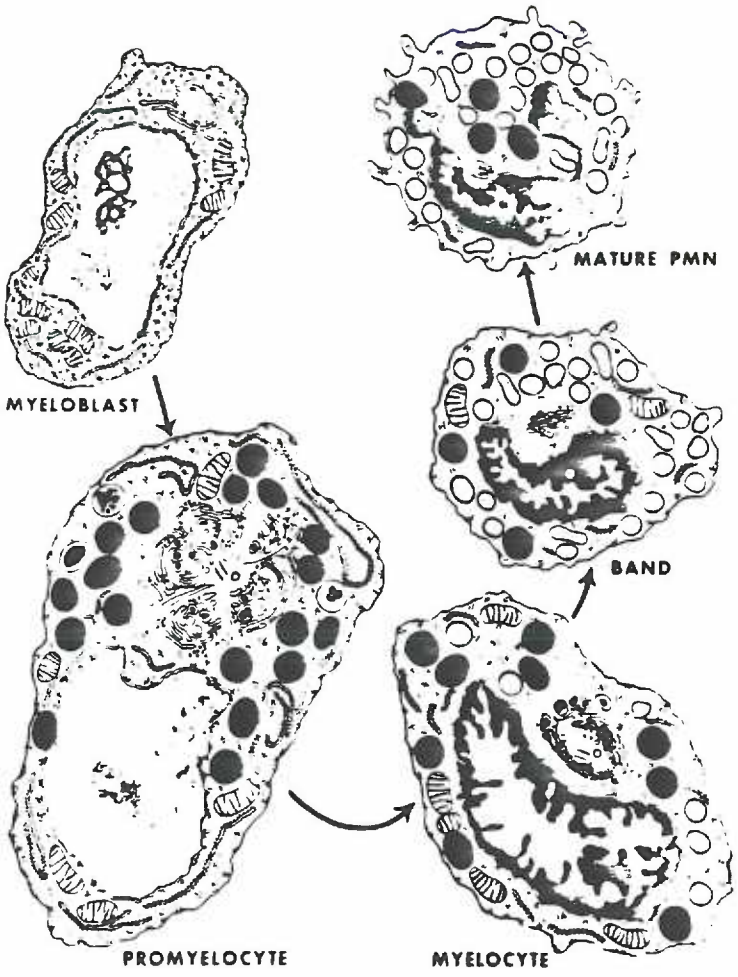


Reprinted from The White Cell by Martin J. Cline

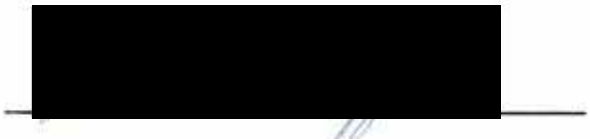
THE DENTAL MANAGEMENT OF NEUTROPENIA IN CHILDREN

James L. Barnett, D.M.D.

Submitted in partial fulfillment of
requirements for a
Certificate of Pedodontics
at the
School of Dentistry
University of Oregon Health Sciences Center

1981

APPROVAL



A. E. Retzlaff, D. D. S.

Chairman

Department of Pedodontics

ABSTRACT

Neutropenia is the reduction in the number of circulating neutrophils. Risk of infection is related to both cell count and the nature of the primary disease. The classification of the neutropenias is arbitrary and ambiguous. Evaluation of the pre-pubertal neutropenic child should determine its severity and whether it is chronic or cyclic. Neutrophil physiology and the host response in periodontal disease are reviewed. Medical treatment is aimed at minimizing the consequences of repeated infections. The oral manifestations of the neutropenias are discussed. Dental therapies reported in the literature are discussed. Six case reports are presented.

ACKNOWLEDGEMENTS

I would like to express my gratitude to the following individuals for their guidance and direction:

Dr. A. E. Retzlaff

Dr. Mike Stapleton

Dr. Derry Ridgeway

Dr. Donald Porter

Dr. Donald Adams

Dr. Chris Martin

Dr. Joseph Low

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

While conducting dental screening examinations on pediatric patients at the University of Oregon Health Sciences Center, I examined a 5-year-old girl. The severity of her periodontal disease caused me some concern and piqued my interest. Inspection of her medical record revealed the underlying cause to be systemic, namely congenital neutropenia.

A search of the literature followed and although there were several articles on childhood neutropenias, few concerned themselves with the dental management of this disorder.

The classification of the childhood neutropenias is somewhat arbitrary and ambiguous. New techniques used to study the host's immune response continues to improve the classification of this disorder. This should enhance the choice of therapy, leading to improved prognosis.

The purpose of this paper is to review the literature as it pertains to the definition, classification, oral manifestations, and the medical and dental management of the childhood neutropenias. Neutrophil physiology and the immune response, related to periodontal disorders, will also be reviewed.

Six case reports will be presented. It is hoped that the bibliography will be useful as a reference list on the subject.

REVIEW OF THE LITERATURE

Definition

Neutropenia is a reduction in the number of circulating neutrophils. Granulocytopenia is a term that is often used but more properly would include neutrophils, eosinophils and basophils. Agranulocytosis indicates a severe degree of neutropenia.[1]

The lower limit for normal neutrophil counts reported in the literature ranges from 1500/mm^3 to 2000/mm^3 for adults and older children.[2,3,4,5] An infant's count (2 weeks - 1 year) may be as low as 1000/mm^3 and still be normal. Blacks may have numbers as low as 1400/mm^3 before being considered abnormal.[2]

Neutropenia may be considered from a kinetic viewpoint: (1) failure or ineffective leucocyte production, in the bone marrow; (2) excess neutrophil destruction in the peripheral blood and tissues; (3) combinations of these abnormalities.[1]

The risk of infection is related to both the cell count and the nature of the primary disease. For instance, many patients with chronic idiopathic neutropenia have counts of less than 500/mm^3 for years without infection, whereas few patients with leukemia or aplastic anemia would be infection free at that level.[3]

Normal leukocyte counts in children are found in Table I.

TABLE I. Normal Leucocyte Counts[4]

Age	Total Leukocytes		Neutrophils'			Lymphocytes			Monocytes		Eosinophils	
	Mean	*(Range)*	*Mean*	*(Range)*	*%*	*Mean*	*(Range)*	*%*	*Mean*	*%*	*Mean*	*%*
Birth	18.1	(9.0–30.0)	11.0	(6.0–26.0)	61	5.5	(2.0–11.0)	31	1.1	6	0.4	2
12 hr	22.8	(13.0 38.0)	15.5	(6.0–28.0)	68	5.5	(2.0–11.0)	24	1.2	5	0.5	2
24 hr	18.9	(9.4–34.0)	11.5	(5.0–21.0)	61	5.8	(2.0–11.5)	31	1.1	6	0.5	2
1 wk	12.2	(5.0–21.0)	5.5	(1.5–10.0)	45	5.0	(2.0–17.0)	41	1.1	9	0.5	4
2 wk	11.4	(5.0–20.0)	4.5	(1.0– 9.5)	40	5.5	(2.0–17.0)	48	1.0	9	0.4	3
1 mo	10.8	(5.0–19.5)	3.8	(1.0– 9.0)	35	6.0	(2.5–16.5)	56	0.7	7	0.3	3
6 mo	11.9	(6.0–17.5)	3.8	(1.0– 8.5)	32	7.3	(4.0–13.5)	61	0.6	5	0.3	3
1 yr	11.4	(6.0–17.5)	3.5	(1.5– 8.5)	31	7.0	(4.0–10.5)	61	0.6	5	0.3	3
2 yr	10.6	(6.0–17.0)	3.5	(1.5– 8.5)	33	6.3	(3.0– 9.5)	59	0.5	5	0.3	3
4 yr	9.1	(5.5–15.5)	3.8	(1.5– 8.5)	42	4.5	(2.0– 8.0)	50	0.5	5	0.3	3
6 yr	8.5	(5.0–14.5)	4.3	(1.5– 8.0)	51	3.5	(1.5– 7.0)	42	0.4	5	0.2	3
8 yr	8.3	(4.5–13.5)	4.4	(1.5– 8.0)	53	3.3	(1.5– 6.8)	39	0.4	4	0.2	2
10 yr	8.1	(4.5–13.5)	4.4	(1.8– 8.0)	54	3.1	(1.5– 6.5)	38	0.4	4	0.2	2
16 yr	7.8	(4.5–13.0)	4.4	(1.8– 8.0)	57	2.8	(1.2– 5.2)	35	0.4	5	0.2	3
21 yr	7.4	(4.5–11.0)	4.4	(1.8– 7.7)	59	2.5	(1.0– 4.8)	34	0.3	4	0.2	3

Classification

A pathophysiologic classification was attempted by Kander and Muer.[6] Although arbitrary and speculative, it has proved to be useful.

1. Decreased production
   - A. Drug induced
   - B. Radiation
   - C. Hereditary
     - Kostmann (autosomal recessive)
     - Glansslen (autosomal dominant)
   - D. deVaal (reticular dysgenesis)
   - E. Agammaglobulinemia and dysgammaglobulinemia
   - F. Chronic hypoplastic neutropenia
   - G. Cyclic neutropenia
   - H. Familial neutropenia (plasma factor)
2. Increased destruction
   - A. Immunoneutropenia
     1. Neonatal neutropenia
     2. Drug induced
     3. Miscellaneous underlying disease
   - B. Splenic neutropenia
   - C. Chronic granulocytopenia in childhood
3. Increased destruction and decreased production
   - A. Cyclic neutropenia
   - B. Cirrhosis
   - C. Dysgammaglobulinemia
4. Ineffective myelopoesis

5. Pseudoneutropenia

6. Miscellaneous

   A. Chronic benign neutropenia of childhood

   B. Pancreatic insufficiency and bone marrow dysfunction

   C. Hyperglycemia

Several other authors including Smith[1] and Cline[7] have also classified the neutropenias. Recently developed techniques for culturing bone marrow in vitro may result in a new classification based on pathogenetic mechanisms.[8]

Evaluation of the Child Patient with Neutropenia

The objectives of the clinical evaluation of the child with suspected neutropenia are to determine its severity and whether it is chronic or cyclic. Smith recommends the following:

1. Complete blood count, platelets, absolute granulocyte count, reticulocyte count (3X weekly for 6 weeks).
2. Bone marrow aspiration and biopsy.
3. Epinephrine stimulation test.
4. Endotoxin and/or hydrocortisone stimulation tests.
5. Rebuck skin window test.
6. Diisopropyl fluorophosphate or Cr. survival study.
7. Antineutrophil antibody assay.
8. Colony-forming unit (CFU-C) assay, colony-stimulating factor assay.
9. Immunologic evaluation (quantitative immunoglobins, skin test reactivity, T and B cell evaluation).
10. Pancreatic exocrine, folate, vitamin B_{12}, copper levels and metabolic deficiency screening evaluation.
11. Collagen vascular disease evaluation with studies of antinuclear antibodies, C3 and C4, LE cell preparation, and rheumatoid factor.
12. Evaluation of other family members for evidence of neutropenia and chest and long bone X-ray films to rule out phenotypic skeletal expressions of neutropenic diseases.[1]

Neutrophil Physiology

Neutrophils arise from hematopoietic stem cells under microenvironmental and hormonal influences. They are produced in the proliferative compartment of the bone marrow, comprised of stem cells, myeloblasts, promyelocytes and myelocytes.

Myelocytes enter the maturation and storage compartment of the bone marrow where they differentiate into neutrophils. The neutrophils leave the marrow to enter the blood and within a few hours enter the tissue where they complete their lifespan in a few days (Figure 1).

Control of the blood levels is exerted on the proliferating compartment and at the point of departure from the storage compartment.[7]

The primary function of the neutrophil is the localization and killing of microorganisms. For locomotion and phagocytosis it depends on glycolytic energy. For killing it utilizes both oxygen-dependent and oxygen-independent systems (Figure 2).

Abnormalities may be induced by drugs, acquired in hematologic diseases or inherited.[7]

Host Response in Periodontal Disease

In periodontal disease, neutrophils are both protective and destructive. Periodontal destruction is increased when these cells are depressed in number, as in cyclic neutropenia, or when their function is impaired as in juvenile periodontitis (periodontosis).[9]

The probable etiologic agents of gingivitis and periodontitis

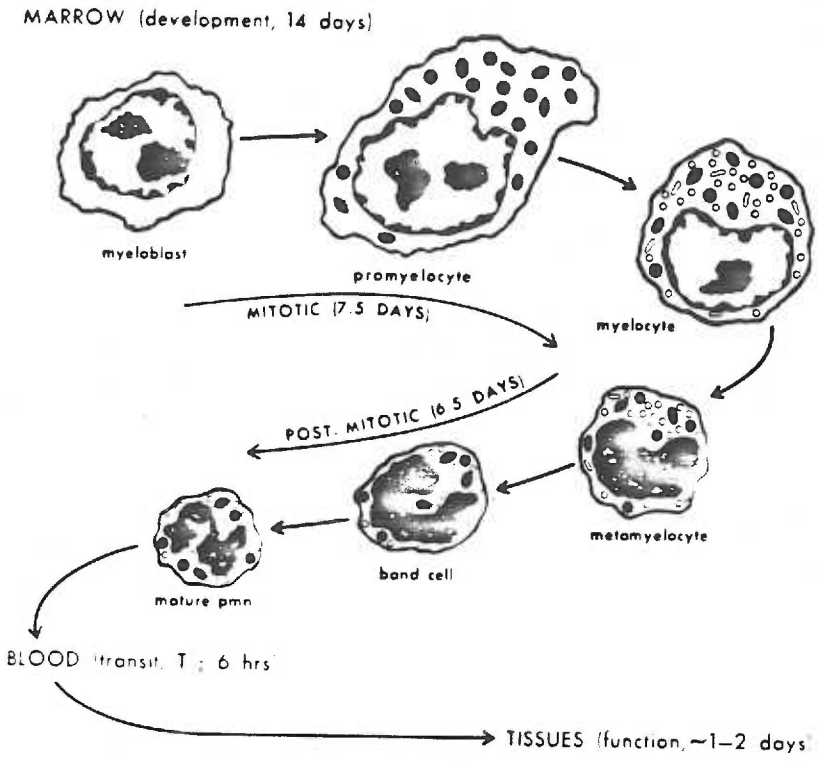


Figure 1. PMN Maturation and Life Cycle[7]

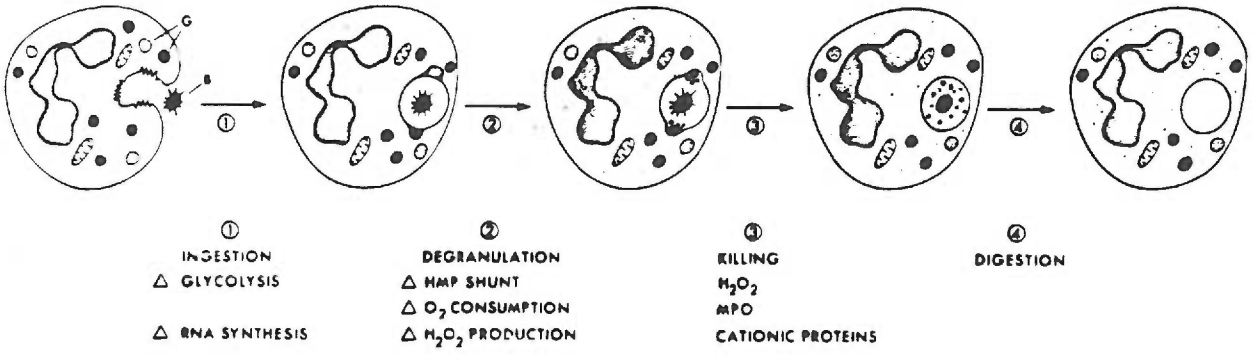


Figure 2. The Events of Phagocytosis[7]

in children are bacteria. However, very little information on bacteriology related to periodontal disease of pre-pubertal children is available.

