Oral sequelae of chronic neutrophil defects: case report of a child with glycogen storage disease type 1b

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A complex group of enzyme reactions is responsible for the breakdown of the large glycogen molecule into glucose, which is used by the body to maintain blood sugar and provide energy. The glycogen storage diseases are a group of inherited disorders involving deficiencies of one or more of the enzymes necessary to store and metabolize glycogen. Glycogen storage disease (GSD) exists in a variety of forms, each involving different enzyme systems of the glycogen metabolic pathway.

GSD type 1b is caused by a lack of glucose-6-phosphatase (G6P) translocase. This prevents the transport of G6P across the endoplasmic reticulum.[1] As a result, glycogen cannot be metabolized into glucose and is deposited in the liver. The mode of genetic transmission of GSD type 1b is autosomal recessive. It is extremely rare, with an estimated incidence of less than 1 in 1,000,000.[1]

This disorder affects patients in a number of ways. Clinical features include hypoglycemia, hepatomegaly, growth retardation, delayed puberty, bleeding diathesis secondary to platelet dysfunction, and enlarged kidneys. Hypoglycemia in children is defined as a blood glucose level < 40 mg/dl.[2] In GSD type 1b, the level of blood glucose may characteristically be < 15 mg/dl, which is profoundly low.[1] This hypoglycemia results from the inability of the body to metabolize glycogen into glucose. Hepatomegaly is secondary to deposition of excessive glycogen in the liver. Glycogen also is deposited within the proximal tubular cells of the kidneys, which causes enlargement of these organs.[3] The etiology of the platelet dysfunction is unclear. Two theories include metabolic disturbances in the liver and reduced activity of glucose-6-phosphatase in the platelets themselves.[2]

Neutropenia, neutrophil dysfunction, and the resulting inability to combat infection are additional important features of GSD type 1b. These are of special interest to the dentist, as they are the underlying causes of the early, severe periodontal breakdown and frequent oral ulcerations seen in patients with this disease.[1-4]

Causes of the neutropenia and neutrophil dysfunc-

tion presently are inconclusive. Various etiologies of neutropenia include abnormal maturation of neutrophil precursors and reduced release of neutrophils from the bone marrow. It is unclear whether either of these is responsible for the neutropenia seen in GSD type 1b. The importance of transport of glucose into neutrophils for chemotaxis has been demonstrated, and this might well be the etiology for the neutrophil dysfunction.[2]

The purpose of this paper is to present, via a report of a patient with GSD type 1b, the short- and long-term effects of a chronic neutrophil defect on the periodontium and oral mucosa.

Case report

Medical history

The patient was an African-American male diagnosed with GSD type 1b at 3 months of age. Presenting symptoms upon admission to the hospital were diarrhea, dehydration, failure to thrive and a massively enlarged liver. A liver biopsy, demonstrating fatty infiltrate and a glycogen content greater than 10%. Subsequent enzyme tests established the diagnosis.

Numerous systemic problems, some related and some unrelated to GSD, complicated the patient's medical treatment. Developmentally, he functioned at a level of mild mental retardation, with IQ scores ranging from 50–60 at ages 6 and 9. This may have been secondary to chronic severe hypoglycemia during crucial periods of brain development.

In addition to seizures precipitated by hypoglycemia, the patient had a history of central seizures. Phenobarbital was used to control the central seizures. To prevent the hypoglycemia, the patient required frequent feedings of glucose or starch. He was capable of eating solid foods, but at age 6, in an attempt to better regulate his blood sugar levels, he began to receive most of his feedings via a nasogastric tube connected to a pump that delivered a nutritional solution 24 hr per day.

Throughout his life, the patient was plagued with neutropenia. Neutrophil levels ranged from less than 100 to 1000 cells/mm³. At age 14, after developing intermittent abdominal pain, occasional diarrhea, loss

of appetite, and weight loss, the patient was diagnosed with Crohn's disease, a chronic ulceration of the gastrointestinal system. The diagnosis was made by barium enema and CT scan. Daily prednisone was used in an attempt to control this condition.

