality is thought to be the paramedian pontine reticular formation, which links the preocular motor nuclei and the vestibular nuclei. It is reasonable to speculate that the site of

neuropathy in idiopathic scoliosis could also be the paramedian pontine reticular formation.

Other authors have deemed the cerebral cortex to be the likely source of postural misinformation. Recent studies involving electromyography and corticosensory evoked potentials in patients undergoing surgery for idiopathic scoliosis have demonstrated abnormal and asymmetrical latencies correlating with the side and indeed the progression of the scoliosis[18,58].

The advent of magnetic resonance imaging has led to renewed interest in abnormal neuroanatomy linked to scoliosis. A cervicothoracic syrinx associated with a Chiari type-I malformation at the foramen magnum has a substantially increased prevalence in patients with idiopathic scoliosis, particularly those who exhibit a juvenile onset of this disorder[5,42,47]. A review of the literature demonstrated that the prevalence of a syrinx in comparable series of patients with scoliosis ranged from 17 to 47 percent[42]. The site and extent of the curve are no different from those found in idiopathic scoliosis without a syrinx, but there is a greater prevalence of left-sided thoracic deformity in patients with a syrinx[5,32]. Neurological function may be normal, although in some patients the abdominal reflexes are asymmetrical[104]. It is not yet known whether this is secondary to the syrinx formation as the first sign of syringomyelia or whether this asymmetry might reflect a more proximal hindbrain or midbrain lesion. Such a lesion could be linked to or even causative of the syrinx, the tonsillar prolapse, and the scoliosis. Alternatively, the Chiari malformation and the syrinx could be the result of traction on the medulla distally through the foramen magnum. It is also possible that growth of the spinal cord is slower in patients with idiopathic scoliosis, resulting in a cord that is shorter than a more rapidly growing vertebral canal, or that reduced growth of the cord is the result of pineal dysfunction, perhaps involving a melatonin deficiency, as discussed elsewhere[57].

Experimental scoliosis has been produced in mammals by both anterior and posterior spinal rhizotomies over several levels[89]. It also occurs when the posterior gray matter and adjacent Clarke columns are damaged in the thoracic spine[75]. These curves have provided useful animal models but are probably unrelated to idiopathic scoliosis *per se,* being more akin to a paralytic or neuropathic deformity. Recently, experimental scoliosis has been produced in rats and rabbits by the creation of microscopic electrocoagulation lesions of the brain with use of stereotactic devices[8,98]. These small lesions lie in the area of the pons and the periaqueductal gray matter, close to the vestibular and preocular nuclei. This zone, the paramedian pontine reticular formation, is the one that Herman et al.[46] suggested was abnormal. It is also consistent with the site of neuropathology in symmetrical horizontal gaze palsy[44]. However, it is important to note that scoliosis developed in only a small proportion of the animals in these experiments, and although the deformity was thought to be idiopathic in at least one study the animals were ataxic[98].

Pinealectomized chickens with induced scoliosis have increased latency of corticosensory evoked potentials[56]. This might suggest damage affecting sensory conduction in the roof of the third ventricle adjacent to the stem of the excised pineal gland. Alternatively, it might reflect a reduction in melatonin levels causing interference with nerve conduction or with the maturation of the nervous system[7,57].

Any hypothesis that proposes a neurological defect must account for the impression that many patients with idiopathic scoliosis have above-average ability in sports. These observations have been largely anecdotal, but a study of girls attending ballet school showed that the prevalence of scoliosis may be as high as 20 percent[93]. It is difficult to account for a neurological defect that allows the patient to excel in activities demanding high proprioception and coordination.

Role of Growth and Development

Idiopathic scoliosis is known to be associated with hypokyphosis; a relative imbalance of growth of anterior and posterior structures has been postulated as a cause of hypokyphosis. According to this hypothesis, the anterior structures grow more rapidly than the posterior ones, and with bending forward the vertebral bodies at the apex tend to move out of the way by rotating to the side. Although this hypothesis is gaining in popularity, few studies have addressed the growth of the spine or spinal growth relative to other body segments. In a prospective study, Nissinen et al.[68] found that children who had scoliosis were taller and had less kyphosis compared with normal children. Those authors also found that children with scoliosis had increased sitting height.

The most comprehensive study of vertebral growth to date was reported by Skogland and Miller[84], who found no substantial differences in the radiographic length of the thoracolumbar spine between patients with idiopathic scoliosis and controls. However, when the lengths of the scoliotic spines were corrected with use of the method of Bjure et al.[11], they were found to be considerably larger than the spines in the control group. Those authors noted that the period of accelerated spinal growth in puberty started about one year earlier in the girls with scoliosis. There were no differences in the maximum growth rate between the two groups. The height of the sixth thoracic vertebra was notably greater in the patients with idiopathic scoliosis. The height-to-width ratio at the sixth thoracic level also was greater in the patients with scoliosis. They noted that girls have been found to have a greater height of the vertebral bodies than boys, and this difference increases with age[91]. Archer and Dickson[6] and Shohat et al.[83] reported that children with larger curves are taller than those with smaller curves. Archer and Dickson attributed this

to flattening of the thoracic kyphosis but provided no data to support this conclusion. Carr et al.[16] concluded that growth is important to the development and progression of scoliosis but is not an etiological factor.

Several authors have studied hormonal control of growth in idiopathic scoliosis; however, the results have been somewhat contradictory and the implications of this research are presently unclear. Misol et al.[62] found no differences in growth-hormone levels between patients with idiopathic scoliosis and controls following glucose-tolerance tests and insulin-induced hypoglycemia. Willner et al.[94] compared somatomedin-A and growth-hormone levels in girls who did and did not have idiopathic scoliosis. They found that the mean fasting growth-hormone levels were higher in the group with idiopathic scoliosis and that the growth-hormone levels after exercise increased more rapidly in this group. Serum somatomedin values were also greater in the group with idiopathic scoliosis. Willner et al. interpreted these findings as showing an altered sensitivity of the growth-hormone-release mechanism in girls with idiopathic scoliosis. They noted that their findings differed from those of Misol et al.[62]. Spencer and Zorab[88] bioassayed somatomedin activity in normal children and children with scoliosis and found no substantial differences.

