Part 2. DEFINITION and CLASSIFICATION.

Necrotizing ulcerative gingivitis (NUG) is the most commonly occurring form of acute gingival disease. It is characterized by gingival inflammation, and destruction by ulceration and necrosis of the interdental, papillary, and in some cases the marginal gingiva.

Cawson [99] classifies NUG as a true gingivitis, on the grounds that it appears to be dependent for its development on the local gingival anatomy, and the balance existing in the local biological environment.

Although its precise aetiology and pathogenesis have still not been definitively determined, it is most frequently described as being an opportunistic endogenous infectious disease which is unlikely to develop unless environmental, i.e. host conditions, are favourable. [99, 100, 101, 102, 103]

Subacute and chronic forms of necrotizing ulcerative gingivitis are frequently described in the literature, although no histological evidence is offered to justify the use of these classifications.

Grant et al. [104] comment that the terms subacute and chronic are a source of disagreement, and that they are not used to describe a particular type of inflammation, but as a clinical differentiation based on the severity, duration and onset of the disease. Although they contend that the classifications are primarily of academic importance, the misuse and misinterpretation of the various histological terms creates considerable difficulty in assessing the literature.

The term subacute inflammation is not universally accepted, but appears to mean a relatively mild and/or persistent form of acute inflammation. It could be interpreted as a stage transitional between acute and chronic, a delayed phase of the acute inflammatory response accompanied by increased mononuclear infiltration.

Wilhelm [105] defines it as an intermediate stage, lying somewhere between acute and chronic lesions in duration. Others [106] suggest that it appears to mean a mild acute inflammation, but that no exact definition is possible and that the term should be discarded.

In describing Infective Bacterial Endocarditis, Walter and Israel [107] comment that the use of the adjective subacute is meaningless, and that the condition should be described in terms of its causative organism. This approach is not applicable to NUG as the causative organism/s have yet to be identified, nor is it yet certain that the condition is primarily infectious.

Thomson and Cotton [108] describe one form of subacute inflammation which is characteristic of the Fallopian tubes, and in which the predominant cellular component is the plasma cell, but state that subacute inflammation is otherwise ill defined.

When applied to NUG, the term, depending on the author, is used to describe the following clinical conditions:-

(a) ... Persistent mild forms of NUG. [109, 110]

(b) ... Continuations of the untreated incipient form. [111]

(c) ... Recurrent forms of acute NUG. [112]

(d) ... NUG in which the signs and symptoms are less severe than in acute forms. [113]

(e) ... A form with symptoms less pronounced than those of NUG, with only partial ulceration of the interdental papillae which are described as being enlarged and of a bluish red colour. [114]

The classification of chronic necrotizing ulcerative gingivitis is equally open to varied interpretations.

Acute inflammation refers to a response of rapid onset and of relatively short duration, accompanied by specific vascular and exudative phenomena (see Page 61). It has as a frequent sequel the resolution of the inflammatory process, and in some cases the restoration of normal structure and function. [115] Although this latter feature is less common in the gingival tissues, the characteristic lesion of NUG is the acute one. [103]

Inflammation is termed chronic when its duration is prolonged for months or years. It may occur as a sequel to acute inflammation, or arise de novo in response to low grade stimuli. Histologically the tissue response is a mixture of the vascular and exudative features of an acute inflammation, together with elements of regeneration and repair. Thus it may be described as a situation of frustrated healing. [115]

The cellular elements of the exudative component of chronic inflammation are predominantly lymphocytes, plasma cells and macrophages, while the features of repair are evidenced by the presence of granulation tissue containing fibroblasts and endothelial cells forming blood and lymphatic vessels. Thus the inflammatory and the healing processes proceed concurrently within the lesion.

The term chronic NUG is now discredited [116], possibly because of the lack of agreement on its supposed signs and symptoms. [113, 114, 117, 118, 119]

Pindborg [114] describes a situation where the gingiva is higher on the buccal and lingual surfaces than interdentally. Presuming that he is referring to the marginal gingiva, the description is of reverse gingival architecture which occurs as a consequence of extensive loss of the interdental tissue, and represents the residual deformity of cumulative

tissue destruction from recurrent NUG.

Jiménez and Baer [113] describe the formation of interdental craters, associated with radiographic evidence of loss of alveolar bone. This situation is more accurately described as recurrent necrotizing ulcerative gingivitis (RNUG) associated with chronic marginal periodontitis.

The description given by Burket [119] more correctly applies to chronic marginal gingivitis or periodontitis, and although he states that the chronic form of NUG is not readily diagnosed on clinical findings alone, he gives no guidelines for establishing the diagnosis. Perhaps this might be determined from the case history, which should reveal earlier acute episodes, but as Burket attempts to make further clear distinction between chronic NUG and recurrent NUG, this lack of definitive diagnostic criteria makes evaluation of his argument difficult.

