Idiopathic scoliosis is a three-dimensional deformity of the spine with lateral curvature combined with vertebral rotation. The primary lesion, however, lies in the median sagittal plane, taking the form of a lordosis. It was first described by Hippocrates, and the term “scoliosis” was first used by Galen (AD 131–201). Although the clinical manifestations of scoliosis have been well described, no one has been able to determine the cause and pathogenesis.

Throughout the 18th and 19th centuries, scoliosis was believed to be caused by postural positioning of the body. Historically, idiopathic scoliosis has been attributed to a wide variety of conditions ranging from poor posture to poor nutrition. Nutritional deficiency was proposed as a cause in the beginning of this century, and most spinal curves were thought to be secondary to rickets. Brunk, however, showed that the curves identified as rickets presumably caused by vitamin D deficiency never became severe and actually were reversible by treatment.

Recently, the search for the cause of idiopathic scoliosis has focused on the structural elements of the spine, spinal musculature, collagenous structures, endocrine system, central nervous system, and genetics. Of all these studies, none has shown convincing evidence of the cause of idiopathic scoliosis. Results of experiments on various animal models and clinical studies have indicated possible anatomic or functional influences in the cause of idiopathic scoliosis, but many of them may be epiphenomena rather than causes.

More recently, Kindsfater et al have reported that the level of platelet calmodulin in skeletally immature patients with a progressive spine curve is significantly higher than in those with a stable curve. Machida et al found significantly decreased nighttime melatonin levels in adolescents with progressive curves, whereas those with stable curves had a level that is normal for adolescents. There is a strong interaction of melatonin with calmodulin. Other researchers have suggested a genetic component in idiopathic scoliosis because of the similarity of curve pattern in twins who both have scoliosis.

This is a review of various causative factors thus far proposed for idiopathic scoliosis and a discussion of where research is heading to determine the cause of idiopathic scoliosis.

Genetics

Clinical observations and results of genetic studies have shown the familial nature of idiopathic scoliosis and have supported the proposal that the cause of this disease is genetic. The method of inheritance, however, is unsolved. Multiple clinical studies support either an autosomal dominant, multifactorial, or X-linked inheritance pattern for familial idiopathic scoliosis. Wynne-Davies demonstrated that this disease is hereditary, suggesting either a dominant- or multiple-gene inheritance pattern, whereas Cowell et al proposed a dominant mode of inheritance, possibly with a sex-linked dominant pattern. Fisher and DeGeorge concluded that there is no simple genetic explanation for this condition when affected pedigrees are definitively diagnosed by spinal radiograph.

The extensive surveys performed in the extended families of index patients tend to show a decreasing frequency from first- to third-degree relations that also supports a multifactorial inheritance in idiopathic scoliosis. At this time, there is no definite proof of any genetic mechanism.

Structural Elements of the Spine

The anatomic abnormalities have been extensively investigated in experimental and clinical studies. It has long been noted that a large portion of the deformity seen in idiopathic scoliosis is caused by wedging of the vertebrae and the intervertebral disc, with the disc usually more deformed than the vertebral bodies. Intervertebral discs consist of collagen and proteoglycan. Pedrini et al found a decrease in the glycosaminoglycan level in the nucleus pulposus, with a concomitant rise in the collagen level and noted that these changes are possibly secondary to the abnormal stress placed on the disc by the curved spine. Zaleske et al also concluded that these changes are results of scoliosis rather than its cause.

Experimental scoliosis was produced by various surgical procedures; operations involved unilateral resection of the ribs, hemilaminectomy, transection of the posterior costotransverse ligaments, fixation of the spine or spinous processes, and subsequent asymmetrical radiation. It can be assumed that initially functional scoliosis ultimately develops into a structural deformity as the spine grows. The epiphysial plates on the concave side of the curve receive abnormally high pressures that decrease growth, whereas on the convex side of the curve the pressure is less, resulting in accelerated growth. Also the lordosis produced by the tether results in increased pressure on the posterior half of the vertebral body with decreased pressure on the anterior half. These two factors contribute significantly to vertebral asymmetry. Enneking and Harrington, however, concluded that scoliosis has an extraosseous cause and the changes in bone...
are secondary to the deformity. Also biomechanical influences seem not to relate directly to the cause of the condition but may have a secondary effect on the possibilities of curve progression.

■ Paravertebral Musculature

Much research has been conducted seeking the association of skeletal muscle with development of idiopathic scoliosis. The diversities of muscle abnormalities include the muscle spindle; individual muscle fiber morphology; histochemistry; electromyography; sarcolemma abnormalities at the muscle tendon junction; calcium, copper, and zinc concentrations; and platelets.