Antigen specific and polyclonal immunologic phenomena may be involved. In the adult, early gingivitis appears to be T cell dominated, while established gingivitis and periodontitis are B cell and plasma cell dominated.

Severe periodontal destruction in adolescence and young adults has been associated with qualitative functional abnormalities such as chemotactic defects in both neutrophils and monocytes. B-cell hyperresponsiveness associated with T-cell regulatory abnormalities have also been implicated. Subjects with severe periodontitis are more responsive to staphylococcal protein A (SPA), which is a T-cell dependent - polyclonal B-cell activator. Unstimulated peripheral leucocytes (PBL) incorporated less ^{3}H-thymidine in these subjects when compared to controls. This may indicate a suppressed autologous mixed lymphocyte culture reaction (AMLR). Abnormal AMLR reflects abnormal T-cell responsiveness and regulatory function.[10]

Figure 3. graphically demonstrates immunologic responses in gingivitis and periodontitis.

Medical Management

In most patients with neutropenia, there is no known means of influencing neutrophil counts and treatment is aimed at minimizing the consequences of repeated infections.[4] This is because often the primary defects are in stem cell development.[12] Management of acquired neutropenias should be aimed

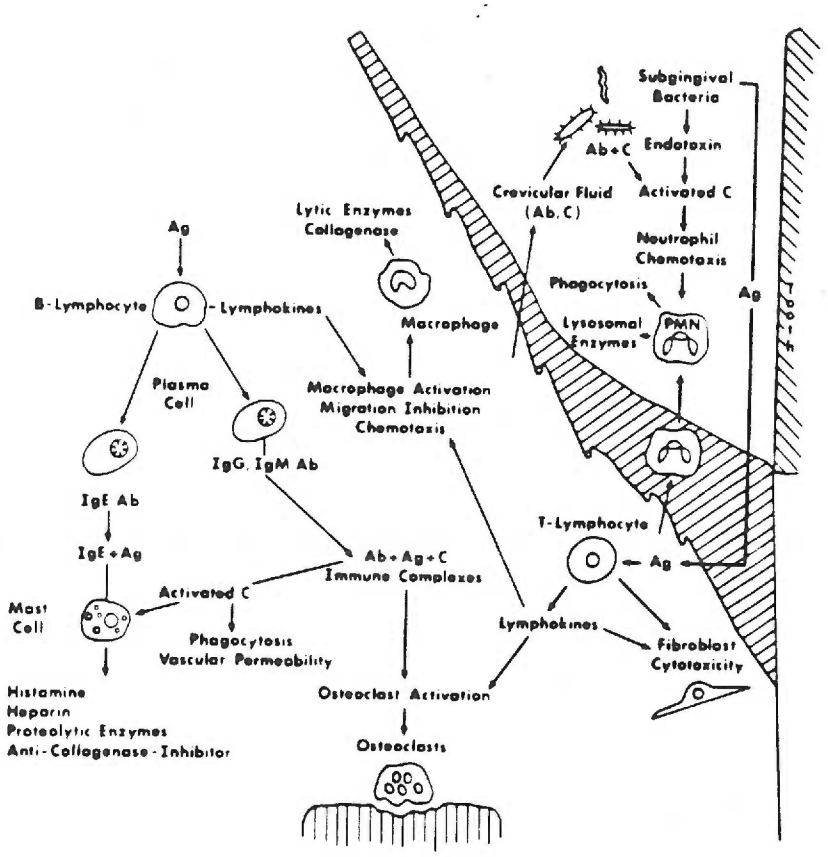


Figure 3. Immunologic Responses in Gingivitis and Periodontitis.[11]

at removal of the responsible agent.[2,4] If an underlying and treatable disease is identified, resolution of the neutropenia should follow proper therapy. For most of the remainder, a spontaneous remission is the best one can hope for.[2]

Marrow Transplant: In general, there is insufficient data to evaluate the results of bone marrow transplant. In aplastic anemia, it is the treatment of choice when there is a donor who matches the patient's four major histocompatibility loci. When a neutropenia is congenital and severe, one should identify normal siblings for possible future transplant.[12]

Complete hemopoetic and lymphoid engraftment was successful in a 20-month-old child with infantile agranulocytosis (Kostmann's syndrome) following bone marrow transplantation which had been preceded by total body irradiation and anti-human thymocyte serum.[13]

Spleenectomy: Reimann has noted that spleenectomy produced improvement in some cases but never a cure.[7] The most common comment in the literature is that it is seldom helpful.[2,4,6]

Steroids: This treatment regimen has rarely been useful and sometimes harmful.[2,6] Benefit seems to be limited to patients with antibody mediated neutrophil destruction.[2]

Granulocyte counts are increased in normal individuals treated with steroids. However, this increase comes about because of an interference with the mechanism by which neutrophils pass from blood to tissue. This could be detrimental to the patient with infection.[6]

Lithium Carbonate: Li_2Co_3 increases circulating PMNs and perhaps granulopoesis in man.[14] 100 mg., T.I.D. of lithium carbonate administered to psychiatric patients results in leucocytosis and neutrophilia. It has been employed in an attempt to curtail prolonged periods of neutropenia and thrombocytopenia following intensive chemotherapy.[12]

It is felt that Li_2Co_3 stimulates normal monocytes to produce granulocyte colony stimulating factor and therefore may be helpful in treating neutropenias with defective colony stimulating activity.[15]

A cautionary note was injected by Arnold Meisler of the University of Rochester Medical Center, he states: "Although initially decreased leukopenia may be observed, successive cycles of therapy including lithium carbonate should result in profound and rapid bone-marrow depletion."[16]

Granulocyte transfusion: Many pediatric centers today are using granulocyte transfusions when treating neutropenic patients with sepsis. Several studies recommend administration of granulocytes once or twice daily for at least a five-day period. This treatment course improves survival and eradicates sepsis in patients with profound granulocytopenia who are also receiving proper antibiotic therapy.[12]

Fresh Normal plasma: Infusions cause a rise in neutrophil counts in very few patients with infantile genetic agranulocytosis and cyclic neutropenia.[4] The neutrophils are released from the bone marrow reserve.[12]

Gammaglobulin: Neutropenia is often seen in patients

with immunoglobulin abnormalities. Replacement of gammaglobulin seldom improves absolute neutrophil count (ANC) in these patients.[12]

Treatment of Infection: Each infection should be managed meticulously.[6] Although vigorous antibiotic treatment of established infections is imperative,[4] prophylactic antibody therapy is condensed because of an increased chance of resistant flora.[12,6] Treatment should also be specific and should be guided by cultures and sensitivity testing when possible.[2]

Preventive measures such as a stool softener (Colace 50-100 mg. q.d.) to prevent rectal fissures and meticulous care of skin punctures (soap wash followed by 5-minute exposure to an iodine-containing compound, such as Betadine or Foamasept-ic) have been successful in some cases.

Oral Manifestations

The child with neutropenia frequently will have oral manifestations of generalized gingivitis sometimes accompanied by aphthous-like ulcerations. If the condition is chronic, periodontitis usually develops. If the condition is periodic, as in intermittent drug therapy or cyclic neutropenia lesions may be sporadic.

Of the several types of neutropenia, Baer in 1974 described four with oral manifestations - agranulocytosis, cyclic neutropenia, chronic idiopathic neutropenia, and familial benign neutropenia. Agranulocytosis is seldom seen in children.[11]

Reichart and Dornow[17] list cyclic neutropenia, chronic familial neutropenia, chronic benign neutropenia and chronic

idiopathic neutropenia as having associated oral pathology.

Cyclic Neutropenia:

In this well known neutropenia, the circulating neutrophils decline in a cyclic pattern. The condition was first described by Leale in 1910.[18] In 1967, Morley reported on 20 more patients.[1] Episodes are reported to occur every 14-30 days,[1,7,18,19] and persist for 5-10 days.[8]

The etiology is usually idiopathic[18,19,20] but may be secondary to agammaglobulinemia in children.[18] Fifty percent of reported cases are diagnosed in the first year of life. The first clinical manifestations are usually oral lesions. Initially the patient presents with gingivitis which develops into chronic periodontitis with repeated gingival insults. Mucous membrane ulcers develop during the neutropenic period.[19] Radiographs show mild to severe bone loss depending on the elapsed time since onset and the dental treatment received.[3,19]

In the absence of a defense mechanism, bacterial invasion, chiefly from the gingival sulcus has been suggested as the pathogenesis.[3] The ulcers may persist for 10-14 days and heal with scarring.

The onset is usually in infancy or childhood, but it may not appear until adult life. There is a tendency to improve with age.[18]

As more is understood about the control mechanism of granulopoesis, we may be able to better understand the nature of cyclic neutropenia.[7]

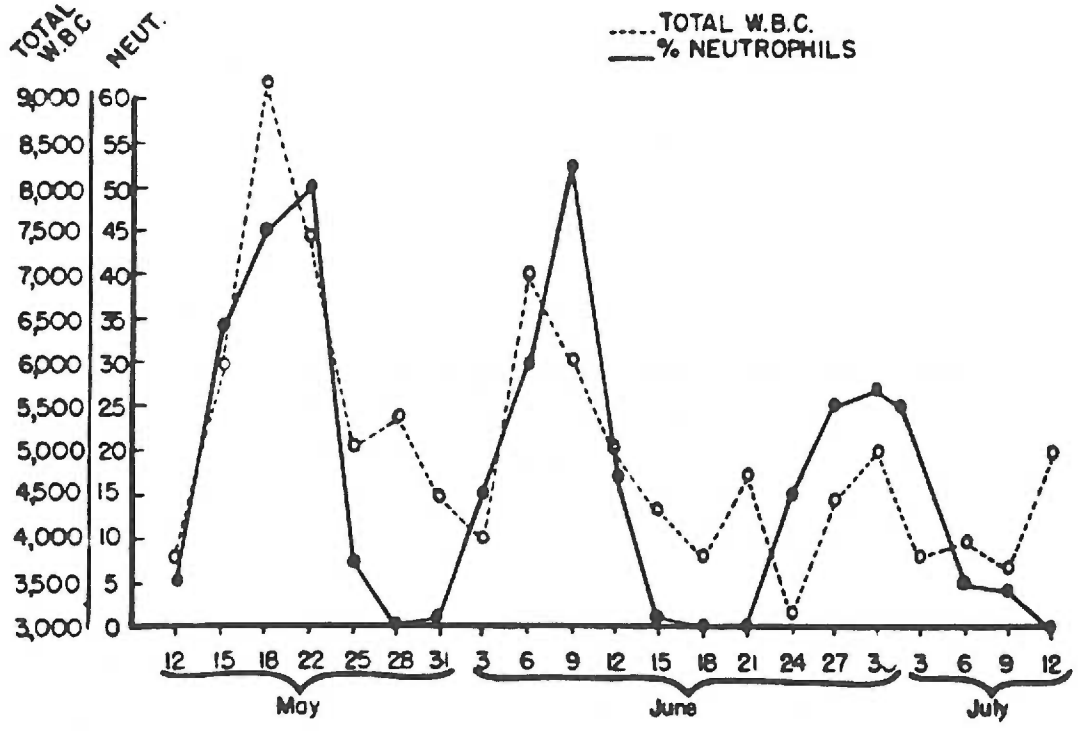


Figure 4. Neutrophil Counts in Cyclic Neutropenia for a 2-Month Period[11]

Chronic Idiopathic Neutropenia; Familial Benign Neutropenia:

These two disease entities are similar except that the latter is inherited as a non-sex-linked dominant characteristic.[7,11] Both conditions exhibit normal to decreased leucocyte counts associated with relative lymphocytosis and monocytosis. In some patients, clinical symptoms are absent.[11]

In those patients with clinical symptoms, periodontal disease is frequently seen. Gingival tissues have been described as being cherry red, soft swollen, and edematous or bright red, or jelly-like hyperplastic gingivitis. Granulomatous lesions may occur cervically at the time of exfoliation of primary teeth or the eruption of permanent teeth. Gingival pockets, bone loss, and oral ulcerations may be present but not all of these conditions in all cases.[11] Long or short-term symptom-free intervals are usual.