In late adolescence, the patient developed a cardiomyopathy. Although the etiology was never definitively determined, his physicians presumed it was a complication of the GSD type 1b. This condition unfortunately continued to progress and led to his death at age 21 from a presumptive congestive heart failure and pulmonary edema. The family refused an autopsy.

Dental history

In 1975, at 4 years old, the patient was referred by his primary care physician to our clinic for routine dental care. The diagnosis of GSD type 1b was well established prior to this time and was made known to the dental clinic by the patient's physician.

Clinical examination at that time showed a complete primary dentition, except for a missing maxillary left primary central incisor. The remaining maxillary primary central incisor displayed great mobility (Fig 1). There was no known history of trauma to the teeth. The finding of bone loss, however, was compatible with the patient's chronic neutropenic condition. The tooth was extracted at that visit because of pain. Radiographs taken several months later show the extensive bone loss not only in the maxillary incisor region, but also the mandibular incisor region (Fig 2).

Poor compliance with scheduled appointments greatly hindered routine dental treatment. The family tended to bring the child in only when there was a perceived emergency.

After a 1 ½-year absence from the clinic, the patient presented at age 6 with an aphthous-like ulcer on the lower labial mucosa (Fig 3). A bland diet was recommended, along with palliative topical application of Kaopectate® (The Upjohn Co, Kalamazoo, MI) and Benadryl® (Parke-Davis, Morris Plains, NJ). An oral exam also revealed generalized marginal inflammation of the gingiva. The mandibular anterior primary dentition showed minimal root resorption, but displayed great mobility secondary to alveolar bone loss.

The patient was seen again 6 months later, at which time the chief complaint was discomfort in the maxillary left primary molar region. Oral examination showed extreme mobility of the maxillary left first primary molar with almost complete resorption of the adjacent buccal alveolar bone (Fig 4). Due to the marked mobility of this tooth, along with the maxillary primary lateral incisors and the four mandibular primary incisors, the decision was made to schedule extractions. Antibiotic prophylaxis was deemed necessary due to the patient's inability to withstand infection. Treatment was canceled because he was hospitalized with a staphylococcal infection. The patient did not present to the dental clinic again for 2 ½ years.
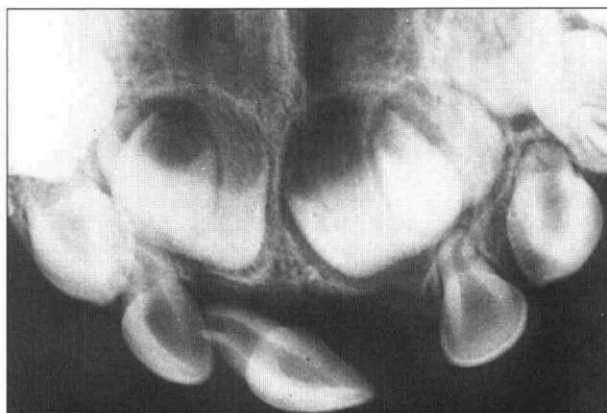

Fig 1. Periapical radiograph of the maxillary primary incisors at age 4.
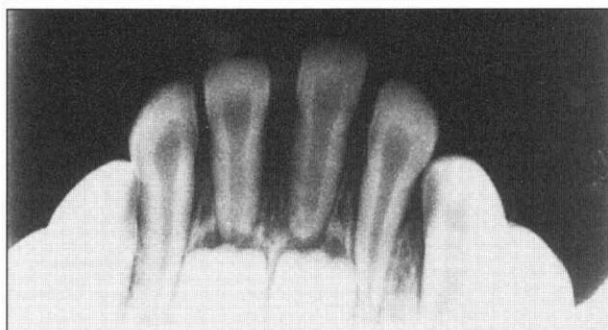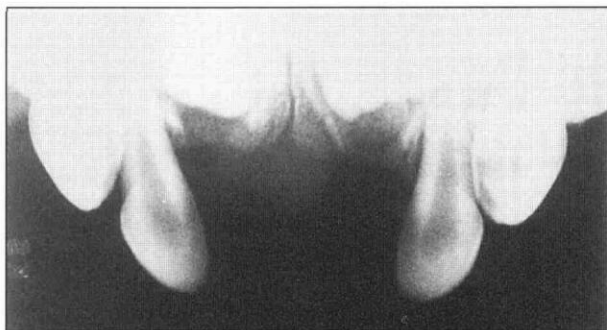

