CASE REPORT

Subacute Bacterial Endocarditis and Marfan's Syndrome

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THIS case report concerns a patient with atypical Marfan's syndrome and cyanotic congenital heart disease complicated by subacute bacterial endocarditis due to *Streptococcus viridans*.

This white female was born on December 10, 1936, after an uncomplicated labour. Her birth weight was 3 lb. 5 oz. She remained in hospital in an incubator for approximately four months after her birth.

It is not now possible to calculate when this patient was conceived, because her mother has forgotten the dates of her menstrual periods in the antepartum period. It would seem reasonable to assume (from the patient's birth weight) a gestation period between 24 and 36 weeks, and thus, a date of conception between mid-April and early July 1936. Her mother recalls having had a febrile illness with rash about the end of May 1936. At that time, German measles appeared to be epidemic in the community in which she lived.

Neither the parents nor the siblings of this patient have been thought to demonstrate the stigmata of Marfan's syndrome. Her father died suddenly and unexpectedly in 1959. Postmortem examination showed his death to have been caused by a large pulmonary embolus. Her mother, aged 59 years in 1961, is in good health.

This patient has defects, presumably congenital in origin, in four systems: (i) *Neurological*—she is thought to be mentally defective; two large plaques of intracranial calcification have been demonstrated by radiographic examination (Fig. 2). (ii) *Skeletal*—she is poorly developed, measuring 4 ft. 11 in. in height and weighing approximately 80 lb. She has a dolichocephalic skull, high arched palate, marked pigeon-breast deformity, and kyphoscoliosis (Fig. 1); her extremities do not appear disproportionately long. (iii) *Ocular*—her visual acuity is grossly impaired; with her right eye she can count fingers at 3 ft., and with her left eye she can count fingers at 2 ft. Both globes appear smaller than normal; the cornea of the right eye measures approximately 9 mm. in diameter and that of the left eye approximately 7.5 mm. in diameter; the corneas are conical and the anterior chambers are relatively deep; the pupils are small and react poorly to mydriatics; the irides are atrophic. On biomicroscopic examination of the right eye, typical apical thinning of keratoconus with striae in Descemet's membrane may be noted—the anterior chamber is deep and the iris stroma appears thin and atrophic—the anterior vitreous shows some fibrillar degeneration

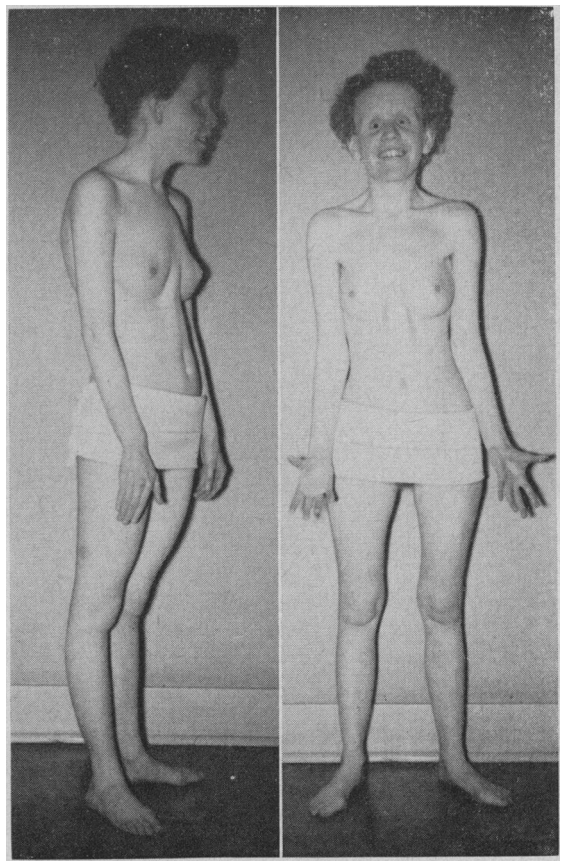

Fig. 1. — Photographs of the patient illustrating her dolichocephaly, pectus carinatum and kyphoscoliosis.