Chronic Benign Neutropenia:

Relatively few reports are available on this condition even though it may be observed with some frequency. Its characteristic features in childhood are essentially normal bone marrow except for the absence of mature neutrophils. Recurrent pyogenic skin and mucous membrane lesions begin in infancy to early childhood. There is no hereditary pattern and the disease follows a self-limiting course.[17]

Dental Management

The role of the dental practitioner is the prevention and control of infection and the interception of dental

disease before surgical intervention is necessary.[21] Consultation with the patient's physician may be necessary if optimal therapeutic choices are to be made. Periodontal and restorative procedures should be performed during a state of remission.[4,22]

Therapeutic measures are frequently disappointing and the prognosis is variable depending on the type and severity of the neutropenia condition. The greatest risk follows any procedure that causes an acute surgical wound or bacteremia, with tooth extraction being the most hazardous procedure.[21]

It is most important to establish good oral hygiene including the dorsum of the tongue which harbors large numbers of microbes. If chronic gingivitis and periodontitis are present, local conservative measures are mandatory. Careful removal of plaque and calculus have been recommended. The use of antimicrobial mouthwashes has been suggested.[17]

In most instances, the role of periodontal therapy should be to reduce patient discomfort due to gingival inflammation and to slow down progressive alveolar bone loss.[21] In cyclic neutropenia, bone loss has been found around primary and permanent molars and in the incisal area.[22]

Alveolar bone loss has also been reported in patients with chronic neutropenia and familial benign neutropenia.[11] Restorative care should be modified where appropriate to minimize periodontal problems.[19]

Antibiotics are indicated in microbial infections for prevention of bacteremia and septicemia.[17] Their role in the

dental management of childhood neutropenias is to combat secondary infection of oral and pharynageal lesions.[23] Penicillin or Erythromycin are frequently the drugs of choice. Systemic prophylactic administration of antibiotics in chronic gingivitis and periodontitis is not indicated.[17]

Tetracycline mouthrinse has been recommended for patients with multiple oral ulcers.[11,23] The contents of a 250 mg. capsule is dissolved in 5 ml. deionized water or diet soft drink after meals and before retiring followed by nothing by mouth for one hour. The suspension is held in the mouth over the area of the lesions and a flushing motion is maintained for a period of at least 2 minutes. The suspension is then expectorated.[11] Reichart[17] cautions against the use of tetracycline mouthrinse in cyclic neutropenia because of the increased risk of allergic reactions.[17]

Nystatin mouthrinse (400,000 units) four times daily or in resistant cases - clortriamazole (100 mg. vaginal tablets) dissolved in the mouth four times a day has been found effective, should candidosis be a problem.

Discomfort from oral ulcerations can be relieved by topical application of triamcinolone acetamide with an oral adhesive (Kenalog in Orabase).[11]

A 2% potassium chlorate solution sprayed on ulcerations has had varying degrees of clinical success.

Xylocaine viscous has been recommended before meals to increase comfort during swallowing.

A mouthwash of equal parts Elixer of Benadryl and

Kaopectate has also been suggested.

Garfunkel reported the use of an Omnivac splint as a reservoir for antibacterial and antifungal medication as being effective in shortening the healing time of ulcers and preventing their spread.[24]

Although not approved by the FDA for use in the United States, Chlorohexidine gluconate mouthrinse may prove to be effective in the treatment of gingivitis and periodontitis associated with the childhood neutropenias. Loë and Rindom-Schiott found that a 0.2% solution used two times daily or a 2.0% solution applied one time daily significantly reduced plaque formations on healthy dental students.[25]

Periodontal surgery should generally be avoided; however, minor surgical corrections such as frenectomy to relieve areas prone to inflammation may prove helpful.[11] Atraumatic surgical technique is desirable because wounds handled roughly but not contaminated develop a higher incidence of infection than those grossly contaminated but handled atraumatically. Polyglycolic acid sutures or chromic catgut sutures have been recommended as they reduce tissue reaction.[21]

Neutropenic patients should be under constant dental professional care including a caries prevention program.[17] Mishkin recommends oral hygiene instruction, sucrose limitation, and an aggressive stannous fluoride gel program. A 0.4% stannous fluoride gel is brushed on the teeth, swished for one minute, and expectorated, nightly.[21]

METHOD AND MATERIALS

The patients selected for this study have within their medical histories a diagnosis of congenital neutropenia, with or without oral manifestations. Their age and availability for treatment were the only considerations.

All patients had at some time been treated at the UOHSC and had files in the hemotology department. Because these disorders are relatively rare, the total number of patients available for examination was limited.

Pertinent information such as age, sex, history of infections, hospitalizations and laboratory tests were extracted and summarized from medical records at the UOHSC or the Child Development and Rehabilitation Center.

The diagnosis of congenital neutropenia was based on a significant reduction in circulating neutrophils as exhibited in repeated white blood cell differential counts, since infancy. Bone marrow aspiration studies were frequently done. Additional work-ups such as neutrophil function studies were not uncommon.

The parents were contacted directly, through the hemotology department, or through the attending pedodontist or periodontist. A parent interview and examination of the child was arranged. The purpose of the interview was to supplement the medical and dental history. An assessment of the patient's home care, diet, and fluoride program was recorded.

Dental examinations were conducted in the dental offices of the attending dentists or in the Graduate Pedodontic Clinic at the UOHSC. A mouth mirror, explorer and dental light were used in all examinations.

The teeth were charted for dental caries. Mobility was noted using Miller's classification. All soft tissue was examined and abnormalities recorded. The color, texture, contour, and consistency of the gingiva was also noted.

Bitewing and/or panoramic radiographs were selected from the patient's file. Earlier films were included in some cases to demonstrate progressive bone loss.

Frontal, left and right side intraoral photographs were taken on each patient. When present, soft tissue lesions were included in the photographic survey.

CASE REPORTS

Patient #1.

The patient, a 6-year-old, white female of Finnish ancestry, is well-known in the pediatric and hemotology departments at the UOHSC where she has been a patient since September 1974.

She had numerous bacterial infections of the skin and mucous membranes beginning 3 months post-natal. Recurrent infections plus pneumonia at age 6 months (in Seattle) prompted studies which included bone marrow aspiration. The studies revealed granulocyte stasis at the myelocyte stage and decreased erythroid precursors, which correlates with neutropenia and normochromic and normocytic anemia. Hospitalizations have been frequent: 4/75 pneumonia; 9/75 otitis media and marrow aspiration; 2/79 abscess drainage; 6/79 pyelonephritis; 1/80 RTA with renal studies which revealed probable type IV renal tubular acidosis. She did not walk until 23 months and has language delay.

Penicillin therapy has been used to control infections. Several years of prednisone treatment was discontinued for lack of success. At the time of evaluation, the patient was receiving 1/2 tsp. Septra every other night for a urinary tract infection and Florinef (2½ tabs) in the hope of correcting the renal tubular acidosis (RTA). Her past history reveals that infections tend to clear with or without antibiotic therapy.

Composite hematologic values are as follows:

WBC.....2.9 - 4.0 x 10^3	PMN.....1 - 4%
RBC.....2.1 - 2.6 x 10^6	Lymphos.....62 - 84%
HGB.....6.1 - 6.9	Bands.....0 - 3%
PL.....150000 - 208000	Monos.....5 - 30%
	Eos.....3 - 9%

Dental Findings

The patient, in the very early mixed dentition stage, was found to have remarkable mobility of the lower teeth (Miller's Class 3), especially #L and #S which are scheduled for extraction. #T and #K may also be lost soon. This would most likely require the placement of an appliance. Gingival recession about the lower teeth ranges from 2-5 mm with deep pocket formation.

The upper teeth are less mobile (Miller's Class 1) and have less gingival recession.

The gingival tissue varies in degree of health but many areas are red and boggy with rolled margins, exhibiting several bleeding spots.

The patient was obviously having some difficulty with oral hygiene. Although she has a history of oral ulcers, none were present at examination.

Patient #2.

The patient, a 3-year-old, white female first presented as a 19-month-old with red, tender and bleeding gingival tissues, separation of the lower primary central incisors, and a single ulcer on the lower lip.

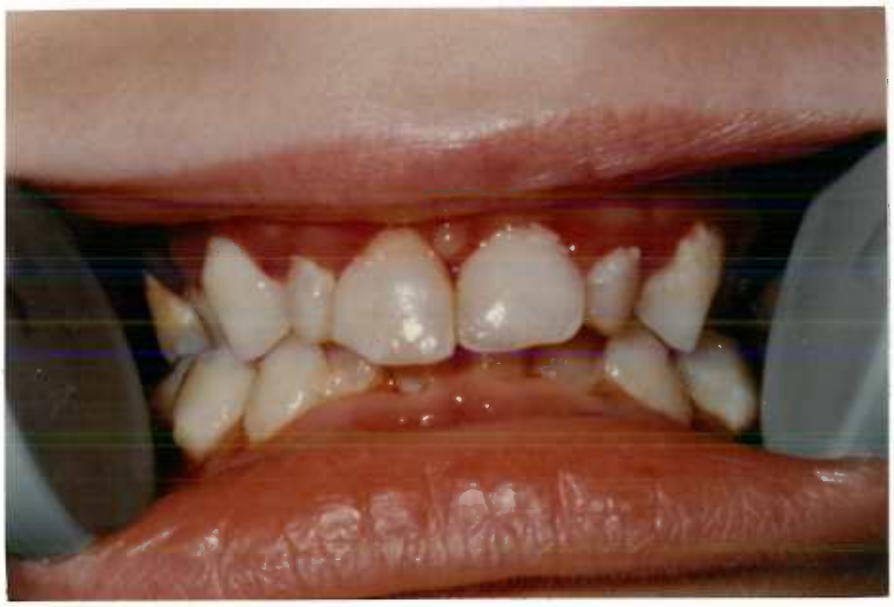


Fig. 5. Patient 1. Age five years, anterior segment shows heavy plaque accumulation, gingival inflammation, exaggerated recession.

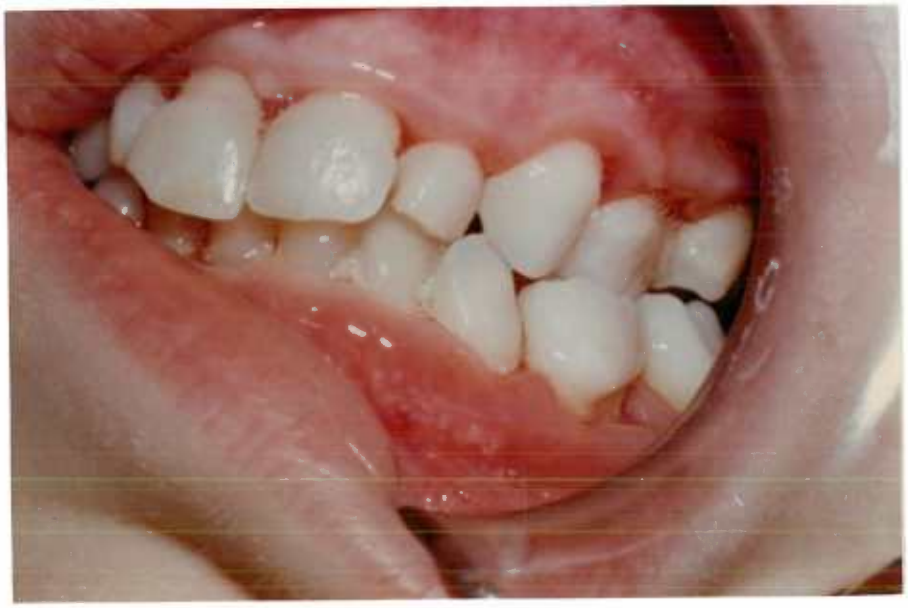


Fig. 6. Patient 1. Age five years, left side shows moderate plaque accumulation, recession around Teeth #E, #F and #L.

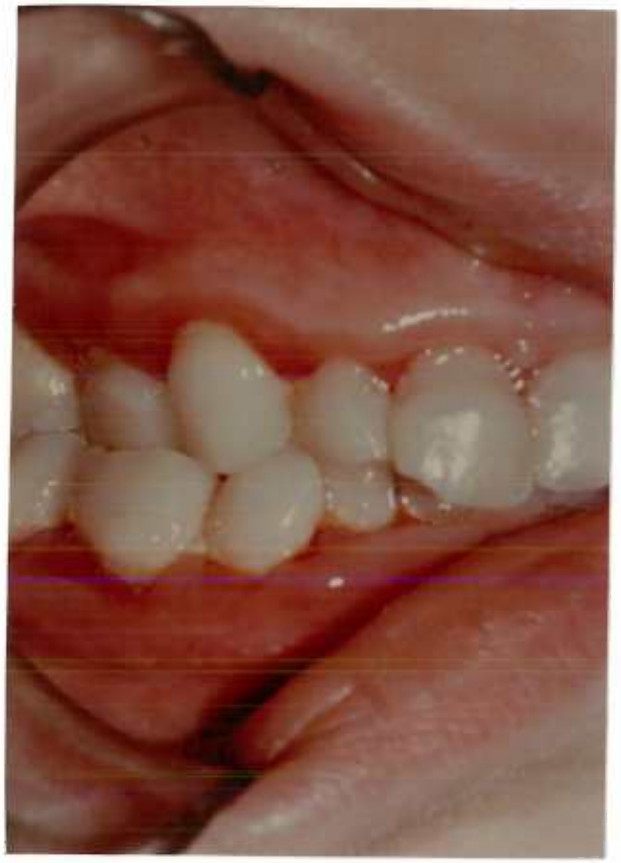


Fig. 7. Patient 1. Age five years, right side shows moderate plaque accumulation, recession around Teeth #B, #E, #F and #S.

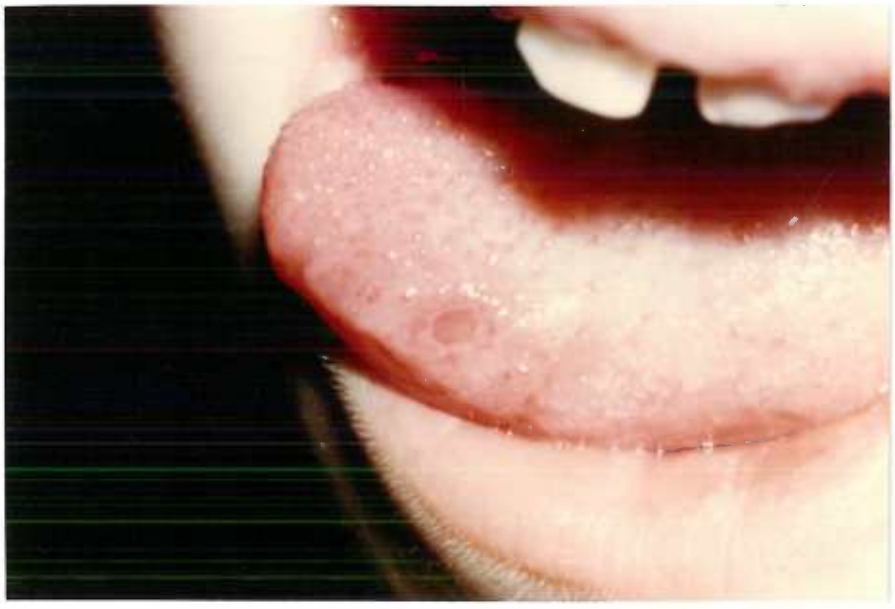


Fig. 8. Patient 1. Age five years, ulceration on tip of tongue.