Fig 2. Periapical radiographs of the maxillary and mandibular primary incisors showing extensive alveolar resorption.
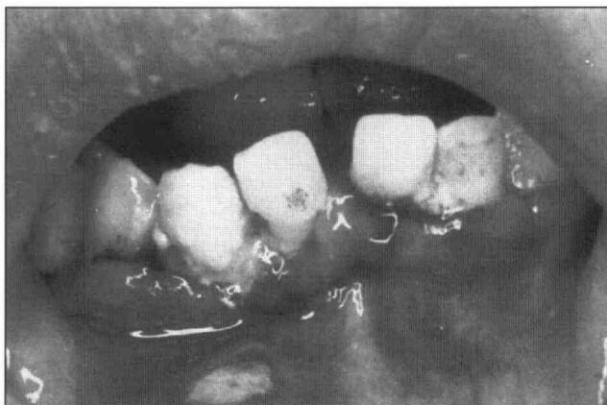

Fig 3. Clinical view of the mandibular incisor region at age 5 ½. Notice ulceration on labial mucosa and gingival recession.
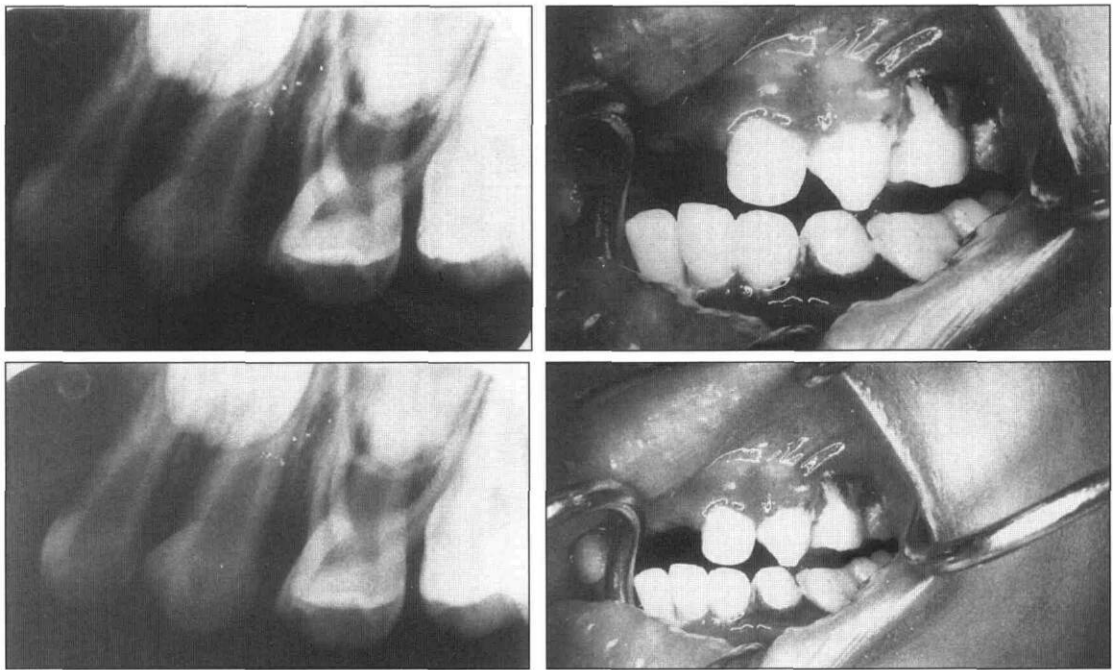