—the lens is cataractous and is dislocated upward and inward so that only the inferior portion of its periphery is apparent. On biomicroscopic examination of the left eye, a slightly smaller globe with the typical apical thinning of keratoconus may be noted—the anterior chamber is deep and clear—the left iris also appears atrophic—on the anterior surface of the left lens, there is a patch of pigment probably resulting from an old posterior synechia formation—the left lens does not appear displaced but is slightly cataractous. Funduscopic examination is very difficult because of the nystagmoid motion of the globes—the media of the right eye is essentially clear except for a few floaters—the nerve head appears pale and atrophic with indistinct margins—no gross areas of chorioretinitis or pigmentary change can be detected. Examination of the left fundus is still more difficult—although a fairly good red reflex may be obtained, the general fundus details cannot be well seen. (iv) *Cardiovascular*—this patient has cyanotic congenital heart disease; she has a systolic thrill and palpable second sound at the "pulmonic" area. On auscultation, she has a grade IV (out of VI) pansystolic murmur at the "pulmonic"

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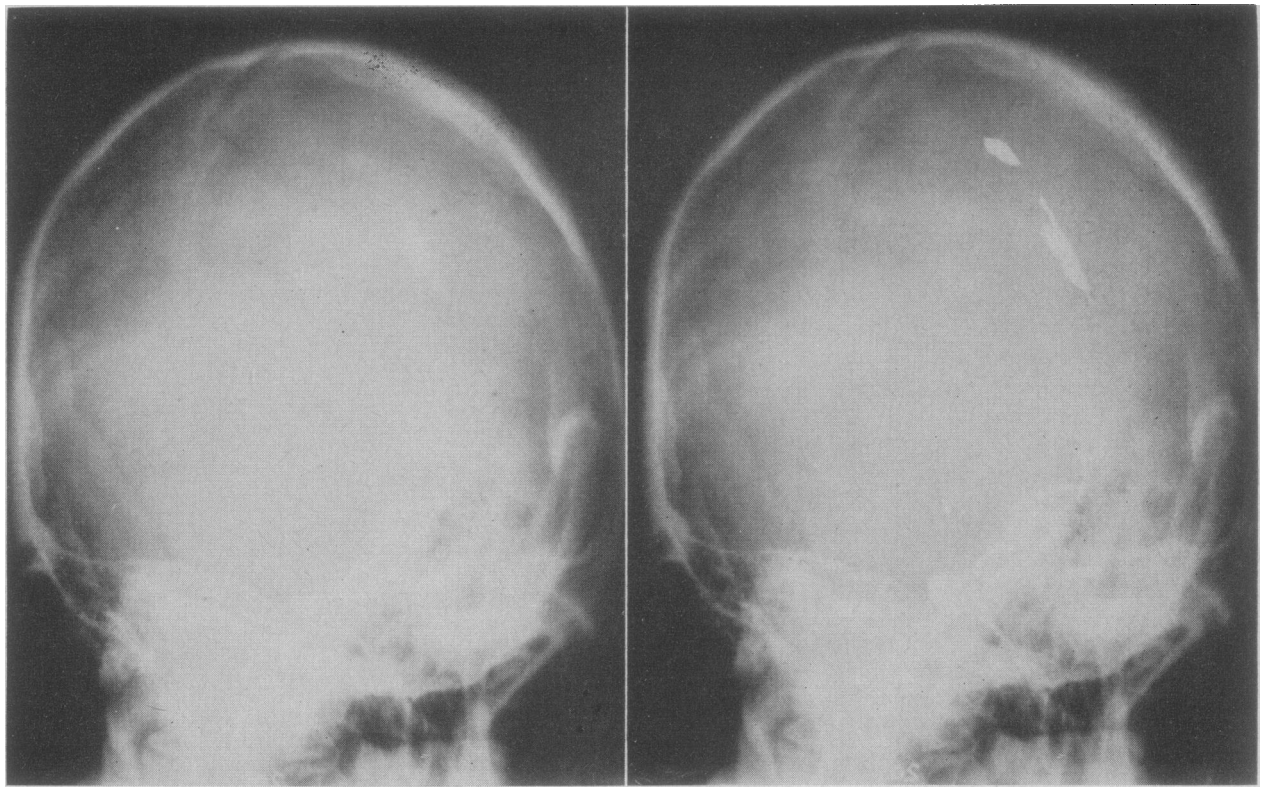