The classification of chronic NUG is histologically unsupportable, as the features of chronic marginal gingivitis and periodontitis are indistinguishable from those which are attributed to so called chronic necrotizing ulcerative gingivitis. [103, 109, 112]

However, on the basis of the duration of the lesion, and evidence of persistent characteristic gingival deformities such as gingival craters and reverse gingival architecture, recurrent NUG may be regarded as a definite clinical entity. It is characterized by a history of periods of exacerbation and remission of NUG, accompanied by chronic destructive periodontal disease which is perpetuated by the morphological defects produced by earlier episodes. [102, 103, 120]

The term necrotizing ulcerative gingivitis will be used in this treatise to denote the acute specific gingival disease, as proposed in the Glossary of Terms of the American Academy of Periodontology. [121] Where necessary, additional descriptions will be used to describe the distribution, location, duration or severity of the lesions, or their recurrence.

PART 3.

DIAGNOSTIC CRITERIA AND CLINICAL FEATURES:

The diagnosis of the disease can only be based on an accurate assessment of the symptoms, and the clinical appearance, location and duration of the lesions. [99, 102, 109, 122]

In the absence of specific, definitive histological, serological or microbiological confirmatory tests, the lack of agreement in the literature on the characteristic signs and symptoms of the disease creates a problem in diagnosis. Those criteria most frequently applied in establishing the diagnosis are not by themselves strictly pathognomic, and the possibility of misdiagnosis is frequently raised. [116, 122, 123, 124, 125, 126]

The most significant and consistent diagnostic criteria are:

(a) ... Bleeding and pain in the involved areas.

(b) ... The presence of interproximal necrosis and ulceration.

(c) ... A history of acute onset.

(d) ... In affluent societies, the disease is primarily one of young adults.

To these may be added the very frequent presence of a slough or pseudomembrane overlying the ulcerated tissues, and the development of halitosis in the later stages of the disease.

Bleeding and pain.

Barnes et al.[123] concluded that gingival bleeding on manipulation was the most consistently observed sign; it occurred in 95.5% of the cases studied. This finding is universally supported by other reports in the literature [112, 118, 122, 127, 128, 129], some of which draw attention to the fact that haemorrhage may be spontaneous. [103, 120, 124, 130]

The suggestion by Burket [119] that blood on the pillowcase may be the first sign of the disease in children is suspect. He describes lesions which may affect not only the gingiva but also the tongue, palate and pharynx. Since NUG is an extremely uncommon finding in children in affluent societies [112], the condition he describes may have been primary herpetic gingivostomatitis.

One study concluded that the haemorrhage was not necessarily profuse or spontaneous. [123] Some 40% of the patients had only slight bleeding on manipulation, and 46% had moderate bleeding. (Table 7).

Such estimates of the severity of the haemorrhage are necessarily subjective. They may be influenced by the method of examination, the extent and location of the ulceration, or the presence or absence of a pseudomembrane [124] which may protect the underlying corium. (Plates 3 and 4).

Pain.

Pain is an important diagnostic feature, as it is an uncommon finding in the more commonly encountered forms of chronic gingival and periodontal disease. Most reports state that pain is almost invariably present in NUG. [99, 102, 112, 129, 130] Some stress that in early or mild cases it may only be noticed when elicited by minor trauma such as pressure, toothbrushing or probing. [100, 122, 123, 127]

Interpretation of the intensity of pain is subjective, and descriptions of its nature and intensity are difficult to compare. Such descriptions could also be expected to vary with the severity and the distribution of the lesions, and the age of the patient.

TABLE 7.
Signs and symptoms in patients with acute necrotizing ulcerative gingivitis and in control patients*

Signs and symptoms	*ANUG subjects*		*Control patients*	
	Number	*Percentage*	*Number*	*Percentage*
Total cases observed	218	100.0%	108	100.0%
Gingival bleeding	208	95.5	51	47.2
(Profuse)	(20)	(9.2)	(0)	(0.0)
(Moderate)	(100)	(45.9)	(9)	(8.3)
(Slight)	(88)	(40.4)	(42)	(38.9)
No bleeding	10	4.5	57	52.8
Blunting of papilla	205	94.0	46	42.3
Pain	188	86.2	22	20.4
(Severe)	(31)	(14.2)	(0)	(0.0)
(Moderate)	(69)	(31.6)	(0)	(0.0)
(Mild)	(88)	(40.4)	(22)	(20.4)
No pain	30	13.8	86	79.6
Fetid odor	184	84.4	17	15.3
Cratering of papilla	174	79.8	13	11.9
Pseudomembrane	160	73.4	2	1.7
Wooden or wedge-like sensation of the teeth	88	40.4	0	0.0
Bad taste in mouth	87	39.9	0	0.0

From: Barnes, G.P. Bowles. W.F. and Carter. H.G.