Fig 4. Radiographic and clinical views of maxillary left first primary molar at age 6. Notice the extensive alveolar and gingival recession.
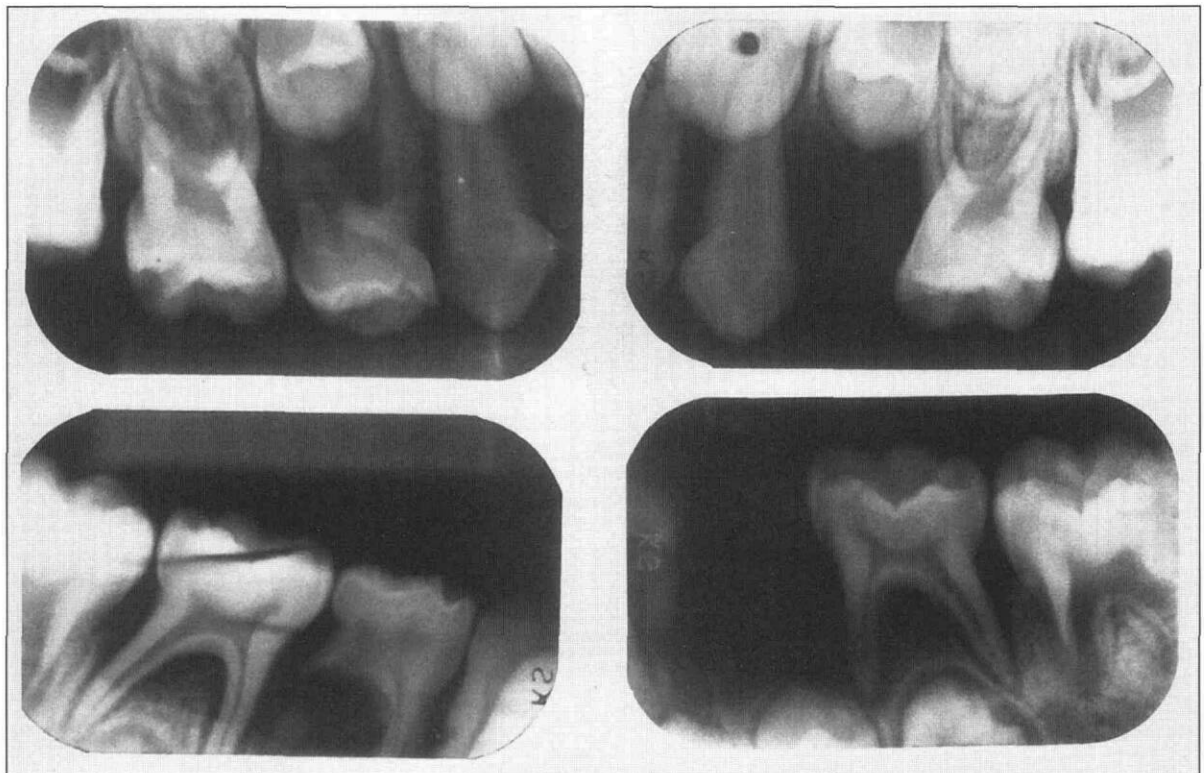

Fig 5. Periapical radiographs of the maxillary and mandibular primary molar regions at age 8 ½. Notice the alveolar resorption.