It is well established that girls with idiopathic scoliosis have a tendency to be taller and more slender than their peers. There are indications that the spine in patients with scoliosis is more slender and longer than that in nonscoliotic children. This spinal pattern has been implicated in a tendency toward column-buckling. As there is a tendency toward rapid growth in early adolescence, just when the scoliosis is most prone to increase, it is presumed that the spine buckles with growth and the posterior ligaments consequently fail to grow in response to anterior growth, acting instead as a tether and forcing the spine into lordosis. Forward bending forces the apical vertebrae of this lordotic segment to translate to the side, resulting in scoliosis.

Interpretation of these studies must take into account two factors. First, the age of the patients studied may be an important variable. If, as several studies suggest, patients with idiopathic scoliosis have rapid growth in early adolescence followed by normal growth later, only younger patients would be expected to show abnormalities. Second, our knowledge of the growth hormone-somatomedin axis has increased considerably in the last decade. Somatomedin A is no longer considered to be a distinct growth factor; its supposed actions are now thought to be the result of other growth factors acting singly or in combination. Therefore, studies that have measured somatomedin-A levels are difficult to interpret in light of the new data.

The control of growth is extremely complex and involves the interaction of many hormones and growth factors. These include hormones such as thyroxine, sexual hormones, and growth hormone and its releasing factor; various growth factors; and modulators such as calmodulin. While the relationship between calmodulin and scoliosis has been well studied, other growth factors, such as fibroblast growth factor, have not been studied in patients with idiopathic scoliosis, to our knowledge. In addition, we know little about the growth-factor receptors in these patients. Previously described effects of melatonin might not be completely separate from the growth-hormone axis. Furthermore, melatonin has recently been shown[3] to independently induce the production of insulin-like growth factor-1; therefore, it may have the capacity to affect growth in a manner independent of growth hormone.

Biomechanical Factors

Biomechanical factors can affect spinal alignment in ways that are often evident in the pathogenesis of idiopathic scoliosis and obvious in some forms of nonidiopathic scoliosis. Mechanical properties of the spinal tissues, alignment of the spine, abnormal loading (either through forces or displacement), and the way that the spine is supported may lead to the development of scoliosis.

The manner in which a structure is supported (the boundary conditions) is an important determinant of its mechanical behavior. This has been recognized in patients with neuromuscular scoliosis, in whom pelvic obliquity is reportedly an important contributor to spinal stability[52]. Scoliosis may develop due to weak or insufficient abdominal musculature that is unable to adequately support the spine[52], but this biomechanical aspect has not been studied extensively in idiopathic scoliosis.

Altered material properties of the tissues of the spine may affect its response to mechanical loading, and this is a possible mechanism for the development of scoliosis. One such material property that is commonly mentioned is axial stiffness, and much of the early research on spinal biomechanics focused on establishing the mechanical characteristics of spinal tissues. However, those were mostly observational studies of tissue from normal spines, and they provided limited insight into tissue from scoliotic spines[4].

Inferior bone quality has been suggested as a possible cause of spinal curvature on the basis of measurements of bone density in children with idiopathic scoliosis and age-matched controls[17,19,76,81,93]. Although subjects with idiopathic scoliosis have different bone material properties, authors have reached different conclusions regarding whether this is etiologically important. At this time, we are not aware of any evidence in the literature supporting inferior bone quality as an important factor in the etiology of idiopathic scoliosis. The results of the bone-density studies are intriguing in that changes were found at skeletal sites remote from the spine that were presumably unaffected by the presence of the scoliosis. Unless these changes are caused by

some subtle aspect of the biomechanics of scoliosis, bone quality may need to be investigated as a possible etiological factor.

Studies of soft-tissue extensibility and joint laxity suggestive of reduced muscular or ligamentous stiffness have yielded contradictory results[10,33,59]. Joint laxity may be an important risk factor for the progression of scoliosis, but there is little evidence that it is an important etiological factor.

One possible etiology of idiopathic scoliosis is asymmetrical loading of the spine, forcing collapse of the overloaded side. Trontelj et al.[91] studied the stretch reflex in normal children, children with neuromuscular scoliosis, and children with idiopathic scoliosis. Those authors concluded that a localized neurogenic defect that causes asymmetrical muscle weakness is a primary factor in the etiology of idiopathic scoliosis. Carpintero et al.[14] demonstrated that lordoscoliosis could be induced in a rabbit by tethering of the spine. Whether these findings are the cause of idiopathic scoliosis or the result of spinal deformity was not demonstrated.

Sevastik et al.[81] proposed a theory referred to as the thoracospinal concept, in which the etiology of thoracic curves is based on an assumption that the thoracic spine is predisposed to rotate to the right; scoliosis develops when this tendency is combined with overgrowth of the left-side ribs. They supported their contention with a series of experiments showing that scoliosis can be induced in rabbits by stimulating unilateral rib growth[1] and that this scoliosis was similar to idiopathic scoliosis in humans[83]. Normelli et al.[69,70], in a study of human ribs from normal subjects and subjects with right thoracic scoliosis, found that the ribs on the left are consistently longer than those on the right in people who have scoliosis. These findings were supported by parallel studies that suggested that the left side is more vascular than the right side and hence is likely to grow more[71]. This work culminated in a recent paper[96] describing a unilateral rib-resection procedure used to treat a child who had a scoliosis of 46 degrees.