Fig. 2.—Reproductions of a skull radiograph demonstrating two plaques of intracranial calcification. In the reproduction on the right, retouching has been employed to accentuate the abnormalities.

area, a markedly accentuated "pulmonary" second sound, and a grade I diastolic murmur along the left sternal border; her blood pressure averages 110/70 mm. Hg. Her chest roentgenograms have been reproduced in Fig. 3, and her electrocardiograms in Fig 4. The authors have concluded, on the basis of the limited diagnostic procedures carried out to date, that she has either a ventricular septal defect or a patent ductus

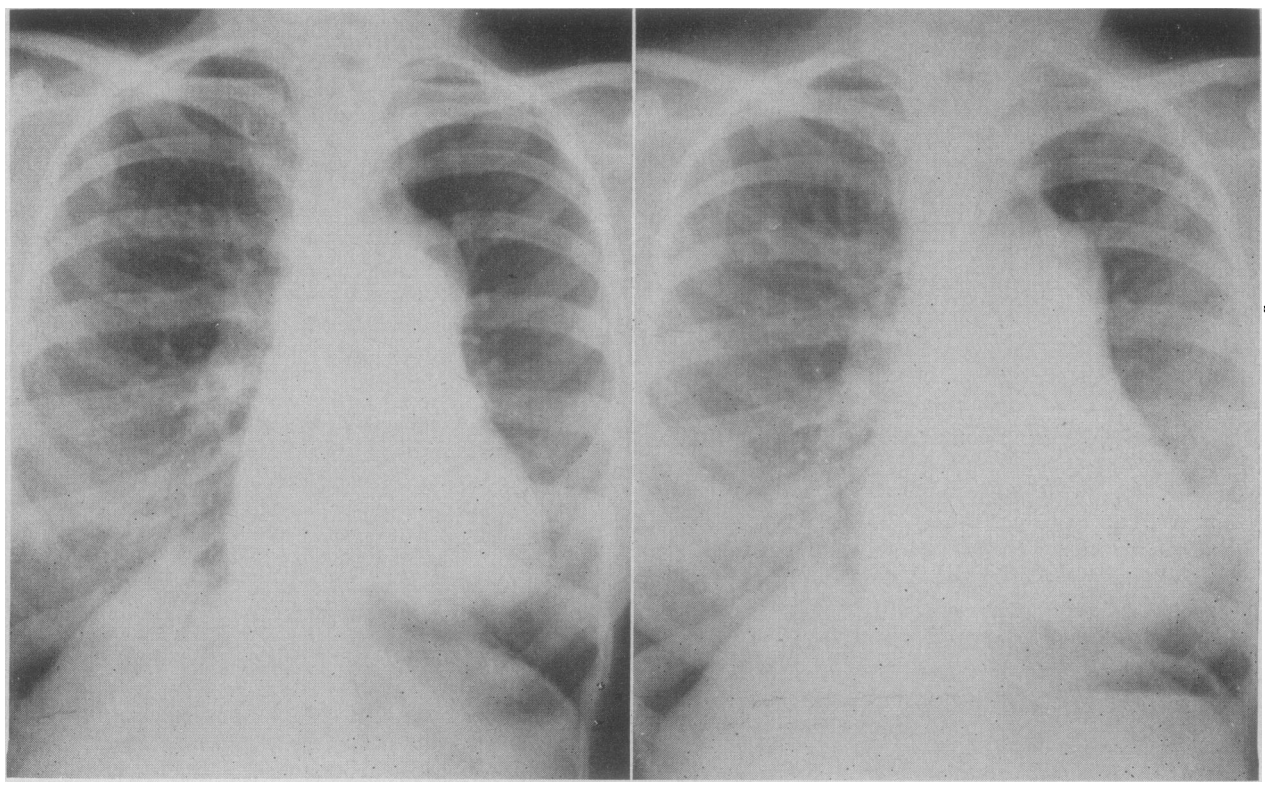

Fig. 3.—Chest roentgenograms before (on the left) and after (on the right) this patient's subacute bacterial endocarditis. Note the spinal scoliosis and the prominent pulmonary arteries.