Acute Necrotizing Ulcerative Gingivitis:

A Survey of 218 Cases. J.Periodontol. 44:1 . 35-42.

Jan. 1973.

PLATE 3. Necrotizing ulcerative gingivitis. Extensive marginal and papillary ulceration. Note presence of pseudomembrane.

PLATE 4. (Author's collection). Necrotizing ulcerative gingivitis during abstinence syndrome due to withdrawal from hallucinogenic drugs and sexual dependency crisis. Patient mentally retarded and emotionally disturbed. Pseudomembrane overlying tips of interdental papillae.

Stammers [131] stated that in his cases the most serious symptom was intense pain causing lack of sleep. His study was undertaken in pseudoepidemic conditions in wartime, and the presenting lesions were frequently severe and not necessarily limited to the gingiva.

Goldberg [126] attached particular significance to the presence of constant, radiating gnawing pain. Glickman [109] gives a similar description, and adds that the lesions are extremely sensitive to touch. Both stress that the pain may be intensified by hot or spicy foods. Burket [119] states that the pain is severe and burning, and occurs at the slightest pressure. Another description is of a superficial "pressure type" of pain. [112]

Pain may be sufficiently severe to interfere with mastication or toothbrushing [104], but it may be absent during the early stages, unless elicited by probing the affected areas.

Barnes et al. [123] concluded that pain was by far the most consistent symptom in NUG patients. It was reported in 96.2% of cases, and its intensity was rated as mild by 40.4%, moderate by 31.6% and severe by only 14.2%. (Table 7).

No attempt was made to actually elicit pain by probing the lesions. Had this been done the proportion of positive findings may have been even higher. [116]

Schluger et al. [116] stress the exaggeration of the pain response, but state that it is dull and endurable. Most of their cases appear to have been mild and localized.

Interproximal necrosis and ulceration.

Historically, John Hunter (1778) is credited with the first description of NUG as a necrotic, ulcerative lesion of the interdental gingiva. [132]

Most clinical descriptions stress the presence of interproximal cratering, necrosis or ulceration as a primary diagnostic feature. [99, 101, 103, 104, 116, 118, 120, 122, 123, 127, 129]

One recent large survey described necrosis and ulceration, with resultant blunting and cratering of the interdental papillae. [123] Similar cratering was an uncommon finding in control patients. [123]

Blunting of the papillae occurred in 94% of the NUG subjects, and cratering was noted in 80%. It was concluded that those few cases in which these features were not observed may have been incipient forms of the disease. [123] This would be in keeping with histological observations that the initial lesion is located within the deep interdental tissues of the col region, rather than at the tip or on the external surface of the interdental papilla. [133, 134] At this stage, prior to ulceration and sloughing, the clinical appearance of the papillary gingiva is one of acute inflammation, swelling and erythema. [103, 116, 123]

There is considerable variation in the extent and severity of gingival involvement. The lesion may remain localized to a single interdental papilla [103, 122, 135], although the distribution is usually more generalized [126] and may eventually involve the whole mouth. [120, 123]

One study indicated that although the symptoms of NUG do not usually involve the whole mouth, 22% of 218 cases presented with lesions in all four quadrants. [123] Those regions most frequently affected are the mandibular and maxillary anterior areas [120, 123, 125, 131, 136], with the mandibular molar area being least often affected. [123]

Subsequent extension of the lesions to involve the marginal [122, 123, 124, 126] and even the attached gingiva [122, 137] is described. Widespread involvement of the attached gingiva or of the alveolar mucosa [100] is now regarded as infrequent, and the condition is today regarded as one of limited consequences unless the host is grossly debilitated. [116]

There are occasional reports of involvements of the palatal masticatory mucosa [129, 138], including the rugae and the palatal vault.