As described earlier, the hypokyphotic spine may be sensitive to axial loads and at risk for buckling. The direction of the collapse depends on local conditions but is often determined by the lateral pressure exerted by the aorta. Somerville[86] described this as rotational lordosis initiated by a growth difference in the thoracic spine, whereby growth of the posterior elements lags behind that of the anterior aspect of the vertebrae (Fig. 2). The amount of growth difference need not be great or symmetrical, but the greater the difference the higher the risk of collapse. The extent of the coronal plane asymmetry differentiates children with true scoliosis from normal children with coronal and transverse-plane asymmetry due to aortic loading. There is considerable circumstantial evidence to support this thesis[21,23,25,26,86,98].

There is no strong scientific evidence implicating any particular biomechanical factor in the etiology of idiopathic scoliosis. Biomechanical properties of the structural elements of the spine, alignment of the spine, abnormal loading, and spine-support conditions are static mechanisms important to spinal alignment, but spinal stability as a mechanical process involves continuous realignment of the spine based on position-sensing on a local scale (at the vertebral level) and involving the head and trunk as well as the spine. This dynamic process might also lead to the development of scoliosis in the presence of a normal biomechanical spinal structure[12]. Research efforts to validate this concept have only recently been initiated.

Mathematical Modeling

Correlating a local pathological process and the associated spatial deformation can aid in understanding the etiology of idiopathic scoliosis. Several authors have tried mathematical modeling of the spine with use of different mathematical tools and kinematic assumptions[4,23,25,26,33,66]. The only solid data that can be acquired with few approximations or assumptions pertains to spatial arrangements of bones, expressed as coordinates

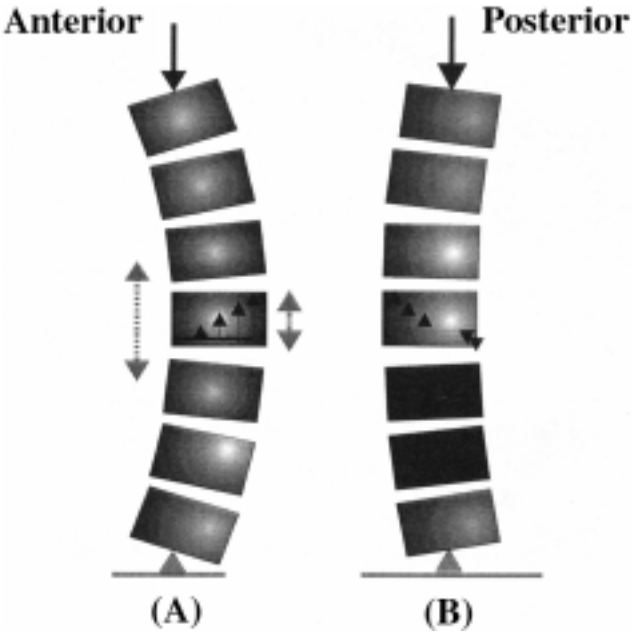

FIG. 2

Growth asymmetries that cause the thoracic spine to develop into a lordotic or hypokyphotic posture can substantially alter the normal stress distribution. *A:* The dashed arrows represent relative growth of the vertebrae, with the longer dashed arrow indicating more anterior growth. The small solid arrows indicate normal stresses due to bending loads developed in response to the resultant superincumbent force (large downward-pointing solid arrow). In this case, the normal stresses through a section at the apex are tensile (small upward-pointing solid arrows), have minimum values at the anterior edge, and increase dorsally. As the spine loses its kyphosis and develops a lordotic configuration, the distribution of the normal stresses changes because of bending. *B:* When the thoracic spine becomes lordotic, there are increased tensile stresses at the anterior aspect of the vertebrae and compressive forces (small downward-pointing arrows) across the posterior sections of the spine. This stress field may then exacerbate a disturbance due to growth asymmetry or an abnormal loading condition due to posterior tethering of the spine.

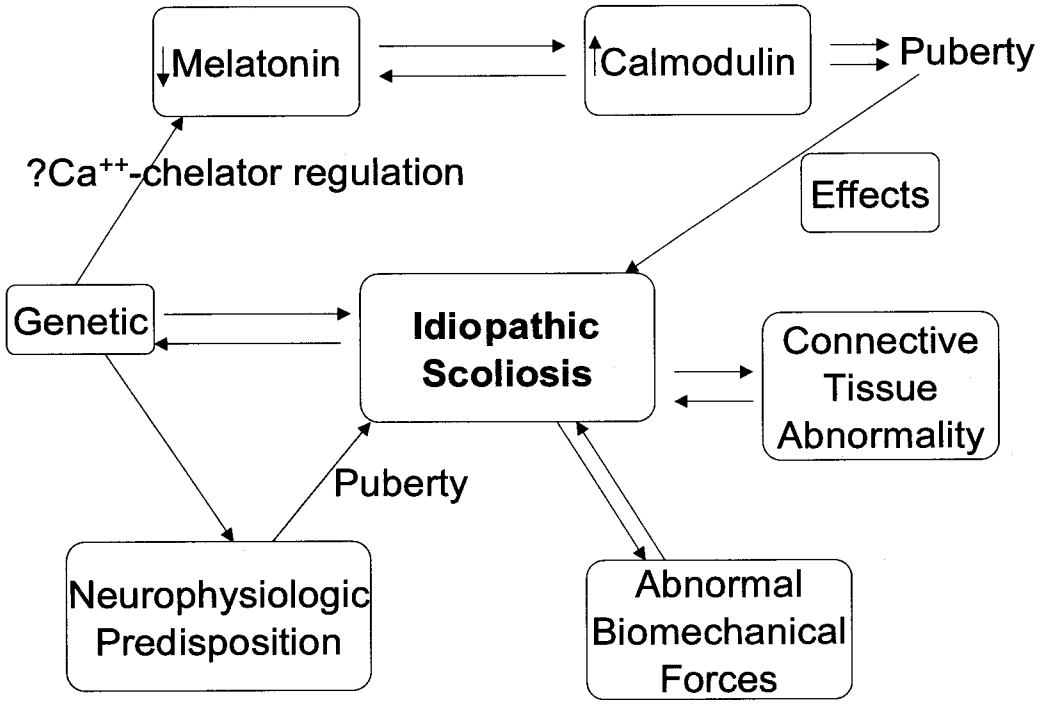

FIG. 3

Suggested interrelationships among various factors that have a potential role in the etiology of idiopathic scoliosis.

in a Cartesian system[66]. These data, both static (spatial arrangement) and dynamic (range of motion), can now be acquired through imaging techniques and can be measured with precision.