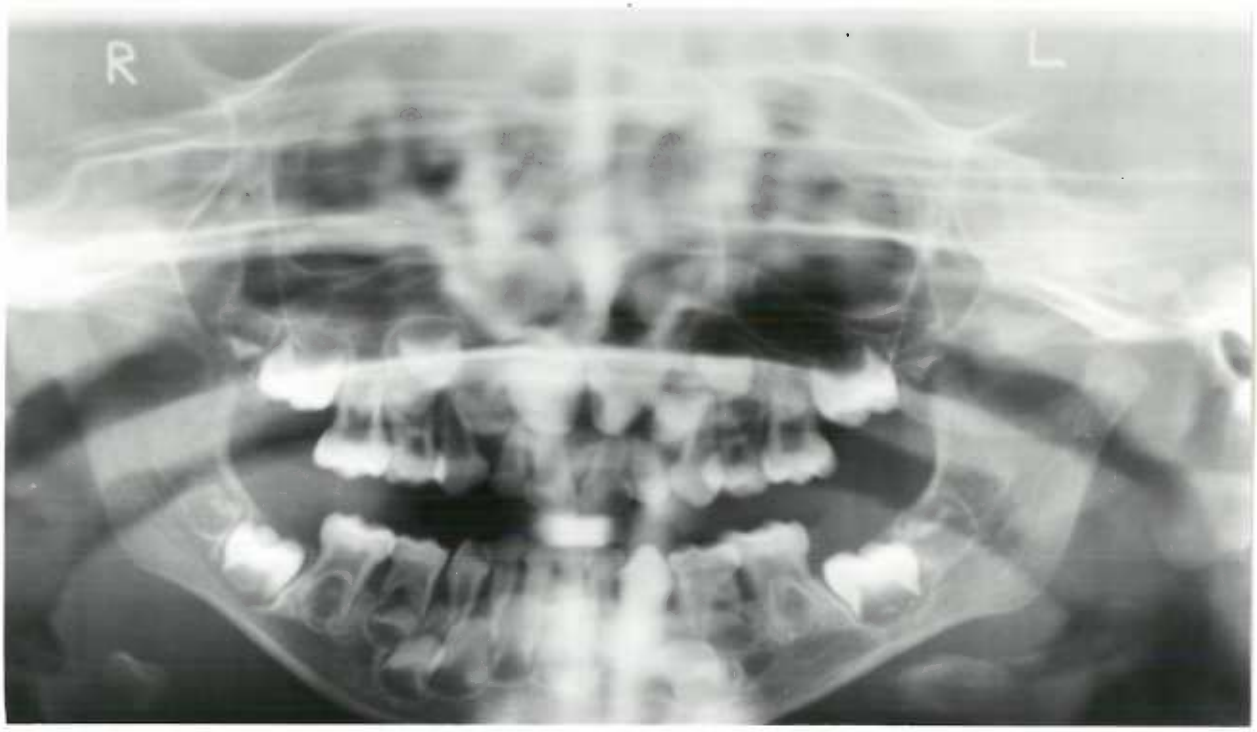


Fig. 9. Patient 1. Age five years, panoramic radiograph showing severe alveolar bone loss.

She had been diagnosed as having chronic benign neutropenia not associated with low immunoglobulin or family history. Her medical history was essentially negative except for occasional upper respiratory infections and one bout with otitis media.

Low dose penicillin therapy (250 mg. BID) was initiated and she was placed under the care of a local pedodontist. A course of periodontal therapy which includes appropriate antibiotics, glyoxide rinses twice daily, frequent prophylaxis, oral hygiene instruction, and diet considerations was followed.

When Erythromycin was tried as an alternative therapy, the patient developed an urticarial rash, and it was promptly discontinued.

The pediatric department recommended four courses of treatment should her periodontal condition become progressive. Their order of preference:

1. Do nothing: follow her
2. Chronic low dose antibiotic therapy
3. Lithium therapy
4. Corticosteroid.

Laboratory Findings

Bone Marrow:

1. No increase in blast cell population
2. Few neutrophils
3. Maturational arrest at the metamyelocyte-band stage
4. Adequate myeloid precursors.

Other Tests:

1. Several counts ruled out cyclic neutropenia
2. Several WBC counts of 3500-4000
3. Generally 2-3% polys and bands
4. Lymphocytes generally 70-80%
5. Monocytes 2-20%.

Dental Findings

Dental examination of the hard and soft tissues revealed slightly red and rolled gingiva with blunted papilla and several bleeding points. There was 2-3mm of recession of attached gingiva in the lower incisor area. Teeth #O and #P demonstrated Class 1 mobility. There was some staining observed on several teeth. This may have been associated with the antibiotic therapy. No ulcerations were noted. Minimal alveolor bone loss was evident in the dental radiographs.

Patient #3.

The patient, a very attractive, cooperative 4-year-old, white female, has had normal growth and development. She had recurrent thrust which was treated several times during infancy. A chin abscess was incised and drained at 6 months of age. At 9 months of age, an ulcer on the tip of the tongue was noted. At 10 months of age, bilateral cellulitis was successfully treated with antibiotics. While in the hospital for evaluation of a fever, the patient was diagnosed neutropenic, congenital type.

There has been no significant loss of family members due to infection and blood tests of both parents were negative.

At 2½ years of age, she had bone marrow cultures taken. The M:E ratio was 5:1 with normal cellularity. Megakaryocytes were present in normal numbers. The myeloid line was active and was represented by cells in all stages of maturity.

A fairly representative white blood cell differential count was taken in September 1979 and produced the following

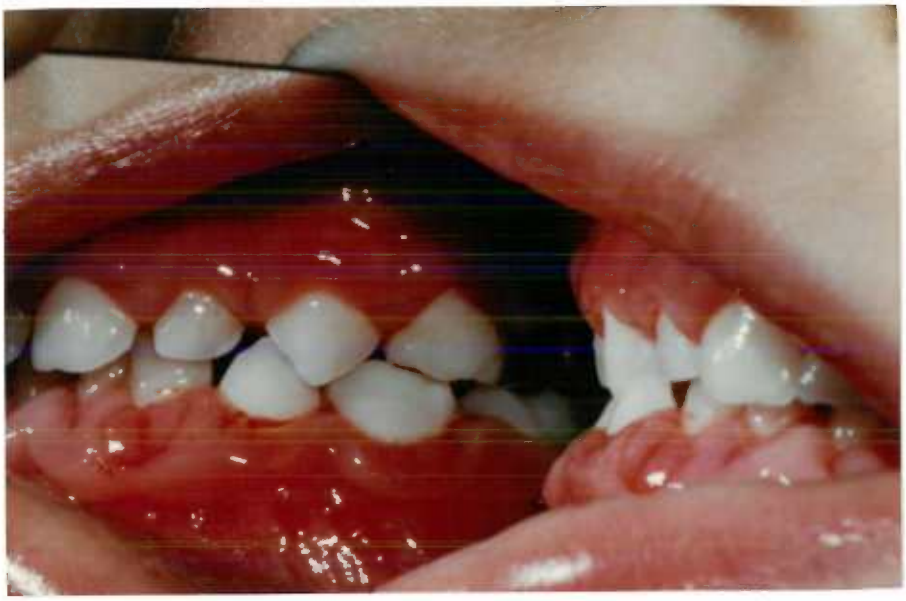


Fig. 10. Patient 2. Age three years, right side shows red, edematous gingival tissue.

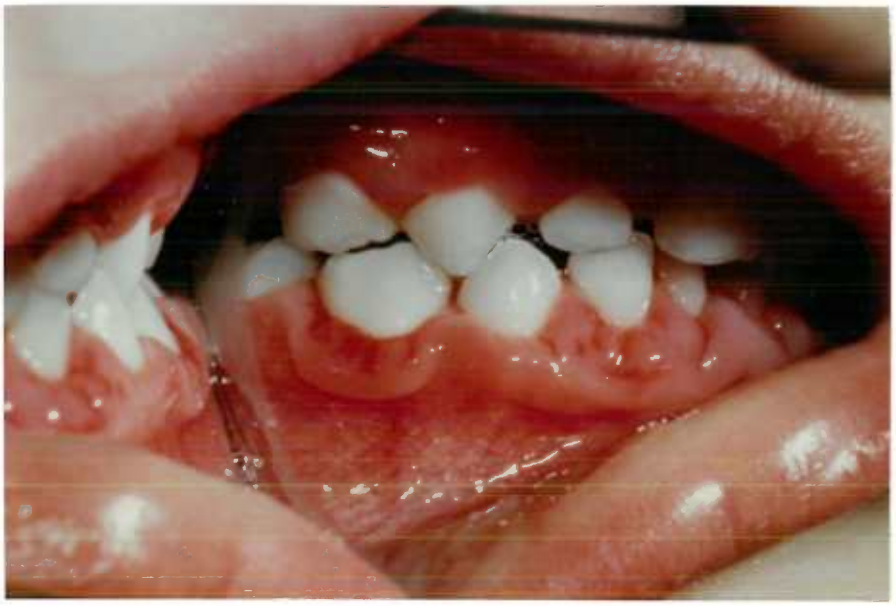


Fig. 11. Patient 2. Age three years, left side shows red, edematous gingival tissue.

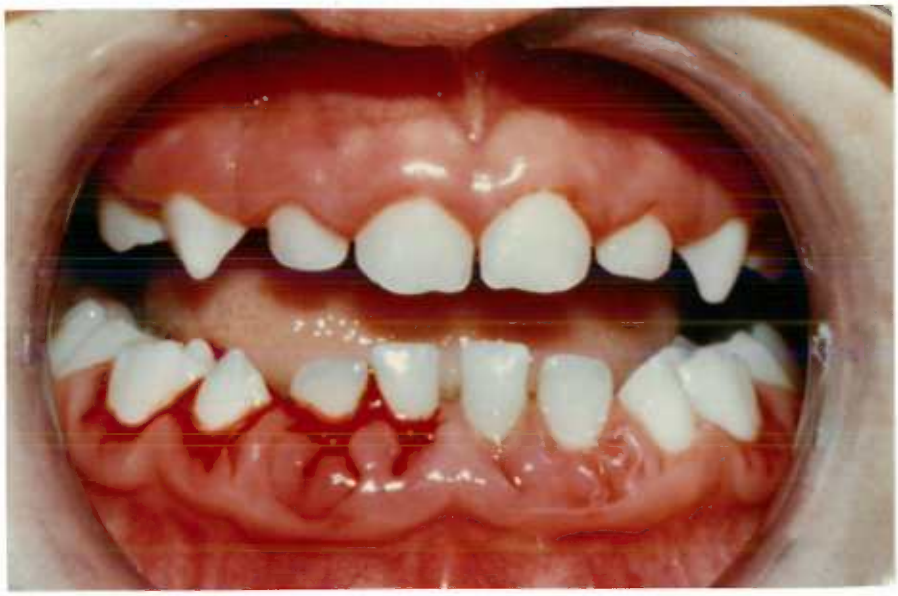


Fig. 12. Patient 2. Age three years, frontal view demonstrates bleeding gingival tissue following mild stimulation.

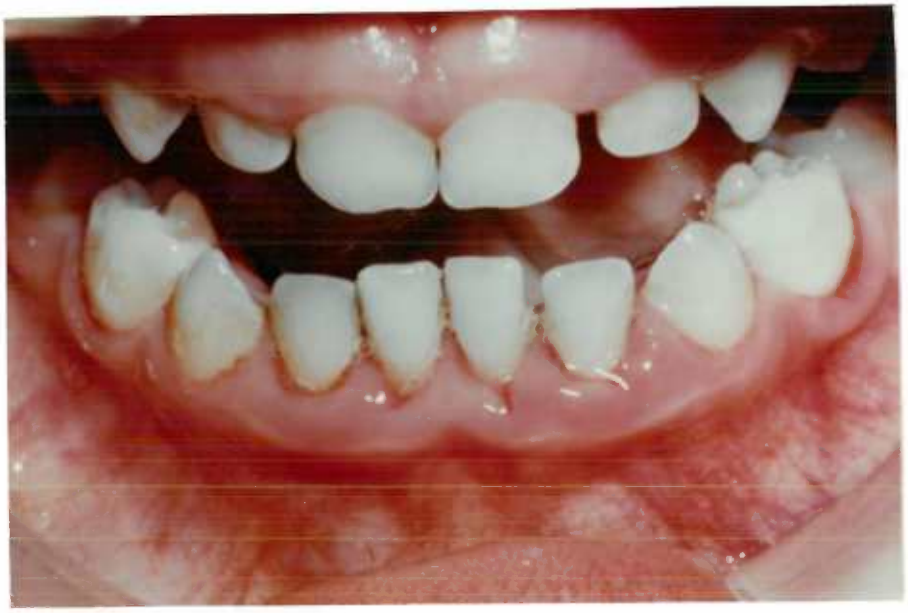


Fig. 13. Patient 2. Age three years, frontal view shows improved gingival tissue following low dose antibiotic therapy, frequent professional visits.

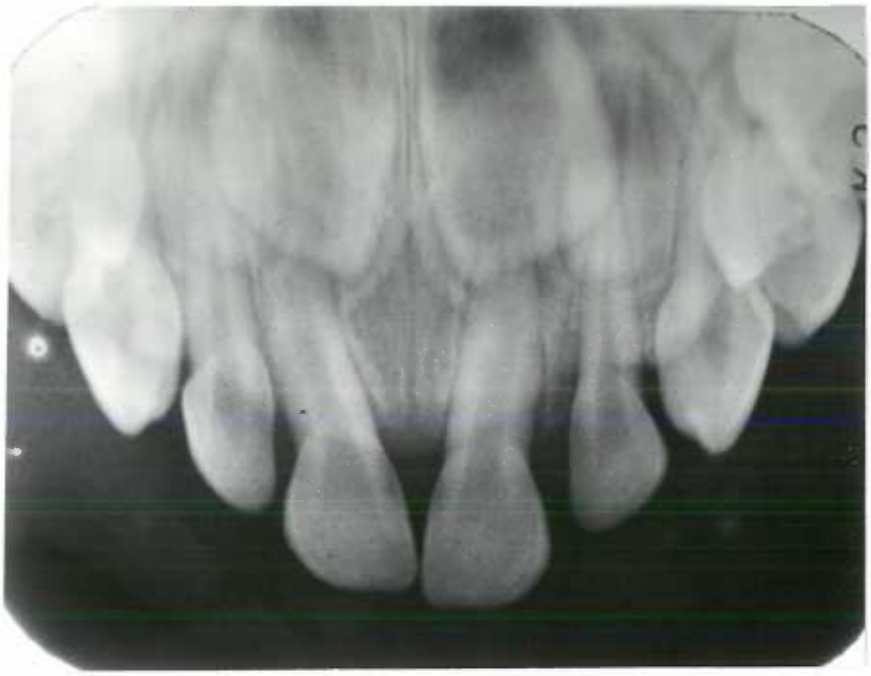


Fig. 14. Patient 2. Age three years, radiograph of upper anterior area shows minimal alveolar bone loss.