At age 8 ½, clinical and radiographic examinations revealed generalized alveolar bone loss with class III mobility of all remaining primary teeth (Fig 5). The mandibular permanent central incisors and all of the first permanent molars had erupted at this time and already displayed some mobility. At this point, he was scheduled for extraction of the remaining primary dentition. Several factors influenced the decision to perform the procedure in the hospital under general anesthesia. First, the patient's level of cooperation for dental
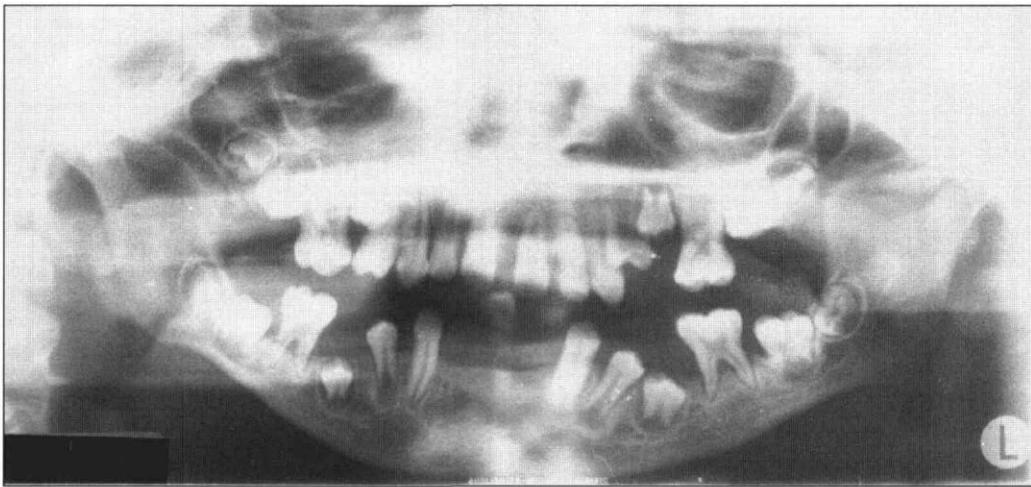
Fig 6. Panoramic radiograph at age 12 demonstrating numerous lost teeth and alveolar bone loss.

treatment had gradually deteriorated. Also, due to the bleeding diathesis secondary to platelet dysfunction, provision for possible blood transfusion was necessary. Intravenous antibiotic coverage was provided due to his inability to combat bacterial infection. The patient was kept in the hospital several days after surgery to continue the antibiotic therapy and for observation.

The patient continued to be seen over the next 6 years on a fairly regular basis. A number of the visits were of an emergency nature due to the frequent and very painful recurrence of oral ulcerations. The patient's progressive periodontal disease was followed through routine scheduled appointments. An attempt was made to manage the problem with aggressive scaling and additional oral hygiene instruction. Despite these measures, chronic gingival inflammation and rapid alveolar bone loss continued. During this time, numerous teeth were lost due to lack of bony support (Fig 6).

When the patient was 14, the decision was made to extract his remaining dentition and fabricate full dentures. The extractions were done in the hospital under general anesthesia, again with antibiotic coverage and provisions made for possible blood transfusion. The patient, however, never wore the dentures on a consistent basis due to continued frequent oral ulcerations.

He continued to be followed in this clinic, primarily for emergency visits, until shortly before his death.

Discussion

This case history demonstrates the devastating and even life-threatening implications of GSD type 1b.

The features of most relevance to the dental practitioner, as mentioned in the introduction, are the severe, rapidly progressing periodontal infections in a pediatric patient and the recurrent oral ulcerations.