Overview

Research into the etiology of idiopathic scoliosis has focused on multiple areas and has demonstrated the complex pathophysiology of this disorder (Fig. 3). Although idiopathic scoliosis may develop from infancy to adolescence, most of the work has focused on adolescent idiopathic scoliosis. It is clear that a complex and probably multifactorial process is involved.

Naturally occurring scoliosis in vertebrates is seen almost exclusively in humans, although a number of animal models for the condition exist. Many authors have observed an array of differences between convexity and concavity of the curve, but it has been difficult to distinguish causative factors from those that may result from the condition[13,36,38,87,100]. The current thinking is that there is a defect of central control or processing by the central nervous system that affects a growing spine and that the spine's susceptibility to deformation varies from one individual to another. Girls may be more vulnerable to this process because of the short and rapid adolescent growth of the spine compared with that in boys.

It is possible that melatonin plays a secondary role in the development of idiopathic scoliosis. However, it seems unlikely that scoliosis results from a simple absence of melatonin. Rather, it could result from alterations in the control of melatonin production, with either direct or indirect consequences upon growth mechanisms. The control of growth is extremely complex and involves the interaction of many hormones and growth factors. A possible relationship between calmodulin and scoliosis has been proposed and should be studied further. In addition, studies of other growth factors in patients with idiopathic scoliosis are needed. Growth hormone and melatonin tend to have a reciprocal relationship, and the presence of one can influence the production of the other.

Most researchers have doubted that a collagen abnormality is a primary etiological factor in the appearance or evolution of idiopathic scoliosis[10,15,33]. These abnormalities are more likely to be associated with the presence of secondary degenerative changes. The same may be true with regard to muscle changes. Many of the morphological changes found in paravertebral muscle have been found in other muscles but to a lesser degree[99,103]. These changes suggest the possibility of a generalized muscle defect, but they are most likely related to asymmetrical muscle-loading resulting from the deformity itself.

The importance of the research of platelet abnormalities in patients with adolescent idiopathic scoliosis is based on the fact that a systemic defect may be present in platelets and skeletal muscle. A small percentage of thrombocytes in patients with idiopathic scoliosis are larger than normal. This finding has not been reported in controls. These changes in platelet morphology and physiology, which are similar to those found in skeletal muscle, suggest a cell-membrane defect that may be genetic

in patients with idiopathic scoliosis.

In attempting to develop a logistical model for causality on the basis of information in the literature, one is impressed by the volume of data that do not appear to be interrelated. The familial aspect of this disorder, however, allows the application of current molecular genetic techniques for the identification of the gene (or genes) involved in the development of scoliosis.

Although idiopathic scoliosis is known to aggregate within families, the pattern of inherited susceptibility is unclear. Multiple contradictory reports emphasize the importance of consistent diagnostic criteria and rigid methods of disease ascertainment in order to provide substantial evidence in support of or against a proposed model of inherited susceptibility[2,20,22,24,34,95]. Once these criteria have been identified, it may be possible to integrate these multiple observations and to develop an understanding of the relationship between the genome, the maturing skeleton, and spinal deformity.

Abnormal magnetic resonance imaging findings, microlesions in the brains of experimental animals, and the most consistent clinical neurological studies point to the pontine and hindbrain regions as the likely sites of primary pathology that could lead to idiopathic scoliosis. High-resolution magnetic resonance images of the midbrain and hindbrain, neurohistological analysis of brain specimens obtained coincidentally from patients with idiopathic scoliosis, and more sophisticated neurological studies should be regarded as high research priorities.

The etiology of idiopathic scoliosis continues to elude investigators, although research has provided much useful information, which has been presented in this review. The consensus is that the etiology is multifactorial. With time, continued research will lead to the identification of the various factors involved in the causation of this disorder, which affects so many children and adolescents. Early identification will lead to earlier treatment and perhaps eventually to eradication of the disease itself.