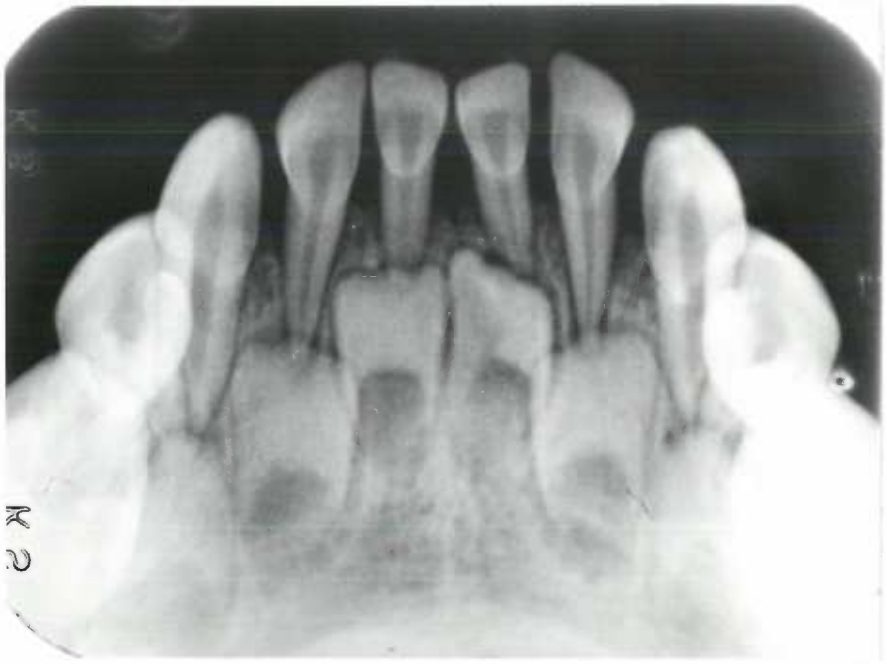


Fig. 15. Patient 2. Age three years, radiograph of lower anterior area shows moderate alveolar bone loss.

values:

PMN..... 2%

Bands..... 1%

Lymphos.....87%

Mono..... 9%

Eos..... 1%

The monocytes typically will increase to 30-40% during periods of infection. No abnormalities in B or T-cell function have been found.

The pediatric department recommended that the patient be managed essentially as a normal child, using early intermittent antibiotics should skin infections or dental problems develop.

Dental Findings

The patient was referred to a pedodontist at age 2½ for a routine examination following a diagnosis of neutropenia. Her dental condition at that time was unremarkable.

In the next year, she had two attacks of "multiple mouth sores". Since then, she has had from one to three mouth sores from time to time.

Carious lesions were present on teeth #A, #J, #K, and #T. The cervical one-third of several teeth exhibited demineralization. Gingival tissue adjacent to the upper and lower primary molars was moderately inflamed. Oral hygiene was only fair. The twenty primary teeth were without mobility and alveolar bone was normal on the dental radiographs. No soft tissue lesions were found.

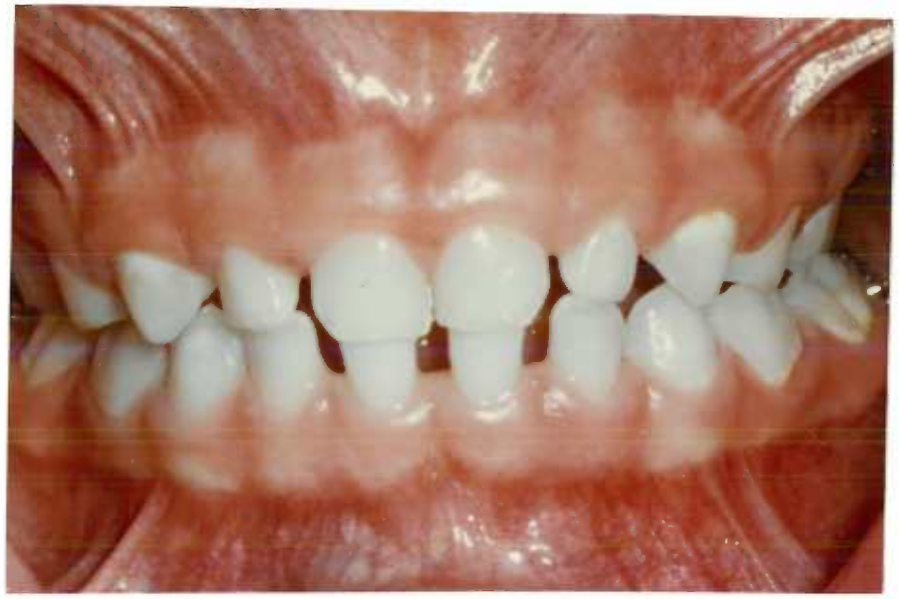


Fig. 16. Patient 3. Age four years, frontal view shows generalized gingivitis, with red, smooth, boggy appearance.

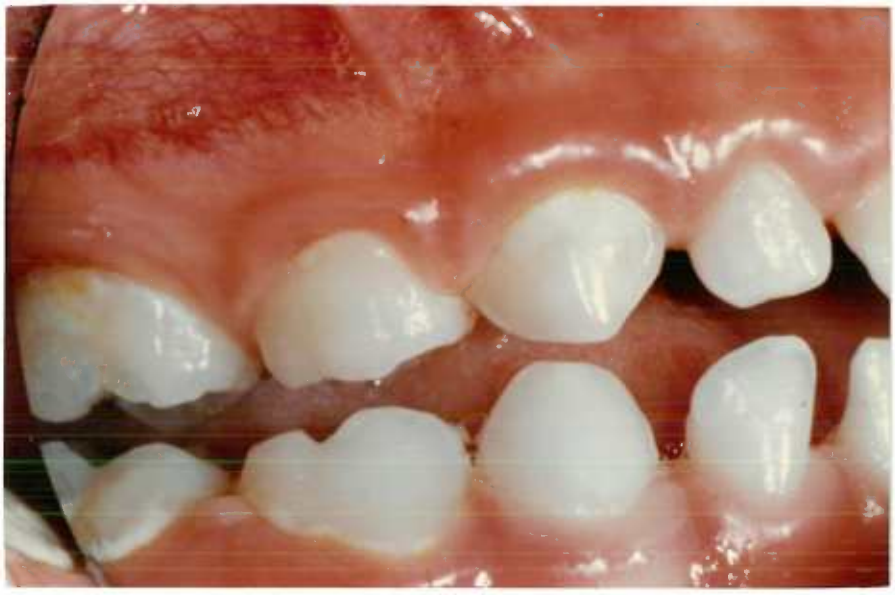


Fig. 17. Patient 3. Age four years, left side view shows generalized gingivitis, with red, smooth, boggy appearance, cervical demineralization.

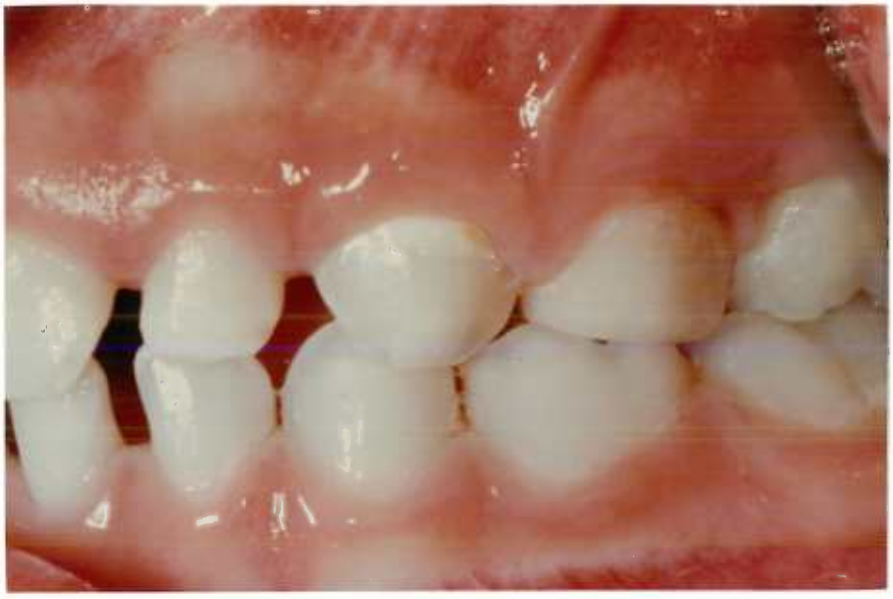


Fig. 18. Patient 3. Age four years, right side view shows generalized gingivitis with red, smooth, boggy appearance, cervical demineralization.

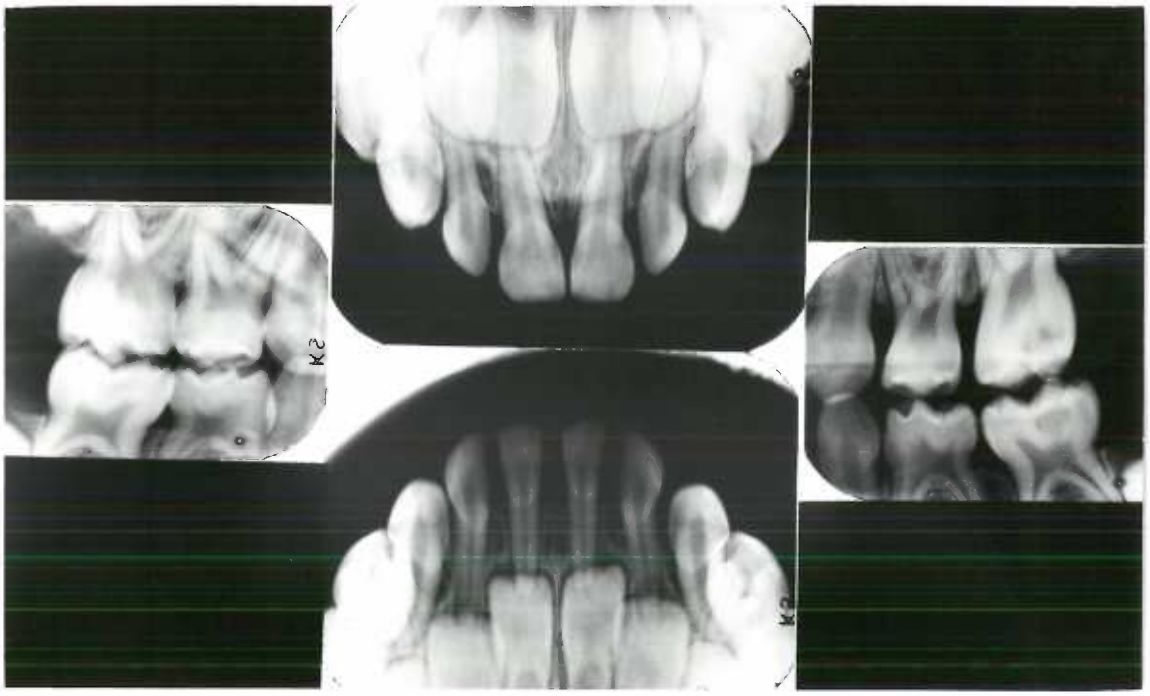


Fig. 19. Patient 3. Age four years, radiographs show no alveolar bone loss.

Patient #4.

At 18 months of age, the patient, a 14-year-old, white male, was hospitalized because of abscess formation (at the site of a DPT injection) and severe anemia. After examination and blood work-up, the impression was congenital hypoplastic anemia - Fanconi's Variety. He was started on Prednisone (15 mg. every other day) with prompt response.

By age 6½, he was taking Penicillin in addition to the Prednisone. His diagnoses at this time was Leucogenesis Imperfecta with leucopenia and aplastic anemia and a variant form of neutropenia (Diamond Blackfan). He presented with an aphthous-like ulcer on the tip of his tongue. His white blood cell counts at this time were in the 600-1400 range.

The bone marrow was slightly hypercellular with marked increase in the erythrocyte series (megablastoid features). The granulocytes were markedly decreased with little maturation beyond the promyelocyte stage. Giant bands, metamyclocytes and eosinophils were frequent.

A CBC taken at age 11 is somewhat typical:

WBC.....800	Lymphos.....72%
HGB.....7.8	Monos.....12%
HCT.....22.9	Eos..... 4%
PMN.....10%	Baso..... 2%
Bands..... 0%	

At the present time, the patient is active in school sports and enjoys wrestling. He tends to get skin boils when his "blood is low". When this happens, his dosage of Penicillin

is increased from 250 mg. BID to 250 mg. QID. He is still taking 15 mg. Prednisone every other day.

Dental Findings

The patient presented with 28 permanent teeth in ideal Class 1 occlusion. The alignment was nearly perfect. There were no restorations or carious lesions present. Marginal gingivitis was generalized. The labial tissue adjacent to the upper and lower anteriors and the lingual tissue adjacent to the upper molars was red, smooth, and boggy in appearance.

Although the patient has a history of chronic mouth sores, none were present on examination. The patient's oral hygiene was only fair.

Patient #5.

The patient, a 10-year-old, white female developed normally until 6 weeks of age when she developed nasal pharyngitis. At 4 months, she had a boil on the back of her neck. During the first year, fever and URI infections were frequent. Spleenomegaly was also noted. A peripheral blood count revealed an unusual differential count and abnormal appearing neutrophils. Antibiotic therapy was nearly continuous.

By age 2½, she had suffered multiple skin, ear, and URI infections, occuring every 6 weeks.

At 4 years of age, leucocyte function studies demonstrated monocytes to be the predominent blood leucocyte. Her monocytes were unable to produce H_2O_2.

A very extensive family pedigree was charted and was unremarkable as to morbidity due to infection.