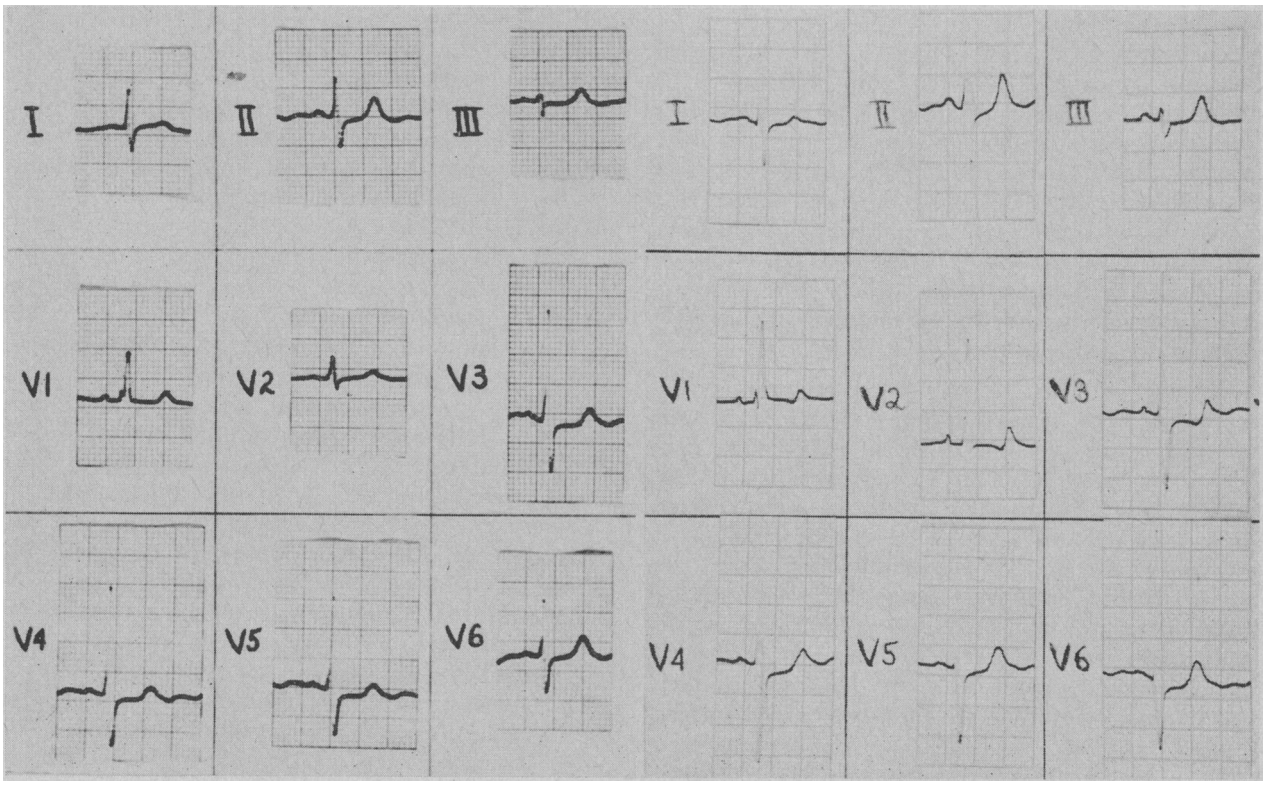

Fig. 4.—Reproductions of this patient's electrocardiograms. The tracing on the left was recorded on April 21, 1960, prior to the patient's endocarditis; the tracing on the right was recorded on June 16, 1961, almost one year after the onset of her endocarditis. The authors interpreted these electrocardiograms as consistent with the diagnosis of right ventricular hypertrophy. In a review[1] of the electrocardiograms from 55 other patients with Marfan's syndrome, the pattern of incomplete right bundle branch block occurred not infrequently, but none of the electrocardiograms were considered indicative of right ventricular hypertrophy.

arteriosus with pulmonary hypertension (Eisenmenger's complex).

She was in her usual state of health until July 3, 1960, when, without previous symptoms, she developed fever and chills. There was no history of preceding dental manipulation. Physical examination did not reveal any explanation for the fever which recurred intermittently; in particular, there were no petechiae or splinter hemorrhages, and there was no enlargement of the spleen. She was admitted to hospital for investigation on July 16. The first five blood cultures proved sterile; two further blood cultures each demonstrated *Streptococcus viridans* sensitive to penicillin and streptomycin. From August 5 to August 19, she received 140 million units of crystalline penicillin by continuous intravenous drip, 3.5 g. of streptomycin intramuscularly, and 3.5 g. of dihydrostreptomycin intramuscularly. There were no complications. Follow-up examination to June 1961 has shown no evidence of recurrence or recrudescence of the endocarditis (or endarteritis).

Her serologic test for syphilis was negative. Complement-fixation tests for toxoplasmosis on sera from the patient and her mother were negative. A "moderate" amount of hydroxyproline was demonstrated by Marko[2] in this patient's urine by the technique of paper chromatography; by the technique employed, Marko is usually unable to demonstrate hydroxyproline in the urine of normal subjects.