References

1. **Agadir, M.; Sevastik, B.; Sevastik, J. A.; Persson, A.;** and **Isberg, B.:** Induction of scoliosis in the growing rabbit by unilateral rib-growth stimulation. *Spine,* 13: 1065-1069, 1988.
2. **Aksenovich, T. I.; Semenov, I. R.; Ginzburg, E. Kh.;** and **Zaidman, A. M.:** Preliminary analysis of inheritance of scoliosis. *Genetika,* 24: 2056-2063, 1988.
3. **Allen, D. B.:** Safety of human growth hormone therapy: current topics. *J. Pediat.,* 128: S8-S13, 1996.
4. **Andriacchi, T.; Schultz, A.; Belytschko, T.;** and **Galante, J.:** A model for studies of mechanical interactions between the human spine and rib cage. *J. Biomech.,* 7: 497-507, 1974.
5. **Arai, S.; Ohtsuka, Y.; Moriya, H.; Kitahara, H.;** and **Minami, S.:** Scoliosis associated with syringomyelia. *Spine,* 18: 1591-1592, 1993.
6. **Archer, I. A.,** and **Dickson, R. A.:** Stature and idiopathic scoliosis. A prospective study. *J. Bone and Joint Surg.,* 67-B(2): 185-188, 1985.
7. **Bagnall, K. M.; Raso, V. J.; Hill, D. L.; Moreau, M.; Mahood, J. K.; Jiang, H.; Russell, G.; Bering, M.;** and **Buzzell, G. R.:** Melatonin levels in idiopathic scoliosis. Diurnal and nocturnal serum melatonin levels in girls with adolescent idiopathic scoliosis. *Spine,* 21: 1974-1978, 1996.
8. **Barrios, C.,** and **Attotegui, J. I.:** Experimental kyphoscoliosis induced in rats by selective brain stem damage. *Internat. Orthop.,* 16: 146-151, 1992.
9. **Beals, R. K.:** Nosologic and genetic aspects of scoliosis. *Clin. Orthop.,* 93: 23-32, 1973.
10. **Binns, M.:** Joint laxity in idiopathic adolescent scoliosis. *J. Bone and Joint Surg.,* 70-B(3): 420-422, 1988.
11. **Bjure, J.; Grimby, G.;** and **Nachemson, A.:** Correction of body height in predicting spirometric values in scoliotic patients. *Scandinavian J. Clin. Lab. Invest.,* 21: 191-192, 1968.
12. **Byl, N. N.,** and **Gray, J. M.:** Complex balance reactions in different sensory conditions: adolescents with and without idiopathic scoliosis. *J. Orthop. Res.,* 11: 215-227, 1993.
13. **Bylund, P.; Jansson, E.; Dahlberg, E.;** and **Eriksson, E.:** Muscle fiber types in thoracic erector spinae muscles. Fiber types in idiopathic and other forms of scoliosis. *Clin. Orthop.,* 214: 222-228, 1987.
14. **Carpintero, P.; Mesa, M.; Garcia, J.;** and **Carpintero, A.:** Scoliosis induced by asymmetric lordosis and rotation: an experimental study. *Spine,* 22: 2202-2206, 1997.
15. **Carr, A. J.; Ogilvie, D. J.; Wordsworth, B. P.; Priestly, L. M.; Smith, R.;** and **Sykes, B.:** Segregation of structural collagen genes in adolescent idiopathic scoliosis. *Clin. Orthop.,* 274: 305-310, 1992.
16. **Carr, A. J.; Jefferson, R. J.;** and **Turner-Smith, A. R.:** Family stature in idiopathic scoliosis. *Spine,* 18: 20-23, 1993.
17. **Cheng, J. C.,** and **Guo, X.:** Osteopenia in adolescent idiopathic scoliosis. A primary problem or secondary to the spinal deformity? *Spine,* 22: 1716-1721, 1997.
18. **Cheng, J. C.; Guo, X.; Sher, A. H.; Chan, Y. L.;** and **Metreweli, C.:** Correlation between curve sensitivity, somatosensory evoked potentials, and magnetic resonance imaging in adolescent idiopathic scoliosis. *Spine,* 24: 1679-1684, 1999.
19. **Cobb, J. R.:** Outline for the study of scoliosis. In *Instructional Course Lectures, The American Academy of Orthopaedic Surgeons.* Vol. 5, pp. 261-275. Ann Arbor, J. W. Edwards, 1948.
20. **Cowell, H. R.; Hall, J. N.;** and **MacEwen, G. D.:** Genetic aspects of idiopathic scoliosis. *Clin. Orthop.,* 86: 121-131, 1972.
21. **Cruickshank, J. L.; Koike, M.;** and **Dickson, R. A.:** Curve patterns in idiopathic scoliosis. A clinical and radiographic study. *J. Bone and Joint Surg.,* 71-B(2): 259-263, 1989.
22. **Czeizel, A.; Bellyei, A.; Barta, O.; Magda, T.;** and **Molnar, L.:** Genetics of adolescent idiopathic scoliosis. *J. Med. Genet.,* 15: 424-427, 1978.
23. **Deacon, P.; Archer, I. A.;** and **Dickson, R. A.:** The anatomy of spinal deformity: a biomechanical analysis. *Orthopedics,* 10: 897-903, 1987.
24. **DeGeorge, F. V.,** and **Fisher, R. L.:** Idiopathic scoliosis: genetic and environmental aspects. *J. Med. Genet.,* 4: 251-257, 1967.
25. **Dickson, R. A.; Lawton, J. O.; Archer, I. A.;** and **Butt, W. P.:** The pathogenesis of idiopathic scoliosis. Biplanar spinal asymmetry. *J. Bone and Joint Surg.,* 66-B(1): 8-15, 1984.
26. **Dickson, R. A.:** The etiology and pathogenesis of idiopathic scoliosis. *Acta Orthop. Belgica,* 58 (Supplementum 1): 21-25, 1992.
27. **Dubousset, J.; Queneau, P.;** and **Thillard, M. J.:** Experimental scoliosis induced by pineal and diencephalic lesions in young chickens. Its relation with clinical findings in idiopathic scoliosis. *Orthop. Trans.,* 7: 7, 1983.