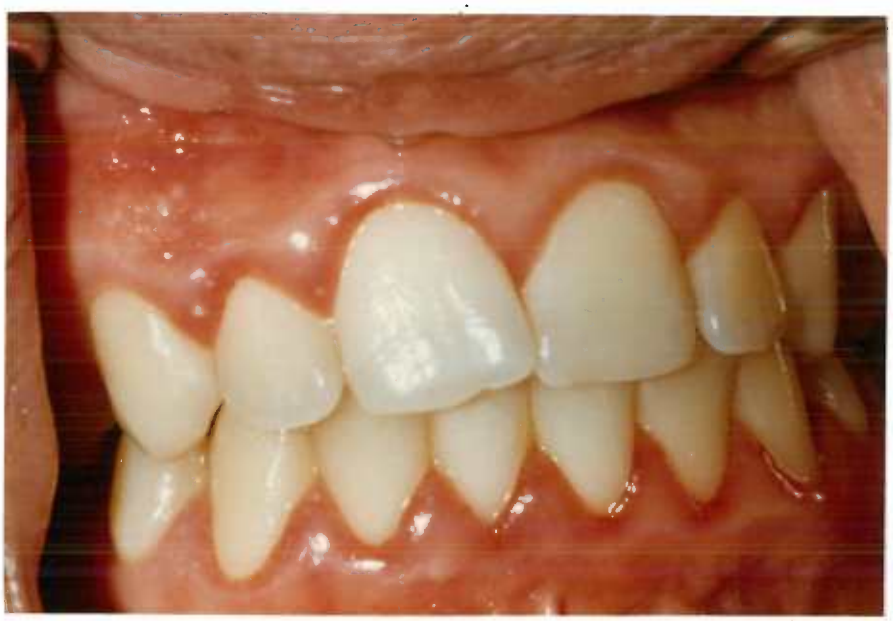


Fig. 20. Patient 4. Age fourteen years, frontal view shows smooth, boggy gingival tissue, distinctly red at the margin.

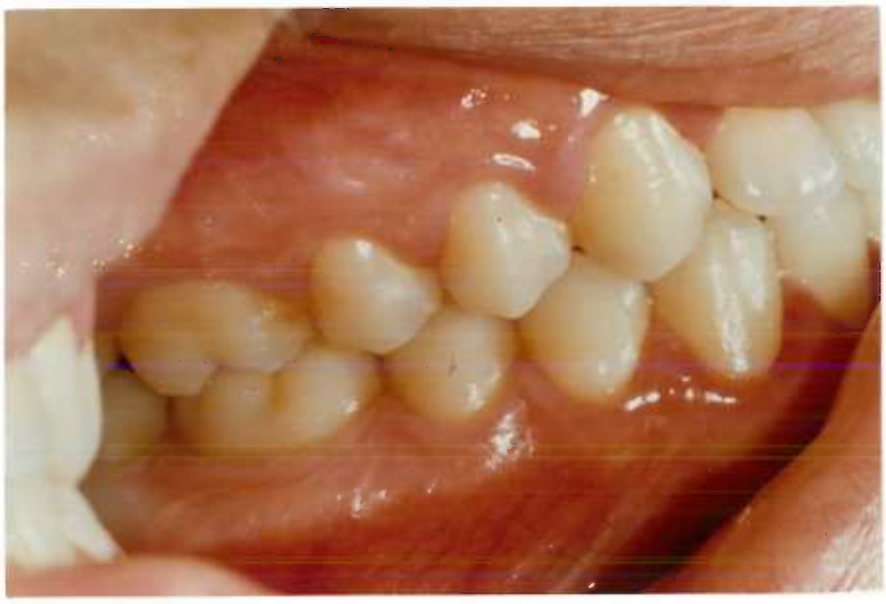


Fig. 21. Patient 4. Age fourteen years, left side view shows smooth, boggy gingival tissue, red at the margin.

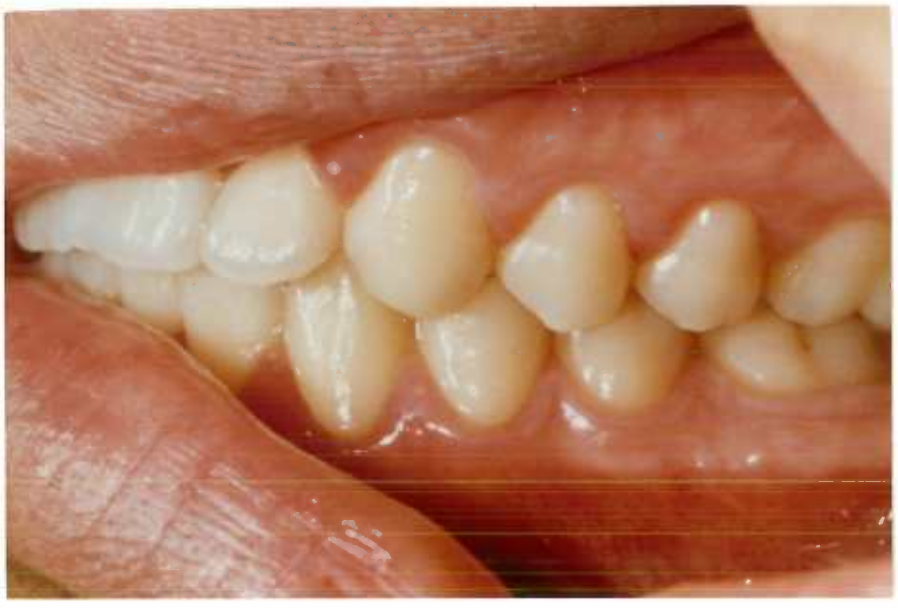


Fig. 22. Patient 4. Age fourteen years, right side view shows smooth, boggy gingival tissue, red at the margin.

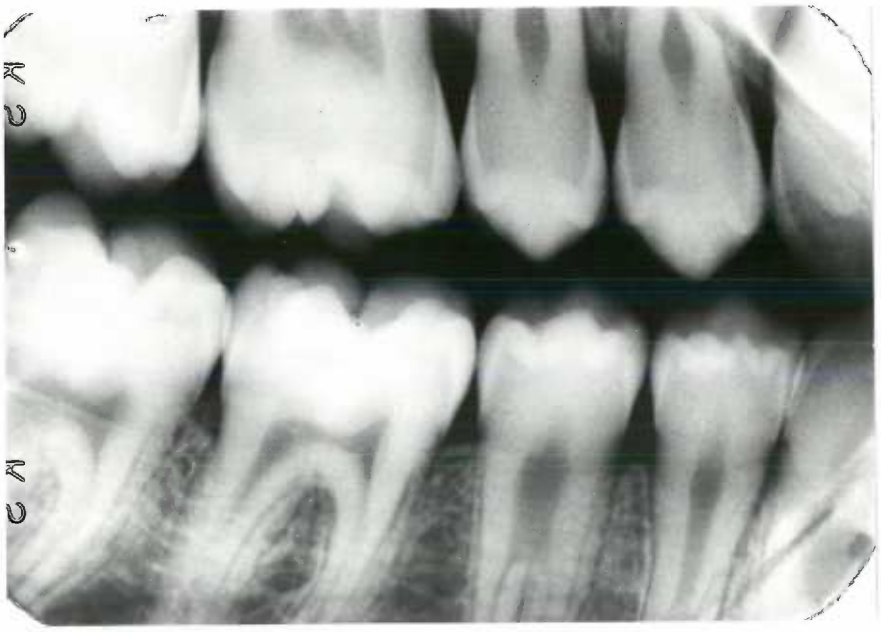


Fig. 23. Patient 4. Age fourteen years, bitewing radiograph shows no alveolar bone loss.

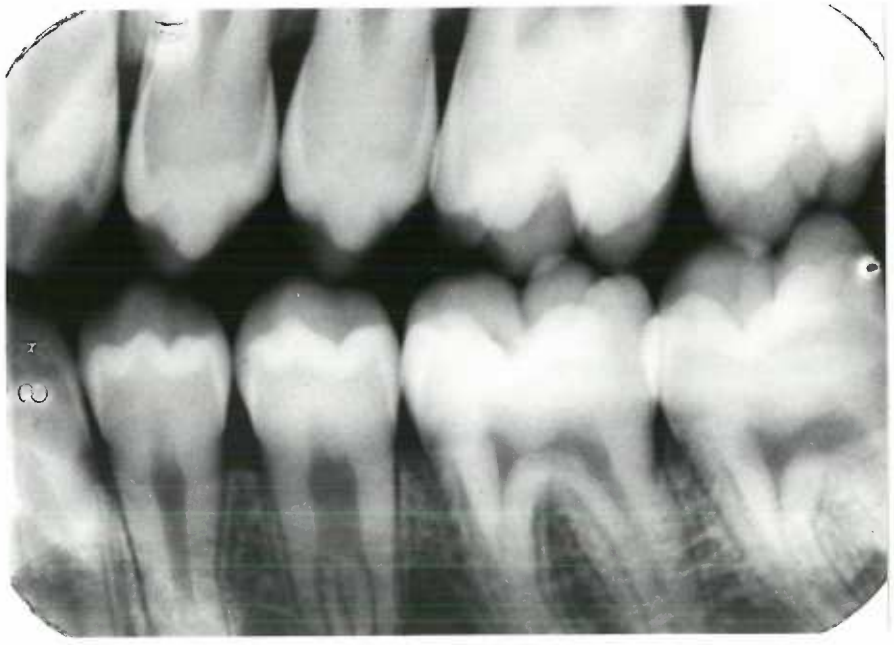


Fig. 24. Patient 4. Age fourteen years, bitewing radiograph shows no alveolar bone loss.

A bone marrow aspiration, taken at age 7, confirmed suspected abnormalities. The predominant cell was the promonocyte. Many monocytes and mature lymphocytes were present.

A differential WBC taken at 8 years of age is somewhat characteristic:

PMN..... 5%	Eos.....2%
Lymphos.....50%	Baso.....2%
Monos.....41%	

The patient has been diagnosed as having congenital neutropenia.

Dental Findings

The patient's dental history is essentially one of severe periodontal disease with alveolar bone loss. By the age of 7½, #K, #M, #T, and #I had been previously extracted. #19 was extracted at age 9 years, 11 months, with antibiotic coverage. She is currently participating in an accelerated (monthly) recall program at a local periodontist's office. She has also been seen in the graduate periodontics program at the University of Oregon Dental School.

At the time of examination, all primary teeth had been extracted or shed, except the upper primary cuspids which were mobile and near exfoliation. The remaining permanent teeth in the upper arch were present. In the lower arch, the bicuspids were unerupted.

Generally, pocket depth was 2-3mm. 4mm pockets were probed on #8, #12, #14, and #31. Tooth #30 was somewhat mobile (Class 2). Gingival tissue was red, smooth and shiny,

especially in the molar region where areas of desquamation were observed distal to #14 and on tissue buccal to #30.

Extra oral findings were negative except for a recently healed boil on the right ear.

Patient #6.

The patient, a nearly 11-year-old, white male is well-known in the Myelomeningocele Clinic at the Child Development and Rehabilitation Center and also at the UOHSC. Despite a very extensive medical record which includes myelomeningocele, mild paraplegia, neurogenic bladder, neurogenic bowel and neutropenia (impression: chronic benign; cyclic not R/O), he enjoys relatively good health. He has not had a history of serious infection. Pertinent history includes frequent otitis media in infancy, right cervical neck mass (1976), bacteruria (1976-78) and pharyngitis (1979). There is no history of pneumonia or skin boils.

He has had several hospital admissions for operations:

1970 Rectal prolapse
1971 Rectal prolapse
1976 Right neck mass
1976 Leg tendon problems
1977 Leg tendon problems
1978 Bladder stones

The patient has been noted to have recurrent neutropenia in the past. Absolute neutrophil counts range from 500-900 and 4-7% granulocytes since at least age 5 months. One WBC count and ANC was normal making it difficult to rule out cyclic neutropenia. But because the patient is doing well, further testing has not been recommended. It has not yet been

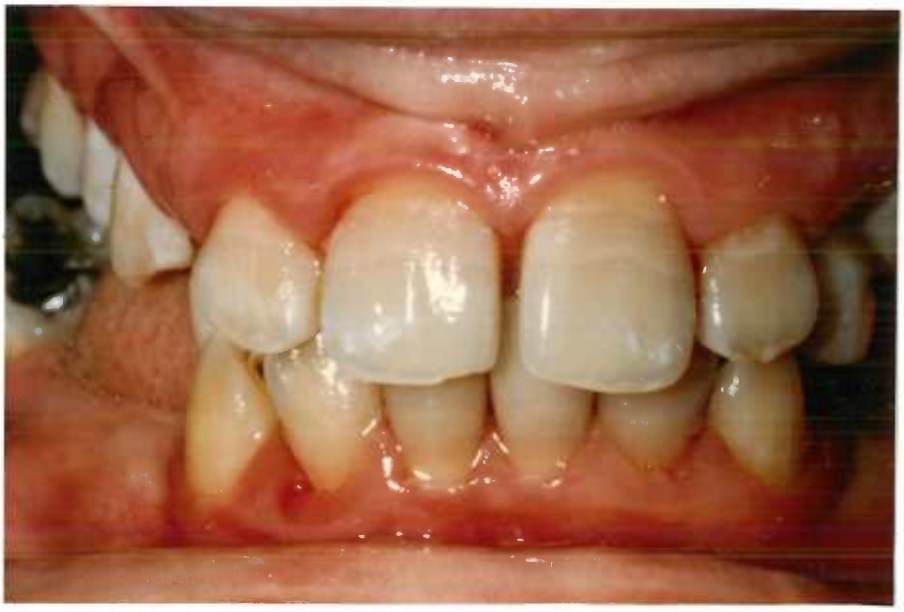


Fig. 25. Patient 5. Age ten years, frontal view shows red, smooth, shiny gingival tissue, early loss of teeth.

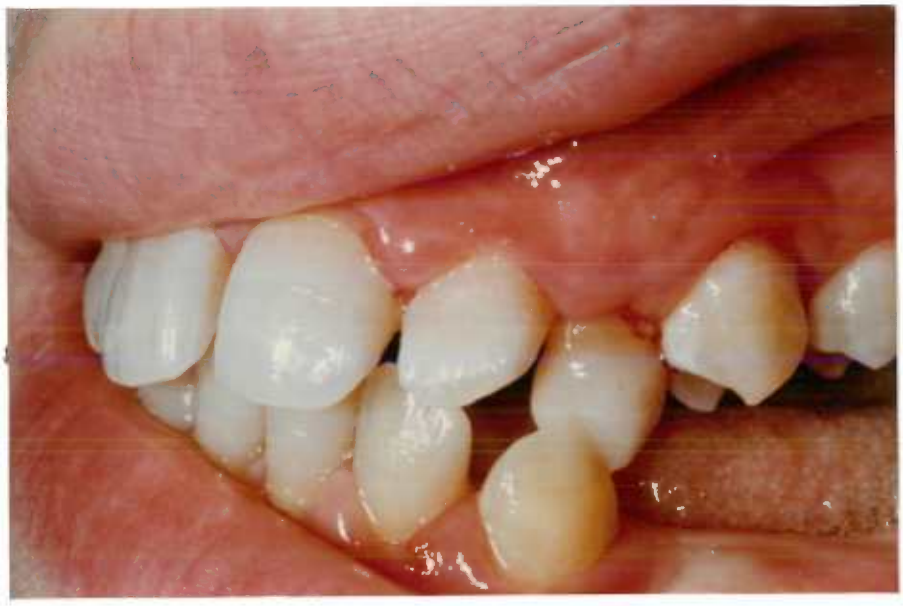


Fig. 26. Patient 5. Age ten years, left side view shows red, smooth, shiny gingival tissue, early loss of primary molars.