DISCUSSION

This patient is considered of interest because of: (1) the possibility that her Marfan's syndrome may have resulted from maternal rubella; (2) the association of cyanotic congenital heart disease with Marfan's syndrome; (3) the complication of her congenital heart disease by subacute bacterial endocarditis; (4) the association of mental deficiency and intracranial calcification with Marfan's syndrome; and (5) the demonstration of an increased excretion of the amino acid, hydroxyproline, in her urine.

While it cannot now be proved that this patient's multiple congenital abnormalities resulted from intrauterine rubella, the chronologic and circumstantial data are consistent with this possibility. In this connection, it is pertinent that Ganther[3] has described a patient with features of Marfan's syndrome after a pregnancy complicated by severe "grippe", and Stettner[4] has suggested that x-radiation during pregnancy may be an etiologic factor in Marfan's syndrome. The possibility that environmental agents may serve as etiologic factors in Marfan's syndrome deserves consideration in any patient with Marfan's syndrome lacking a family history of this disorder.

Since the report by Baer, Taussig and Oppenheimer[5] concerning aortic disease in Marfan's syndrome, congenital heart disease has been recognized as a rare "complication" of Marfan's syndrome. Early reports indicating that defects in the atrial septa frequently occurred in association with

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Marfan's syndrome have not been confirmed in recent studies of large series[6] of patients with Marfan's syndrome. Patients with Marfan's syndrome and an associated ventricular septal defect have been described by McKusick[6] (his Fig. 30) and by Keith, Rowe and Vlad.[7] Anderson and Pratt-Thomas[8] have reported the occurrence of a patent ductus arteriosus in a patient with Marfan's syndrome. While a definitive diagnosis has not been established in the case reported here, the diagnosis of Eisenmenger's complex is strongly supported by the clinical data.