28. **Dubousset, J.,** and **Machida, M.:** Melatonin. A possible role in the pathogenesis of human idiopathic scoliosis. In *Proceedings of the Tenth International Philip Zorab Symposium on Scoliosis,* abstract 3.19. Oxford, Oxford University Press, 1998.
29. **Echenne, B.; Barneon, G.; Pages, M.; Caillens, J. P.; Guibal, C.; Jarrousse, Y.; Dimeglio, A.;** and **Pous, J. G.:** Skin elastic fiber pathology and idiopathic scoliosis. *J. Pediat. Orthop.,* 8: 522-528, 1988.
30. **Enneking, W. F.,** and **Harrington, P.:** Pathological changes in scoliosis. *J. Bone and Joint Surg.,* 51-A: 165-184, Jan. 1969.
31. **Esteve, R.:** Idiopathic scoliosis in identical twins. *J. Bone and Joint Surg.,* 40-B(1): 97-99, 1958.
32. **Evans, S. C.; Edgar, M. A.; Hall-Craggs, M. A.; Powell, M. P.; Taylor, B. A.;** and **Nordeen, H. H.:** MRI of 'idiopathic' juvenile scoliosis. *J. Bone and Joint Surg.,* 78-B(2): 314-317, 1996.
33. **Fernandez-Bermejo, E.; Garcia-Jimenez, M. A.; Fernandez-Palomeque, C.;** and **Munuera, L.:** Adolescent idiopathic scoliosis and joint laxity. A study with somatosensory evoked potentials. *Spine,* 18: 918-922, 1993.
34. **Filho, N. A.,** and **Thompson, M. W.:** Genetic studies in scoliosis. In Proceedings of the Scoliosis Research Society. *J. Bone and Joint Surg.,* 53-A: 199, Jan. 1971.
35. **Fisher, R. L.,** and **De George, F. V.:** A twin study of idiopathic scoliosis. *Clin. Orthop.,* 55: 117-126, 1967.
36. **Ford, D. M.; Bagnall, K. M.; Clements, C. A.;** and **McFadden, K. D.:** Muscle spindles in the paraspinal musculature of patients with adolescent idiopathic scoliosis. *Spine,* 13: 461-465, 1988.
37. **Garland, H. G.:** Hereditary scoliosis. *British Med. J.,* 1: 328-334, 1934.
38. **Gibson, J. N.; McMaster, M. J.; Scrimgeour, C. M.; Stoward, P. J.;** and **Rennie, M. J.:** Rates of muscle protein synthesis in paraspinal muscles: literal disparity in children with idiopathic scoliosis. *Clin. Sci.,* 75: 79-83, 1988.
39. **Goff, C. W.:** Louis Bauer, orthopaedist extraordinary. *Clin. Orthop.,* 8: 3-6, 1956.
40. **Goldstein, L. A.,** and **Waugh, T. R.:** Classification and terminology of scoliosis. *Clin. Orthop.,* 93: 10-22, 1973.
41. **Gregoric, M.; Pecak, F.; Trontelj, J. V.;** and **Dimitrijevic, M. R.:** Postural control in scoliosis. A statokinesimetric study in patients with scoliosis due to neuromuscular disorders and in patients with idiopathic scoliosis. *Acta Orthop. Scandinavica,* 52: 59-63, 1981.
42. **Gupta, P.; Lenke, L. G.;** and **Bridwell, K. H.:** Incidence of neural axis abnormalities in infantile and juvenile patients with spinal deformity. Is a magnetic resonance image screening necessary? *Spine,* 23: 206-210, 1998.
43. **Hadley-Miller, N.; Mims, B.;** and **Milewicz, D. M.:** The potential role of the elastic fiber system in adolescent idiopathic scoliosis. *J. Bone and Joint Surg.,* 76-A: 1193-1206, Aug. 1994.
44. **Hamanishi, C.; Tanaka, S.; Kasahara, Y.;** and **Shikata, J.:** Progressive scoliosis associated with lateral gaze palsy. *Spine,* 18: 2545-2548, 1993.
45. **Harrington, P. R.:** The etiology of idiopathic scoliosis. *Clin. Orthop.,* 126: 17-25, 1977.
46. **Herman, R.; Mixon, J.; Fisher, A.; Maulucci, R.;** and **Stuyck, J.:** Idiopathic scoliosis and the central nervous system: a motor control problem. *Spine,* 10: 1-14, 1985.
47. **Isu, T.; Chono, Y.; Iwasaki, Y.; Koyanagi, I.; Akino, M.; Abe, H.; Abumi, K.;** and **Kaneda, K.:** Scoliosis associated with syringomyelia presenting in children. *Childs Nerv. Syst.,* 8: 97-100, 1992.
48. **Kawabata, H.; Ono, K.; Seguchi, Y.;** and **Tanaka, M.:** [Idiopathic scoliosis and growth — a biomechanical consideration.] *Nippon Seikeigeka Gakkai Zasshi,* 62: 161-170, 1988.
49. **Keessen, W.; Crowe, A.;** and **Hearn, M.:** Proprioceptive accuracy in idiopathic scoliosis. *Spine,* 17: 149-155, 1992.