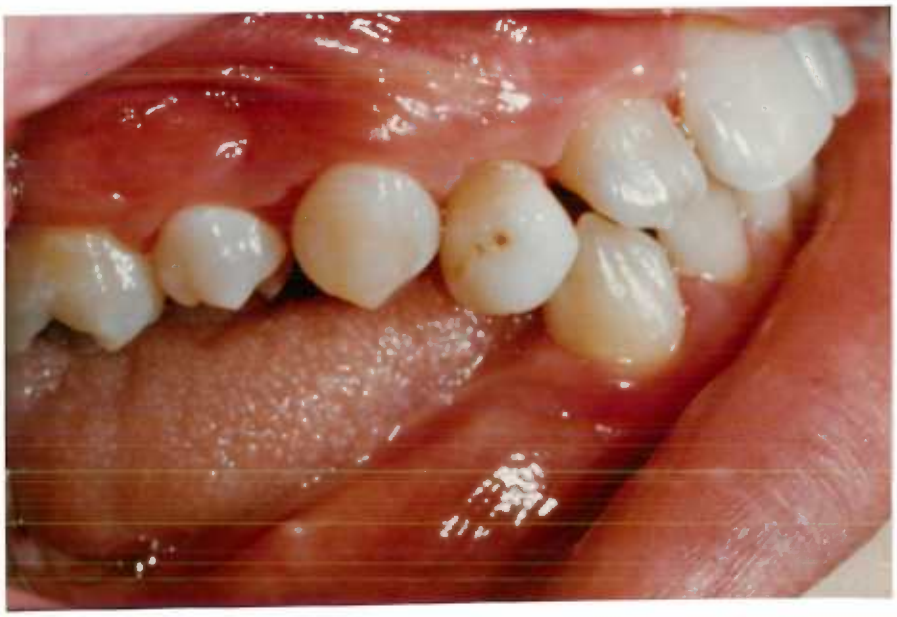


Fig. 27. Patient 5. Age ten years, right side view shows red, smooth, shiny gingival tissue, early loss of primary molars, lower first permanent molar.

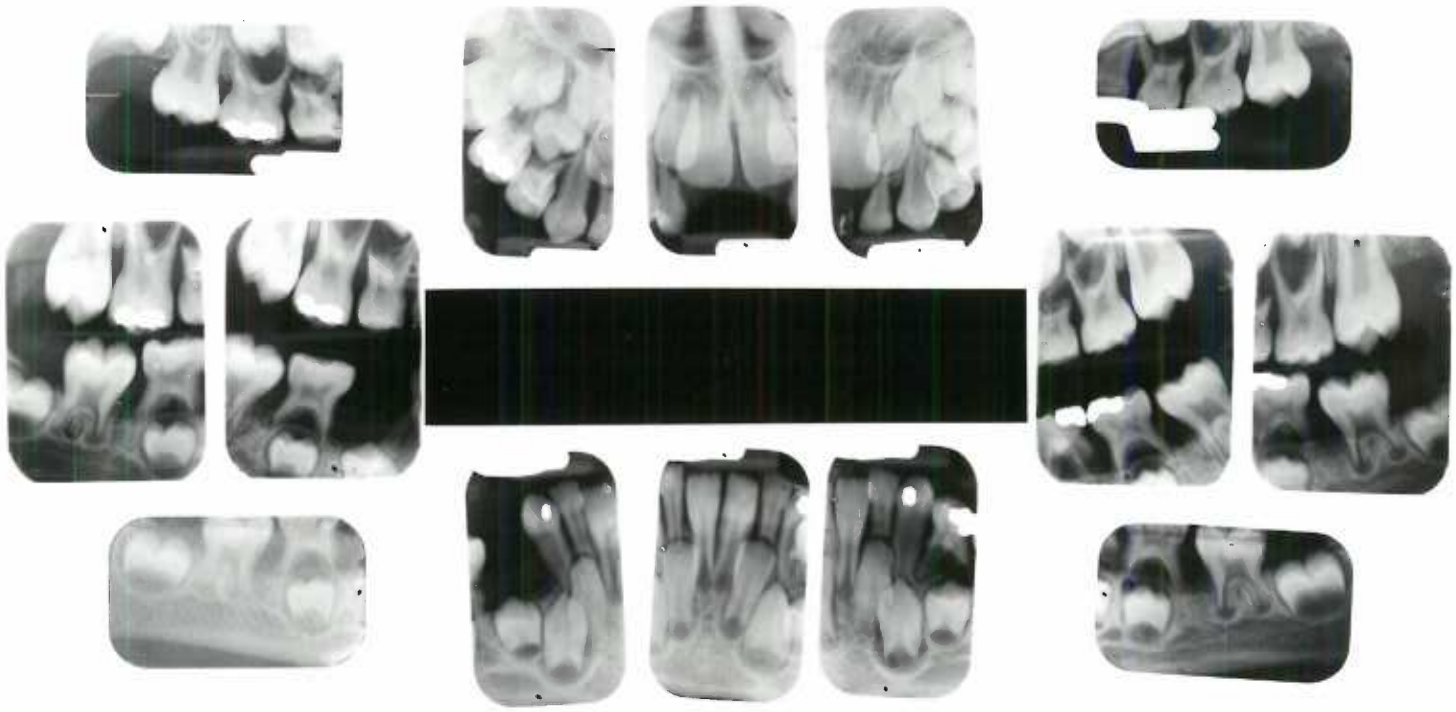


Fig. 28. Patient 5. Age six years, panoramic radiograph shows severe alveolar bone loss in the molar region.

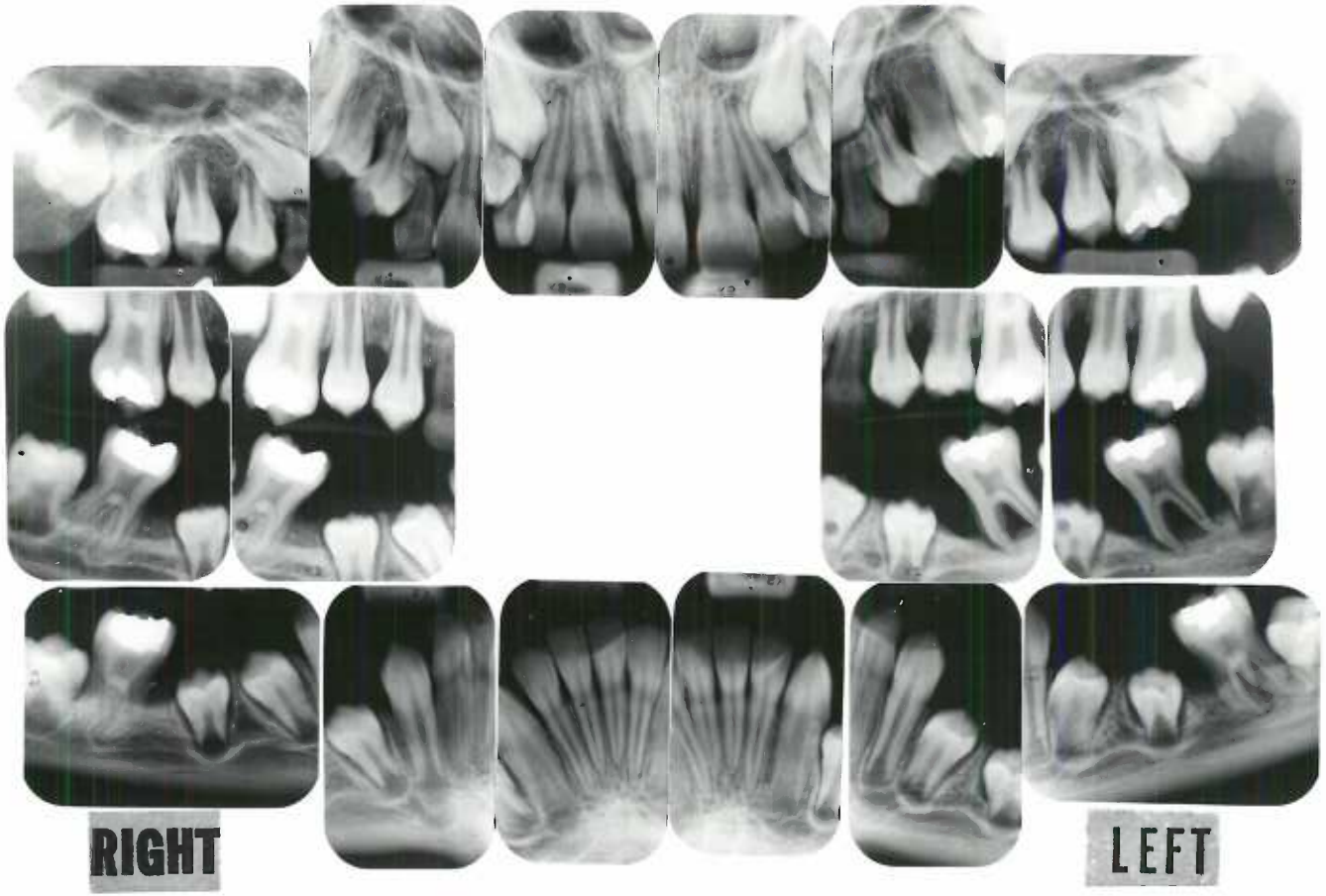


Fig. 29. Patient 5. Age ten years, panoramic radiograph shows inconsistent pattern of alveolar bone loss.

documented that he is at increased risk of infection when he is neutropenic.

A series of differential WBC counts taken in the fall of 1978 on four consecutive days was interesting because of the high degree of variability.

	9/22	9/23	9/24	9/25
PMN	12	47	30	32
Lymphos	43	16	31	35
Bands	27	19	30	20
Monos	15	16	5	13
Eos	0	0	1	0
Others	3	2	3	0

Dental Findings

The patient has been treated at a local dental clinic funded by the government. The hygenist at the clinic reported that he has difficulty following direction and that his response to oral hygiene instruction has been limited.

The stage of development was late mixed dentition with a Class II occlusal relationship. Attached gingiva was red, smooth, and shiny. There was no evidence of the severe periodontal disease seen in some patients. Dental restorations were noted on the first permanent and second primary molars. Plaque accumulation was moderate. There were no soft tissue lesions.

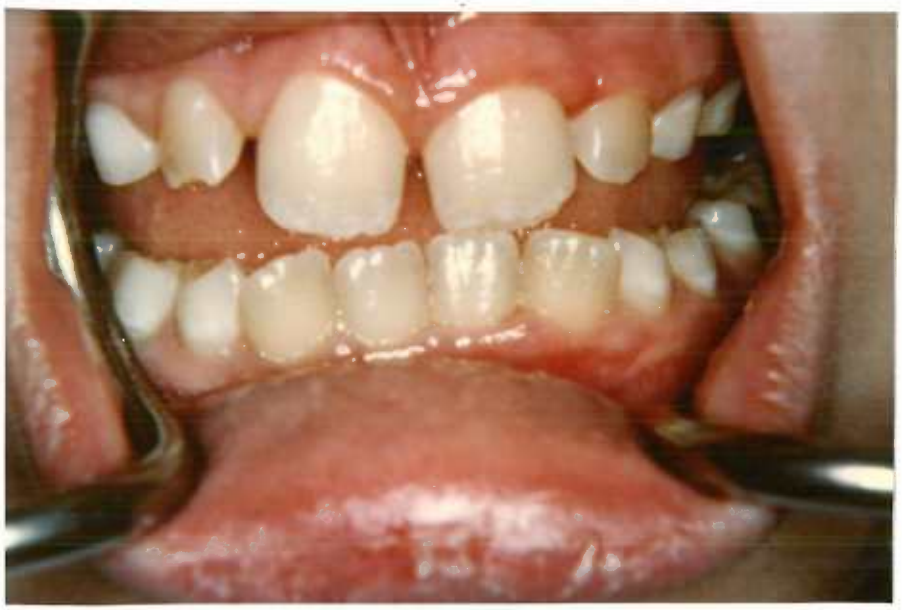


Fig. 30. Patient 6. Age ten years, frontal view shows red, smooth, shiny gingival tissue, recently fractured lateral incisor.

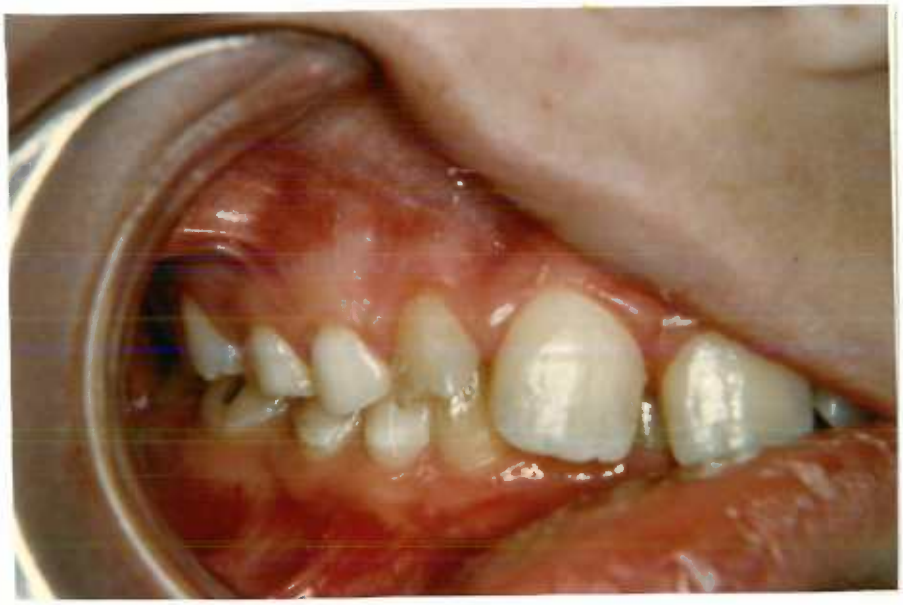


Fig. 31. Patient 6. Age ten years, right side view shows red, smooth, shiny gingival tissue.