Langenskiöld and Michelsson thought that a disturbance in growth of paravertebral muscle might be a factor in the pathogenesis of idiopathic scoliosis. Paravertebral muscle abnormalities noted in patients with idiopathic scoliosis include increased numbers of Type I fibers on the convexity and loss of Type II fibers on the concavity of the curve. Increased electromyographic activity has also been noted in the muscles of the convexity of the curvature.

These muscle changes are, however, related to asymmetrical muscle loading due to the deformity of idiopathic scoliosis and may be more effectual than causal in the pathogenesis of idiopathic scoliosis.

■ Metabolic and Chemical Factors

Since Ponseti created spinal deformities by poisoning the growth plate with lathyrisin, extensive research has been performed on the metabolic aspects in the intervertebral disc and connective tissue. Intervertebral disc is rich in collagen and proteoglycan content. Pedrini et al found a decrease in the glycosaminoglycan level in the nucleus pulposus with a concomitant rise in the collagen level. They proposed that these changes are possibly secondary to the abnormal stress placed on the disc by the curved spine. Zaleske et al also concluded that these changes reflect the effect of idiopathic scoliosis rather than its cause.

Nordwall investigated the collagen of patients with idiopathic scoliosis. He was unable to find any difference in elastic stiffness of the tendon or the interspinous ligaments. Similar findings were reported by Waters and Morris. Later investigational work by Bradford et al and Venn et al led to the same conclusion: Collagen metabolism is normal in patients with idiopathic scoliosis. Thus, it does not appear that the cause of idiopathic scoliosis is attributable to abnormal collagen.

■ Endocrine

Patients with idiopathic scoliosis are often taller than age-matched control subjects, but at the end of the growth period, their height is the same as their nonaffected peers. This fact has raised the possibility that an abnormality of growth-producing hormones may be responsible for the deformity. Willner and Nilson reported increased levels of growth hormone in girls with scoliosis compared with normal girls. He also found an increased somatomedin levels. On the other hand, Misol et al found no increase in the level of growth hormone in idiopathic scoliosis. Skogland and Miller proposed that a different growth pattern in patients with idiopathic scoliosis is secondary to a higher blood level of growth-promoting hormones; however, they did not propose this as a primary cause for the development of spine deformity.

■ Central Nervous System

Scoliosis may be present in various neurologic disorders involving different sites of the central nervous system. Scoliosis developed in some of the animals with affected central nervous systems. These animals were found to have damage on the convex side of the spinal cord, particularly in the posterior horn and posterior central gray matter. These findings have promoted the theory that asymmetrical weakness of the paravertebral muscles can be caused by loss of proprioceptive innervation. Pincott et al have shown in primates that resection of the dorsal spinal nerves can create scoliosis with convexity to the side of the resection. Yamada et al were able to induce scoliosis in bipedal rats, by electric stereotaxic destruction of the brain stem and the posterior hypothalamus, which caused a disturbance in the reticular formation of the brain stem.

Yamada et al emphasized that virtually any disruption of the postural reflex system can result in scoliosis and proposed that the disruption of postural reflex is the cause of scoliosis. Investigating right reflex, drift reaction, and optokinetic nystagmus in idiopathic scoliosis, they further demonstrated dysfunction in the postural reflex and the proprioceptive reactions as well as in the ocular reflex system. Also they demonstrated significant positive correlation between the amount of equilibrium disturbance and the degree of the spine curvature. These neurologic disturbances lead to the anatomic and functional involvement of the brain stem, which integrates afferent information from different sources essential for postural equilibrium.

Vestibular dysfunction in idiopathic scoliosis was reported by Sahlstrand et al who showed the abnormal nystagmus measured by electronystagmography using a caloric test or postrotational state. There is a vestibular imbalance in a high proportion of patients with idiopathic scoliosis. Abnormal nystagmus can be seen in the siblings of those with idiopathic scoliosis. A recent study, however, found no difference between patients with idiopathic scoliosis and control subjects with postrotatory nystagmus. Yamada et al was unable to find any significant vestibular disorder. Also, it is known that hearing-impaired children have a high incidence of vestibular dysfunction. Nonetheless, hearing-impaired children have a lower incidence of scoliosis than normal children.
Herman hypothesized that vestibulo-ocular reflex asymmetry results from asymmetric maturation of higher cortical centers. Findings in electroencephalographic studies have demonstrated some variation in subjects with scoliosis compared with control subjects. Asymmetry was not related to the curve, and there was no difference between progressive and nonprogressive scoliosis. Asymmetrical maturation of higher cortical control for equilibrium fitting proposed by Dowling and Goldberg requires further work and confirmation.