Neutropenia is considered to be an absolute neutrophil count below 1800 cells/mm^3. Some African-Americans, however, may have a count as low as 1200 cells/mm^3 without being symptomatic.[10, 11] The patient in this paper was chronically in the extremely severe to

TABLE. CONDITIONS EXHIBITING NEUTROPHIL DISORDERS WITH ORAL MANIFESTATIONS

Condition	Neutrophil Disorder	Oral Manifestation
Chediak-Higashi disease	⇓ chemotaxis ⇓ phagocytosis	Severe periodontal disease, ulcerations
Papillon-Lefèvre syndrome	⇓ chemotaxis	Severe periodontal disease
Infantile genetic agranulocytosis	Neutropenia	Gingival inflammation, ulcerations
Cyclic neutropenia	Neutropenia	Gingival inflammation, ulcerations
Benign chronic neutropenia	Neutropenia	Gingival inflammation, ulcerations
Down syndrome	⇓ chemotaxis	Periodontal disease
Diabetes mellitus	⇓ chemotaxis	Periodontal disease
Job's syndrome (hyper-immunoglobulin E)	⇓ chemotaxis	Gingival inflammation, ulcerations
Chronic granulomatous disease	⇓ cell killing	Gingival inflammation, ulcerations
Juvenile periodontitis	⇓ chemotaxis	Periodontal disease
Crohn's disease	Neutropenia ⇓ chemotaxis	Ulcerations
GSD type 1b	Neutropenia ⇓ chemotaxis	Severe periodontal disease, ulcerations

moderate neutropenic range, with levels varying from less than 100 to 1000 cells/mm^3. Although neutrophil function tests never were done on this patient, neutrophil dysfunction — specifically defective chemotaxis — is a reported feature of GSD type 1b, and it was presumed that the patient also had this problem.[1,5]

Many authors have cited neutropenia and/or neutrophil dysfunction as important etiologic factors in periodontal disease and oral ulcerations.[2,4,7-11] Several conditions in which this relationship has been well established are listed in the Table.

In a patient presenting with progressive periodontal disease and/or recurrent oral ulcerations who does not have a previously established medical diagnosis, these diseases could serve as a basis for a differential diagnosis.

Given the relentless nature of this patient's periodontal disease together with the established diagnosis of GSD type 1b, it is reasonable to assume that the quantitative and qualitative neutrophil disorders were responsible for the problem rather than other possibilities such as osteoporosis and malabsorption syndrome. The same applies to the mucosal ulcerations. Non-neutrophil related etiologies for oral ulcerations could include trauma due to convulsive disorders, uremia, and anemia. However, this patient's seizures were very well controlled and he was never shown to be uremic or anemic. His medical history points to neutrophil problems as being the most likely etiology for his mucosal ulcerations.

It also has been speculated that the need for frequent high-carbohydrate meals in patients with GSD type 1b might exacerbate the poor periodontal condition.[9] Our patient, however, received this nourishment through a nasogastric tube and did not consume meals by mouth regularly. Despite this, his periodontal decline continued rapidly and unabated, which we feel eliminates carbohydrate intake as an important etiologic factor.

The diagnosis at age 14 of Crohn's disease suggests that the oral ulcerations were not an isolated entity, but were actually a manifestation of Crohn's disease. This is not inconsistent with the patient's neutropenic condition, however, as inflammation of the gastrointestinal tract (which can include Crohn's disease) has been noted to be a complication of neutropenia and neutrophil dysfunction.[12,13]

If and when a diagnosis of a neutrophil disorder is made, then the question is: to what extent can aggressive dental treatment, both clinically and at home, alleviate the periodontal and oral mucosal problems commonly seen in these patients? The prognosis is correlated closely with the extent of neutrophil impairment. A person with periodic and/or cyclic neutropenia could gain much better control over his oral health than a person whose cells are chronically in the neutropenic range. The same holds true for neutrophil function. The effectiveness of antibiotics to prevent periodontal disease and mucosal ulcerations in neutropenic patients is also of a highly speculative nature.[4,7]

This patient's opportunity for optimum dental treatment was compromised in a number of ways. First, there was difficulty in keeping regularly scheduled appointments, which was due in large part to the patient's illness. The patient was also reluctant to devote much time or care to oral hygiene at home, despite repeated instruction from the dental staff. We do not feel that his developmental level was responsible for the difficulty with home care, as he was easily capable of performing much more difficult tasks, such as inserting his own nasogastric tube on a daily basis.