50. **Kesling, K. L.,** and **Reinker, K. A.:** Scoliosis in twins. A meta-analysis of the literature and report of six cases. *Spine,* 22: 2009-2015, 1997.
51. **Kindsfater, K.; Lowe, T.; Lawellin, D.; Weinstein, D.;** and **Akmakjian, J.:** Levels of platelet calmodulin for the prediction of progression and severity of adolescent idiopathic scoliosis. *J. Bone and Joint Surg.,* 76-A: 1186-1192, Aug. 1994.
52. **Lam, K. S.,** and **Mehdian, H.:** The importance of an intact abdominal musculature mechanism in maintaining spinal sagittal balance. Case illustration in prune-belly syndrome. *Spine,* 24: 719-722, 1999.
53. **Low, W. D.; Chew, E. C.; Kung, L. S.; Hsu, L. C. S.;** and **Leong, J. C. Y.:** Ultrastructures of nerve fibers and muscle spindles in adolescent idiopathic scoliosis. *Clin. Orthop.,* 174: 217-221, 1983.
54. **McInnes, E.; Hill, D. L.; Raso, V. J.; Chetner, B.; Greenhill, B. J.;** and **Moreau, M. J.:** Vibratory response in adolescents who have idiopathic scoliosis. *J. Bone and Joint Surg.,* 73-A: 1208-1212, Sept. 1991.
55. **McKinley, L. M.,** and **Leatherman, K. D.:** Idiopathic and congenital scoliosis in twins. *Spine,* 3: 227-229, 1978.
56. **Machida, M.; Dubousset, J.; Imamura, Y.; Iwaya, T.; Yamada, T.; Kimura, J.;** and **Toriyama, S.:** Pathogenesis of idiopathic scoliosis: SEPs in chicken with experimentally induced scoliosis and in patients with idiopathic scoliosis. *J. Pediat. Orthop.,* 14: 329-335, 1994.
57. **Machida, M.; Dubousset, J.; Imamura, Y.; Iwaya, T.; Yamada, T.;** and **Kimura, J.:** Role of melatonin deficiency in the development of scoliosis in pinealectomised chickens. *J. Bone and Joint Surg.,* 77-B(1): 134-138, 1995.
58. **Maguire, J.; Madigan, R.; Wallace, S.; Leppanen, R.;** and **Draper, V.:** Intraoperative long-latency reflex activity in idiopathic scoliosis demonstrates abnormal central processing. A possible cause for idiopathic scoliosis. *Spine,* 18: 1621-1626, 1993.
59. **Mattson, G.; Haderspeck-Grib, K.; Schultz, A.;** and **Nachemson, A.:** Joint flexibilities in structurally normal girls and girls with idiopathic scoliosis. *J. Orthop. Res.,* 1: 57-62, 1983.
60. **Miller, N. H.; Mims, B.; Child, A.; Milewicz, D. M.; Sponseller, P.;** and **Blanton, S. H.:** Genetic analysis of structural elastic fiber and collagen genes in familial adolescent idiopathic scoliosis. *J. Orthop. Res.,* 14: 994-999, 1996.
61. **Miller, N. H.; Schwab, D.; Sponseller, P.; Shgert, E.; Bell, J.;** and **Maestri, N.:** *Genomic Search for X-Linkage in Familial Adolescent Idiopathic Scoliosis.* Burlington, Vermont, International Research Society of Spinal Deformities, 1998.
62. **Misol, S.; Ponseti, I. V.; Samaan, N.;** and **Bradbury, J. T.:** Growth hormone blood levels in patients with idiopathic scoliosis. *Clin. Orthop.,* 81: 122-125, 1971.
63. **Muhlrad, A.,** and **Yarom, R.:** Contractile protein on platelets from patients with idiopathic scoliosis. *Haemostasis,* 11: 154-160, 1982.
64. **Murdoch, G.:** Scoliosis in twins. *J. Bone and Joint Surg.,* 41-B(4): 736-737, 1959.
65. **Nachemson, A.,** and **Sahlstrand, T.:** Etiologic factors in adolescent idiopathic scoliosis. *Spine,* 3: 176-182, 1977.
66. **Nachemson, A.,** and **Pope, M. H.:** Concepts in mathematical modeling. *Spine,* 16: 675-676, 1991.
67. **Nathan, P. W.:** The etiology of lateral curvature. *Am. J. Orthop. Surg.,* 6: 379-390, 1909.
68. **Nissinen, M.; Heliovaara, M.; Seitsamo, J.;** and **Poussa, M.:** Trunk asymmetry, posture, growth, and risk of scoliosis. A three-year follow-up of Finnish prepubertal school children. *Spine,* 18: 8-13, 1993.
69. **Normelli, H.; Sevastik, J.;** and **Akrivos, J.:** The length and ash weight of the ribs of normal and scoliotic persons. *Spine,* 10: 590-592, 1985.