There seems to be some basis for the contention that in idiopathic scoliosis there is some degree of neurologic deficit relating to the afferent side of the reflex postural control system. Obviously, more evidence is needed from several fields of research to clarify the role of postural control in the pathogenesis of idiopathic scoliosis.

### Role of Melatonin, Serotonin, and Calmodulin

Since the first experiment by Thillard, experimental scoliosis has been induced in chickens by pinealectomy (Dubousset et al and Machida M et al). Pinealectomy, performed in chickens shortly after they hatch, consistently produces scoliosis that has anatomic features similar to those of human idiopathic scoliosis (Figure 1). In fact, the pinealectomized chicken has become one of the prime experimental models for idiopathic scoliosis.

The prime function of the pineal gland is the production of melatonin, and the effect of pinealectomy in causing scoliosis in chickens has therefore been attributed to melatonin deficiency. It has also been shown that intraperitoneal injection of melatonin prevents the development of scoliosis in pinealectomized chickens that otherwise would have developed scoliosis. These findings led to the postulation that a defect of melatonin synthesis or metabolism contributes to experimental scoliosis.

Recently, Machida et al used rats instead of chickens, because rats are mammals and phylogenetically closer to humans than chickens. Induced experimental scoliosis developed only in pinealectomized bipedal, but not quadrupedal, rats (Figure 2). It was concluded that melatonin deficiency secondary to pinealectomy alone does not produce scoliosis if the quadrupedal condition is maintained. These results indicate that the bipedal condition, as in chickens or humans, may play an important role in development of scoliosis. This in turn suggests a critical influence of postural mechanism for the development of scoliosis.

Melatonin is an indole produced from tryptophan by a series of four enzymatic reactions. Serotonin is an intermediary in this pathway, and melatonin is produced from it through successive acetylation steps. Serotonin has its own set of complex neurologic interactions, and it also may be involved in the production of scoliosis in the chicken model. However, serotonin does not prevent development of scoliosis, but 5-hydroxytryptophan, a precursor of serotonin that can pass through the blood–brain barrier, appears to halt the progression of scoliosis.

![Figure 1. Thoracic spine in pinealectomized chicken. The scoliotic deformity is lordoscoliosis with vertebral rotation. The vertebral body is compressed from above downward on the concave side leading to a wedge-shape deformity. The posterior elements of a scoliotic vertebra show much more complicated deformity.](image-url)
in pinealectomized chickens. However, 5-hydroxytryptophan is not effective in correcting deformed vertebral bodies.

Recently, Kinsfater et al.\textsuperscript{24} measured the levels of calmodulin with specific radioimmunoassays. Cohen et al.\textsuperscript{11} found a 2.5- to 3-fold increase in the activity of calmodulin, measured by a kinetic assay in the platelets of patients with idiopathic scoliosis. Kindsfater et al. demonstrated a marked increase in the levels of calmodulin in the platelets in patients who had progressive idiopathic scoliosis. They suggested that platelet calmodulin level may be a better predictor for progression of the curve than the Risser sign alone. Some of these abnormalities appear to be related to multiple defects in the platelets. These include elevation of intracellular calcium and phosphorous, decreased activity of intracellular contractile proteins, decreased platelet aggregation, increased intracellular udense bodies, a higher number of metallophilic cells, higher negative surface charge of platelets, higher calmodulin activity, abnormality of peptide structure in the myosin chains, and a decreased number of α-adrenergic receptor sites on platelets. These changes in platelet morphology and physiology indicate a cell membrane defect in patients with idiopathic scoliosis that may be genetically determined.