The patient was frequently on antibiotics for various staphylococcal infections, with no noticeable effect on the oral ulcerations or periodontal disease.

Although chlorhexidine gluconate is not approved or proven as a treatment for periodontitis, a practitioner treating a patient with GSD Type 1b today might consider it as an adjunct to good home care to help minimize gingival inflammation and bleeding. This was not an option for us at the time before this patient lost his teeth, as chlorhexidene had not yet been approved for oral use in the United States.

Dentures were fabricated very carefully for this patient, with the realization that the prostheses might intensify his oral ulcerations. As a young adolescent, however, the patient and his family had great concerns about his appearance and self-esteem. After numerous requests from the patient, dentures were fabricated with the caveat that he should present to the dental clinic should any problems develop. As it was, the dentures were rarely worn due to continued mucosal ulceration.

Conclusions

Severe chronic gingival inflammation and periodontal disease are rare in children who are otherwise healthy. In prepubertal patients, the disease entity most frequently associated with gingival tissue is a marginal gingivitis without accompanying alveolar bone loss.[13]

This patient presented to the dental clinic with an established diagnosis. There may be instances, however, when oral lesions are an important diagnostic sign in an otherwise undiagnosed systemic disease. This is especially true in entities such as cyclic neutropenia and acute agranulocytosis.

The point is that severe oral mucosal inflammation, alveolar bone loss, and chronic oral ulcerations in children should not be assumed to be due solely to local factors. Once all local etiologies are taken into account, any one of these warrants referral to a physician for further investigation of possible systemic factors.

Although the effectiveness of aggressive oral treatment measures in patients with neutrophil disorders may depend on the patient's level of neutrophil impairment, every patient deserves the implementation of a strictly monitored oral hygiene program in an effort to preserve the dentition for as long as possible, as well as to minimize discomfort caused by mucosal ulcerations and periodontal disease.

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African-American children with cancer fare as well as Caucasian children with equal access to treatment

PREVIOUS SURVIVAL RATE GAP HAS DISAPPEARED

With equal access to effective contemporary treatment, African-American children with cancer fare as well as Caucasian children when treated at a pediatric oncology research center, according to an article in a recent *Journal of the American Medical Association.*

Ching-Hon Pui, MD, from the Departments of Hematology-Oncology, Biostatistics, and Pathology and Laboratory Medicine, St. Jude Children's Research Hospital, Memphis, Tenn., and colleagues conducted a study to determine whether there is a racial difference in prognosis among childhood cancers.

The researchers found: "We have shown that contemporary anticancer treatment can equally benefit black children who, as a group, are economically disadvantaged compared with white children in our referral area.

"It is conceivable that socioeconomic factors could affect the outcome of children with cancer, as has been demonstrated in studies of adult mortality for major disease categories. However, all of the patients we studied were treated without regard to insurance status or ability to pay, negating unequal access to care as a potential factor in treatment outcome."

The study included 798 black and 4,507 white children with newly diagnosed malignancies treated from January 1962 through June 1992 at St. Jude Children's Research Hospital, in Memphis, Tenn. These patients were accepted for treatment regardless of their financial status.

The researchers found that in the early stage of the study period, black children had a poorer survival rate than white children In the later stages of the study period, there were no significant differences in treatment outcomes.

The authors believe that a number of conditions need to exist if there is to be equal treatment outcomes among children.

They write: "The first condition is effective, intensive, risk-directed therapy, which increasingly overrides the importance of other prognostic factors in many childhood cancers — particularly acute lymphoblastic leukemia. The second is treatment in facilities equipped to provide the sophisticated supportive care that is essential to the safe and timely delivery of these therapies and, hence, to improved cure rates.

"Finally, there is the issue of access to care. While not a factor in our study population, unequal access to care may well explain, at least in part, the growing gap in mortality rates between relatively advantaged and disadvantaged adults."