Previous reports of subacute bacterial endocarditis in Marfan's syndrome have suggested that the mitral valve leaflets in these patients are particularly prone to infection.* For example, Olcott's[11] patient had a fenestrated posterior mitral valve cusp with nodular calcified masses adherent superiorly, and friable elevated masses along the line of closure. Similarly, the patient described by Vivas-Salas and Sanson[12] had fenestrated mitral valve cusps with adherent nodules which proved on histologic examination to be inflammatory vegetations containing Gram-positive cocci. McKusick's[6] patient (his Fig. 28) was found to have positive blood cultures for *Streptococcus viridans* during life, and vegetations typical of active bacterial endocarditis on the mitral valve at necropsy examination; and the patient described by Miller and Pearson[13] had "vegetations of an old healed bacterial endocarditis" on the anterior mitral cusp together with a ruptured chorda tendinea. To the authors' knowledge, no successfully treated case of bacterial endocarditis in Marfan's syndrome has been fully documented in the medical literature. Sinclair and his associates[14] mentioned briefly that one of their patients with Marfan's syndrome (their Case 15) had a past history of subacute bacterial endocarditis which had been treated successfully. Pappas, Mason, and Denton[15] also reported that one of their patients with Marfan's syndrome gave a history of successfully treated subacute bacterial endocarditis (their Case 2). Schorr and his associates[16] reported a patient with arachnodactyly, aneurysmal dilatation of the thoracic aorta, and a recurrent fever which appeared to respond (at least temporarily) to antibiotics; despite the fact that blood cultures were repeatedly negative, they assumed that their patient had subacute bacterial endaortitis.

The uneventful and apparently successful treatment of the infection in the patient described in the present case report may be related to the short history of the infection (one month) and to the intensity of the treatment program. (Despite the short duration of this infection, the authors have chosen to refer to the infection as subacute endocarditis rather than as acute endocarditis because of the clinical course of this illness and because of the characteristics of the infecting organism.)

Although mental retardation has, at times,[17, 18] been emphasized as a feature of Marfan's syndrome, intracranial calcification has not, to the authors' knowledge, been reported previously in this disorder. It is interesting that, in the patient reported here, the syndrome of a maternal febrile eruption followed by congenital blindness and intracranial calcification in the child should have been proved not to result from toxoplasmosis.

Sjoerdsma and his associates[19, 20] were the first to report an increased urinary excretion of the amino acid, hydroxyproline, in patients with Marfan's syndrome. Since hydroxyproline constitutes 14% of collagen, Sjoerdsma's observation has been considered to support the concept that Marfan's syndrome is a result of a basic defect in connective tissues. It is of confirmatory interest that an increased urinary excretion of hydroxyproline should have been demonstrated in the patient described in this report.

*Nodular excrescences on the valve leaflets in patients with Marfan's syndrome have been reported frequently since their initial description by Salle.[9] In some of these patients, such lesions have undoubtedly resulted from rheumatic fever; in others, active or healed bacterial endocarditis may have caused the valvular deformities. It is probable, however, that in some patients with Marfan's syndrome, such valvular abnormalities are an intrinsic part of this diffuse disorder of connective tissues. For example, Tung and Liebow[10] have described in detail, and illustrated beautifully, mitral valve abnormalities in a 53-month-old female patient with Marfan's syndrome (their Case 1); in their patient, on careful histologic study of the mitral leaflets, they noted numerous lacunae in the collagenous substance filled with a homogeneous basophilic material strikingly similar to the lesions of aortic cystic medionecrosis.

SUMMARY

A patient has been described in whom Marfan's syndrome was associated with bilateral microphthalmos, keratoconus, unilateral ocular lens dislocation, mental retardation, intracranial calcification, cyanotic congenital heart disease, subacute bacterial endocarditis, and an increased urinary excretion of hydroxyproline.

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