Machida et al.\textsuperscript{31} investigated melatonin levels in 15 normal adolescents (Figure 3), 30 of which had idiopathic scoliosis. Significantly decreased integrated concentrations of melatonin through 24 hours and at night was found in 12 adolescent with progressive curves (Figure 4), whereas those with stable curves had levels similar to those of control subjects. They also measured the melatonin levels in infantile type idiopathic scoliosis. Some cases were progressive, and others were of the nonprogressive or resolving type. In progressive cases the melatonin level was significantly lower compared with that in the nonprogressive cases. There may be transient melatonin deficiency associated with continued deterioration of scoliosis. The level of melatonin appears to be a useful predictor for progression of spine curvature in patients with idiopathic scoliosis. In other types of scoliosis, such as progressive cases of congenital scoliosis, the melatonin level was normal.
Hilibrand et al., in analyzing morning and evening urine samples, were unable to confirm the difference in melatonin level between nine adolescents with idiopathic scoliosis and 18 control subjects. Contrary to expectation, urine levels of melatonin were actually slightly higher in those with scoliosis than in the control subjects. The four patients in their study who subsequently had progressive curves had lower values than the patients with stable curves or the control subjects; however, the difference was not statistically significant. Fagan et al. assayed melatonin from a 24-hour urine collection that was divided into consecutive day and night collections of 12 hours each. In their study, there was also no difference in melatonin levels between 19 adolescents with nonprogressive idiopathic scoliosis and control subjects. Bagnall et al. measured serum melatonin levels in an older age group of seven adolescents with idiopathic scoliosis. They were unable to show statistically significant differences in melatonin levels in serum samples collected at 2 AM and 2 PM. However, the patients, on average, had lower early morning levels. They noted that their patients’ ages were 2–3 years beyond the point of maximum progression of curvature and commented that studies of adolescents during the maximal growth phase should be conducted. They also alluded to the reciprocal diurnal activity of growth hormone and melatonin and suggested that melatonin activity may be mediated by growth hormone.

Machida et al. reported a case of Turner syndrome in which marked progression of scoliosis occurred during treatment with growth hormone. In this patient, melatonin levels throughout the night were much less than in the control subjects, and the levels of melatonin and growth hormone had an inverse correlation (Figure 5). Smythe and Lazarus suggested that such an action is responsible for the opposing effects of melatonin and serotonin on growth hormone secretion and that this indicates one mechanism by which the pineal gland may regulate growth.

The nocturnal serum melatonin concentration changes dramatically with age. There is little or no melatonin secreted before age 3 months. As melatonin production begins, melatonin secretion adopts a circadian rhythm. The highest nocturnal level is achieved between 1 and 3 years of age. Subsequently, the nocturnal peak level declines progressively by 80% until the adult level is reached. The biologic significance of this melatonin alteration is presently unknown. If melatonin levels decrease more than 80% through childhood and adolescence, risk of development of scoliosis may be increased.

The question is, what is the relation between calmodulin and melatonin in human idiopathic scoliosis? Many studies support the existence of specific melatonin membrane receptors, mainly in the neurons of the central nervous system associated with known melatonin effects. However, the multiple metabolic and cellular re-
Idiopathic scoliosis is a common cause of spinal deformity in children and adolescents. Despite extensive study, the cause and pathogenesis remain unknown. Idiopathic scoliosis may be of multifactorial origin rather arising from a single cause. If the cause of idiopathic scoliosis relates to the maturation disturbances of the central nervous system including neurohormonal transmitters or neuromodulators secondary to genetic defect, extensive epidemiologic studies are needed along with further investigation of the pathologic mechanisms of idiopathic scoliosis.

**References**


**Figure 6.** The mechanism of idiopathic scoliosis. The diagram shows the potential sites of action of pineal melatonin. The hypothalamus is one of the primate sites of action of pineal melatonin and of the opposing actions of melatonin and serotonin on growth hormone secretion. This indicates one mechanism by which the pineal gland may regulate growth. Dysfunction of the central nervous system caused by deficiency of melatonin may contribute to the imbalance and asymmetrical development of the spine and the paraspinal muscles.

**Conclusion**

Idiopathic scoliosis is a common cause of spinal deformity in children and adolescents. Despite extensive study, the cause and pathogenesis remain unknown. Idiopathic scoliosis may be of multifactorial origin rather arising from a single cause. If the cause of idiopathic scoliosis relates to the maturation disturbances of the central nervous system including neurohormonal transmitters or neuromodulators secondary to genetic defect, extensive epidemiologic studies are needed along with further investigation of the pathologic mechanisms of idiopathic scoliosis.


Consensus Summary

Adolescent idiopathic scoliosis may not be a single disorder. Nearly all etiological work has been carried out on individuals with thoracic curves. Much less is known about thoracolumbar or lumbar curves, or multiple curve patterns. Although these are common, they may have quite different etiologic consideration.

The deformity is a three-dimensional composite of lordosis in the sagittal plane, lateral curvature in the frontal plane, and torsion in the transverse plane. Various notions exist as to how deformity precisely develops, but an essential lordosis does have considerable biomechanic and biologic support.

Of much interest are other etiologic variables that may be important factors or cofactors in the development and progression of the deformity? For instance, neuromuscular abnormalities are well documented in the established case, but there is very clear evidence that this is a familial condition with genetic factors playing a crucial role.

What is needed to answer these questions is a very large longitudinal investigation focusing on familial issues. This would require large-scale institutional or government funding, perhaps under the auspices of the Scoliosis Research Society and the European Spinal Deformity Society.