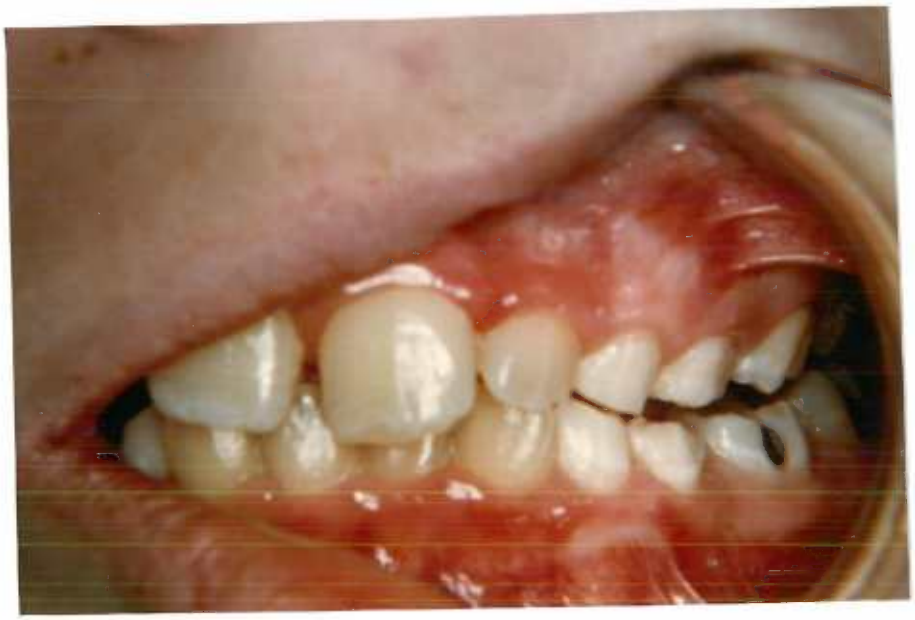


Fig. 32. Patient 6. Age ten years, left side view shows red, smooth, shiny gingival tissue.

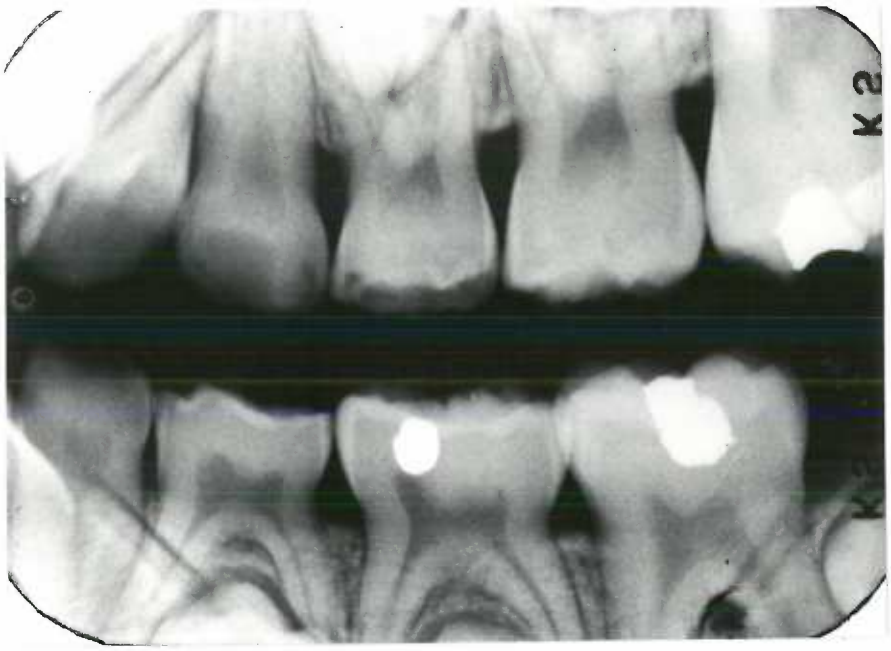


Fig. 33. Patient 6. Age ten years, bitewing radiograph shows lack of alveolar bone loss.

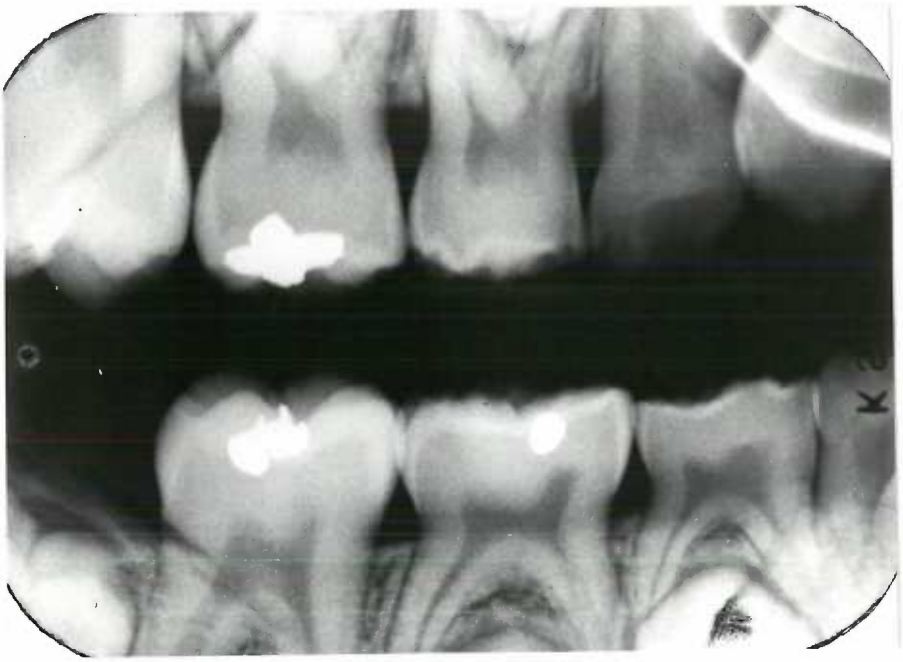


Fig. 34. Patient 6. Age ten years, bitewing radiograph shows lack of alveolar bone loss.

DISCUSSION

Severe periodontal disease does not occur in pre-pubertal children in the absence of systemic disease. Among these disorders are the neutropenias, hypophosphatasia, and syndromes associated with dermatologic disorders such as Papillon-Lefevre syndrome.

In hypophosphatasia, deficiencies in alkaline phosphatase result in cementum formation deficit and subsequent premature exfoliation of primary teeth.

The pathogenesis associated with Papillon-Lefevre syndrome is unknown. Characteristically severe periodontal disease is accompanied by hyperkeratosis of the palms of the hands and soles of the feet.[10]

It is imperative that the child with neutropenia receive adequate dental care. The following recommendations are reported in the literature or were suggested for patients in this study.

1. Consult with the appropriate medical authority.
2. Frequent professional visits for oral prophylaxis, home care monitoring and routine dental care.
3. Caries prevention program; i.e., oral hygiene instruction, dietary counseling and appropriate fluoride therapy.
4. Systemic antibiotic therapy (frequently Penicillin

or Erythromycin) to control oral infections. General experience indicates that chronic antibiotic therapy has not been very effective.

5. Antimicrobial and/or antifungal mouthwash may be helpful adjuncts to therapy.
6. Local palliative measures to alleviate the discomfort associated with oral lesions.

Chemical plaque control has been shown to be effective in preventing human gingivitis. Glyoxide rinses used twice daily was an integral part of periodontal therapy in Patient #2. A mouth rinse of 0.2% chlorhexidine gluconate solution used twice daily proved to be highly successful in a short-term study.[25] Although not approved by the FDA for use in this country, the rationale for its use in some neutropenic children may have merit.

1. Proven effective in plaque reduction.
2. Decreases gingivitis.
3. Is not associated with an increase in fungal infections.
4. Minimal sensitivities compared to antibiotic therapy.
5. Broad effect on bacteria and yeast.
6. Low toxicity.
7. Widely used in clinical medicine.[25,26]

The long-term effect on the microflora of the mouth has not yet been documented.

Several patients in this study had increased numbers of monocytes in their differential white blood cell counts. Kay

and his associates studied leucocyte function in a case of chronic benign neutropenia in an infant and found monocytes equal to PMNs in chemotaxis, phagocytosis and intracellular killing of S aureus.[27] Biggar studied the metabolism and function of monocytes in congenital neutropenia and suggests that:

1. Monocytes compensate for the lack of neutrophils.
2. There is a 2-4 hour delay in monocytic cell migration.
3. Bactericidal capacity of monocytes compared favorably with neutrophils.
4. Monocytes and neutrophils were similar in stimulation of oxygen consumption, hexosemonophosphate pathway activity, and iodide function during phagocytosis.[28]

The patients in this study had several characteristics in common. All had been diagnosed neutropenic (congenital, chronic benign). All had received chronic or intermittent antibiotic therapy, usually Penicillin. Bone marrow and differential white blood cell counts were abnormal. All had recurrent infections, frequently involving the skin and mouth. There were no familial similarities reported in any of the patients. During periods of infection, monocytes typically compensated for the patient's deficient neutrophils (well documented in #1, #2, #3, and #5). All patients had either gingivitis or moderate to severe periodontal disease. Oral hygiene was frequently disappointing.

SUMMARY

1. Neutropenia is a reduction in the number of circulating neutrophils (below 1500-2000/mm^3 in adults and older children; 1000/mm^3 in infants.
2. The classification of the neutropenias is somewhat arbitrary and ambiguous.
3. Clinical evaluation of the child should determine the severity of the neutropenia and whether it is chronic or cyclic.
4. A short review of neutrophil physiology is presented.
5. The host response in periodontal disease is reviewed.
6. There is no known means of influencing neutrophil counts and medical treatment is aimed at minimizing the consequences of repeated infections.
7. Severe periodontal disease in pre-pubertal children is generally associated with systemic disorders.
8. The oral manifestations of different types of neutropenias are discussed.
9. In the neutropenic child, the role of the dental practitioner is to prevent, control or minimize the consequences of periodontal disease and other oral infections. Six recommendations are presented.
10. Chlorhexidine mouth rinse may prove to be an adjunct to therapy in the neutropenic child. Long-term effects on the oral microflora are not known.
11. Monocytes partially compensate for deficient neutrophils in children with neutropenia.
12. Six case reports are presented.

BIBLIOGRAPHY

1. Miller, D. R. and Pearson, H.A. Smith's Blood Diseases of Infancy and Childhood, St. Louis, The C. V. Mosley Co., 1978, pp. 502-513.

2. Conn, Howard F. Current Therapy 1980, Philadelphia, W. B. Saunders Co., 1980, pp. 259-61.

3. Shafer, William Jr., et al. Text Book of Oral Pathology, Philadelphia, W. B. Saunders Co., 1974, pp. 677-82.

4. Rudolf, Abraham M. Pediatrics, ed 16, Appleton-Century Crafts, 1977, pp. 306, 323, 943, 1129, 1176-82.

5. Nelson, W., Vaughan, V. and McKay, J. Textbook of Pediatrics, ed. 10., 1975, pp. 1138-43, 480-81, 1110.

6. Kauder, E. and Mauer, A. Neutropenias of Childhood, Medical Progress, July 1966, 69:147-157.

7. Cline, Martin J. The White Cell, Cambridge, Mass., Harvard University Press, 1975, 1, 2, 3, 4, 5, 8, 9.

8. Golde, David W. and Cline, Martin J. Regulation of Granulopoesis, N. Eng. J. Med., Dec. 26, 1974, 291:1388-1395.

9. Corranza, Fermin Jr. Glickman's Clinical Periodontology, Philadelphia, W. B. Saunders Co., 1979, pp. 354-73.

10. Ranney, R. R., et al. Pathogenesis of gingivitis and periodontal disease in children and young adults, Pediatric Dentistry, May 1981, 3:89-97.

11. Baer, P.N. and Benjamin, S. O. Periodontal Disease in Children and Adolescents, ed. 1, Philadelphia, J. B. Lippincott Co., 1974, pp. 183-86.

12. Gellis, Sydney S. and Kagan, Benjamin M. Current Pediatric Therapy, Philadelphia, W. B. Saunders Co., 1980, pp. 264-69.

13. Rappeport, J., et al. Correction of infantile agranulocytosis (Kostmann's Syndrome) by allogenic bone marrow transplantation, Am J Med, 1980, Apr. 1968, 4:605-9.

14. Greco, F. A. and Brereton, H. D. Effect of lithium carbonate on neutropenia caused by chemotherapy: a preliminary clinical trial, Oncology, 1977, 34(4):153-5.

15. Thompson, R. B. Disorders of the Blood, A Textbook of Clinical Heamatology, Edinburgh, Churchill Livingstone, 1977, pp. 458-61.

16. Meisler, A. Lithium carbonate in chemotherapy induced neutropenia (letter), N Eng J Med, Nov. 24, 1977, 297(21): 1179-80.

17. Reichart, P. A. and Dornow, H. Gingivoperiodontal manifestations in chronic benign neutropenia, J Clin Perio, Feb. 1978, 5(1):74-80.

18. deGruchy, G. C. Clinical Haematology in Medical Practice, Oxford, Blackwell Scientific Publications, 1978, pp. 404-420.

19. Binon, Paul and Dykema, Roland. Rehabilitative management of cyclic neutropenia, J Pros Dent, 1974, 31:52-60.

20. Cohen, M. M. and Morris, A. L. Periodontal manifestations of cyclic neutropenia. J Periodontol, 1961, 32:159.

21. Mishkin, D. J., et al. Congenital neutropenia: Report of a Case and a Biorational for Dental Management, Oral Surg, Dec. 1976, 42(6):738-45.

22. Goldman, H. Periodontal Therapy, ed 6, St. Louis, C. V. Mosby Co., 1980, pp. 283-4, 166-7.

23. Dignan, E. J. Infected oral lesions of cyclic neutropenia, J Oral Med, Jan.-Mar. 1973, 28:29-31.

24. Garfunkel, A. A., et al. Local therapeutic approach to agranulocytic oral ulcers, Pharmacol Ther Dent, 1979, 4(1):21-5.

25. Loë, H. and Rindom-Schiott, C. The effect of mouth rinses and topical application of chlorhexadine on the development of dental plaque and gingivitis in man, J Periodontal Res, 1970, 5:79-83.

26. Rylander, H. and Ericsson, I. Manifestations and treatment of periodontal disease in a patient suffering from cyclic neutropenia, J Clin Perio, Apr. 1981, 8:77-87.

27. Kay, A. B., et al. Leukocyte function in a case of chronic benign neutropenia of infancy associated with circulatory leucoagglutinins, Br J of Haematology, 1976, 32:451-457.

28. Biggar, W. D., et al. Metabolic and functional studies of monocytes in congenital neutropenia, Br J of Haematology, 1974, 28:233-243.