70. **Normelli, H.; Sevastik, J.;** and **Wallberg, H.:** The thermal emission from the skin and the vascularity of the breasts in normal and scoliotic girls. *Spine,* 11: 405-408, 1986.
71. **Normelli, H.; Sevastik, J. A.; Ljung, G.;** and **Jonsson-Soderstrom, A. M.:** The symmetry of the breasts in normal and scoliotic girls. *Spine,* 11: 749-752, 1986.
72. **O'Beirne, J.; Goldberg, C.; Dowling, F. E.;** and **Fogarty, E. E.:** Equilibrial dysfunction in scoliosis — cause or effect? *J. Spinal Disord.,* 2: 184-189, 1989.
73. **Oegema, T. R., Jr.; Bradford, D. S.; Cooper, K. M.;** and **Hunter, R. E.:** Comparison of the biochemistry of proteoglycans isolated from normal, idiopathic scoliotic and cerebral palsy spine. *Spine,* 8: 378-384, 1983.
74. **Pedrini, V. A.; Ponseti, I. V.;** and **Dohrman, S. C.:** Glycosaminoglycans of intervertebral disc in idiopathic scoliosis. *J. Lab. Clin. Med.,* 82: 938-950, 1973.
75. **Pincott, J. R.,** and **Taffs, L. F.:** Experimental scoliosis in primates. A neurological cause. *J. Bone and Joint Surg.,* 64-B(4): 503-507, 1982.
76. **Riggins, R. S.; Lewis, D. A.; Benson, D. R.; McCarrey, J. R.;** and **Franti, C. E.:** Mechanical properties of the tibia from chickens with idiopathic scoliosis. *J. Biomech.,* 16: 59-67, 1983.
77. **Riseborough, E. J.,** and **Wynne-Davies, R.:** A genetic survey of idiopathic scoliosis in Boston, Massachusetts. *J. Bone and Joint Surg.,* 55-A: 974-982, July 1973.
78. **Roberts, S.; Menage, J.;** and **Eisenstein, S. M.:** The cartilage end-plate and intervertebral disc in scoliosis: calcification and other sequelae. *J. Orthop. Res.,* 11: 747-757, 1990.
79. **Sahgal, V.; Shah, A.; Flanagan, N.; Schafer, M.; Kane, W.; Subrami, V.;** and **Singh, H.:** Morphologic and morphometric studies of muscle in idiopathic scoliosis. *Acta Orthop. Scandinavica,* 54: 242-251, 1983.
80. **Sahlstrand, T.,** and **Petruson, B.:** A study of labyrinthine function in patients with adolescent idiopathic scoliosis. I. An electronystagmographic study. *Acta Orthop. Scandinavica,* 50: 759-769, 1979.
81. **Sevastik, B.; Xiong, B.; Sevastik, J.; Hedlund, R.;** and **Suliman, I.:** Vertebral rotation and pedicle length asymmetry in the normal adult spine. *European Spine J.,* 4: 95-97, 1995.
82. **Sevastik, J.; Agadir, M.;** and **Sevastik, B.:** Effects of rib elongation on the spine. I. Distortion of the vertebral alignment in the rabbit. *Spine,* 15: 822-825, 1990.
83. **Shohat, M.; Shohat, T.; Nitzan, M.; Mimouni, M.; Kedem, R.;** and **Danon, Y. L.:** Growth and ethnicity in scoliosis. *Acta Orthop. Scandinavica,* 59: 310-313, 1988.
84. **Skogland, L. B.,** and **Miller, J. A.:** The length and proportions of the thoracolumbar spine in children with idiopathic scoliosis. *Acta Orthop. Scandinavica,* 52: 177-185, 1981.
85. **Slager, U. T.,** and **Hsu, J. D.:** Morphometry and pathology of the paraspinous muscles in idiopathic scoliosis. *Devel. Med. and Child Neurol.,* 28: 749-756, 1986.
86. **Somerville, E. W.:** Rotational lordosis: the development of the single curve. *J. Bone and Joint Surg.,* 34-B(3): 421-427, 1952.
87. **Spencer, G. S.,** and **Eccles, M. J.:** Spinal muscle in scoliosis. Part 2. The proportion and size of type 1 and type 2 skeletal muscle fibres measured using a computer-controlled microscope. *J. Neurol. Sci.,* 30: 143-154, 1976.
88. **Spencer, G. S.,** and **Zorab, P. A.:** Plasma somatomedin activity in normal and scoliotic children. *Pediat. Res.,* 11: 883-885, 1977.
89. **Suk, S. I.; Song, H. S.;** and **Lee, C. K.:** Scoliosis induced by anterior and posterior rhizotomy. *Spine,* 14: 692-697, 1989.
90. **Taylor, T. K. F.; Ghosh, P.;** and **Bushnell, G. R.:** The contribution of the intervertebral disk to the scoliotic deformity. *Clin. Orthop.,* 156: 79-90, 1981.
91. **Trontelj, J. V.; Pečak, F.;** and **Dimitrijević, M. R.:** Segmental neurophysiological mechanisms in scoliosis. *J. Bone and Joint Surg.,* 61-B(3): 310-313, 1979.
92. **Warren, M. P.; Brooks-Gunn, J.; Hamilton, L. H.; Warren, L. F.;** and **Hamilton, W. G.:** Scoliosis and fractures in young ballet dancers. Relation to delayed menarche and secondary amenorrhea. *New England J. Med.,* 314: 1348-1353, 1986.
93. **Whitman, A.:** Observation on the corrective and operative treatment of structural scoliosis. *Arch. Surg.,* 5: 578-630, 1922.
94. **Willner, S.; Nilsson, K. O.; Kastrup, K.;** and **Bergstrand, C. G.:** Growth hormone and somatomedin A in girls with adolescent idiopathic scoliosis. *Acta Paediat. Scandinavica,* 65: 547-552, 1976.
95. **Wynne-Davies, R.:** Familial (idiopathic) scoliosis. A family survey. *J. Bone and Joint Surg.,* 50-B(1): 24-30, 1968.
96. **Xiong, B.; Sevastik, J.; Hedlund, R.;** and **Sevastik, B.:** Sagittal configuration of the spine and growth of the posterior elements in early scoliosis. *J. Orthop. Res.,* 12: 113-118, 1994.
97. **Xiong, B.,** and **Sevastik, J. A.:** A physiological approach to surgical treatment of progressive early idiopathic scoliosis. *European Spine J.,* 7: 505-508, 1998.
98. **Yamada, K.; Yamamoto, H.; Nakagawa, Y.; Tezuka, A.; Tamura, T.;** and **Kawata, S.:** Etiology of idiopathic scoliosis. *Clin. Orthop.,* 184: 50-57, 1984.
99. **Yarom, R.; Robin, G. C.;** and **Gorodetsky, R.:** X-ray fluorescence analysis of muscles in scoliosis. *Spine,* 3: 142-145, 1978.
100. **Yarom, R.,** and **Robin, G. C.:** Studies on spinal and peripheral muscles from patients with scoliosis. *Spine,* 4: 12-21, 1979.
101. **Yarom, R.; Blatt, J.; Gorodetsky, R.;** and **Robin, G. C.:** Microanalysis and x-ray fluorescence spectrometry of platelets in diseases with elevated muscle calcium. *European J. Clin. Invest.,* 10: 143-147, 1980.
102. **Yarom, R.; Meyer, S.; More, R.;** and **Robin, G. C.:** Metal impregnation abnormalities in platelets of patients with idiopathic scoliosis. *Haemostasis,* 12: 282-288, 1982.
103. **Yekutiel, M.; Robin, G. C.;** and **Yarom, R.:** Proprioceptive function in children with adolescent idiopathic scoliosis. *Spine,* 6: 560-566, 1981.
104. **Zadeh, H. G.; Sakka, S. A.; Powell, M. P.;** and **Mehta, M. H.:** Absent superficial abdominal reflexes in children with scoliosis. An early indicator of syringomyelia. *J. Bone and Joint Surg.,* 77-B(5): 762-767, Sept. 1995.