Some clinical descriptions continue to stress widespread extensions into marginal gingiva and alveolar mucosa, or faucial and pharyngeal extensions. [119, 139] The latter are more accurately described as necrotizing ulcerative stomatitis or mucositis. [140] Such descriptions are presumably based on the severe manifestations of the disease associated with gross debility [102, 127], or with its occurrence under wartime conditions of deprivation, monotonous diet, severe psychological stress, fatigue, poor hygiene and extremely heavy tobacco consumption. [99, 112, 131]

A distinction should therefore be made between descriptions based on the presenting lesions in the severely debilitated patient, and those in the otherwise well young adult in an affluent society in whom the disease now occurs most frequently. [103, 123, 130]

MacPhee et al. [100, 137] have proposed a classification of NUG lesions, based on two different clinical manifestations of ulceration:

(a) ... Deep Interpapillary Ulceration which involves the interdental tissues of the embrasure (col) region, and the tips of the interdental papillae. There is a minimal involvement of the lateral surface of the papillae and the gingival margins. This form

is stated to be the more common of the two, although both forms may be present in different areas of the same mouth.[100]

(b) ... Lateral Ulceration, characterized by necrosis of the external surfaces of the papillary and marginal gingiva. This form is stated to occur in those cases in which there is little evidence of predisposing periodontal disease. It results in a more superficial type of tissue destruction, with less risk of permanent gingival deformity if treated early.[100, 137]

The different distribution of the necrosis in these two forms of ulceration is attributed to differences in the sources and distribution of the major blood supply to these two regions of the gingiva.[100]

Acute Onset.

The sudden onset of NUG assists in differentiating it from most other forms of gingivitis.[101, 116]

Presenting symptoms are usually a short history of gingival bleeding and soreness of apparently sudden onset. [99, 103, 117, 118, 124, 127] There is no obvious prodromal stage.[141]

Seidberg[130] states that the onset is so sudden that the that the patient can frequently recall the date of appearance of the symptoms. Spouge[103] also comments on this sudden awareness of pain by the patient.

Age of onset.

In North America[123, 124, 130], the United Kingdom[120, 142], Europe[127, 143] and Australia[141], the disease is primarily one affecting older adolescents and young adults, although it may occur in older persons. In these regions, the vast majority of patients

are from 15 to 30 years of age. [123, 142, 143, 144, 145, 146, 147]

One long term study recorded a maximum incidence in men 17 to 22 years old, and in women aged 16 to 17. [143] The age of high incidence in men extended over 11 years from 16 to 26 years of age, in women it extended only five years from 16 to 20. Maximum prevalence was stated to be approximately the same in both sexes, but more men were affected as their period of susceptibility persisted longer. The earlier peak incidence in women was attributed to systemic hormonal factors related to their earlier age of maturation. [143]

Although there are occasional exceptions [148], the disease is virtually never seen in younger children in these Western countries. [112, 143, 149]

One report draws attention to the fact that the incidence in non-Caucasian adults in these countries is considerably lower than in the adult Caucasian population. [123]

A high incidence of NUG has been reported in very young children in Africa [150, 151, 152], India [153, 154], and South America. [113] Its occurrence appears to be related to predisposing debilitating diseases, and to poor nutrition and hygiene associated with socio-economic deprivation. [150, 155, 156]

In one study on the treatment of NUG, Davies et al. [157] reported that of 15 African patients, 73% were aged 11 years or less, and nearly 50% were aged three years or less. No medical or nutritional history was given for these children.

Pindborg [154] found the incidence of NUG in South Indian children to be high; 58% of the patients studied were below 10 years

of age. Enwonwu [150] found a similarly high incidence in grossly deprived Nigerian children, with peak incidence in the two to six year age group. This confirmed Malberger's [152] findings on the incidence of acute necrotizing oral diseases in Gambian children.

Emslie [158] reported that NUG affected children as young as 18 months old in Nigeria. He saw no case occurring in young adults, and its reported incidence in adults was rare.

Sheiham [151] confirmed that in Nigeria the disease was entirely confined to children aged two to 12 years. It was seldom seen in subjects over seven years of age, and that no case was seen in adults. He suggested that the severity of the attack in childhood might confer a form of immunity. [151]

The figures of the age of occurrence in deprived children are very similar to those reported for the occurrence of NUG in retarded individuals.

Brown [159] documented a high incidence of NUG in both non-mongoloid and particularly in mongoloid retarded patients. The youngest mongoloid affected was aged 2.3 years, and the youngest non-mongoloid five years.

Two other features which are of considerable importance are halitosis and the presence of a pseudomembrane.

Halitosis.

This is frequently described as a characteristic finding in NUG [103, 109, 118, 131, 160], considered by some to be a diagnostic feature of major importance. [119, 124, 125]

Halitosis is accentuated in tissue degenerative conditions, due to the release of volatile compounds as a result of proteolysis. An extremely objectionable form may be related to food avoidance. [161]

Both these conditions may be present in NUG, but also occur in other circumstances.

Prichard [162] describes a typical necrotic odour, which he states frequently enables a diagnosis to be established before the mouth is examined. Others also state that the odour is typical [112, 117], or that it is present in all cases and is the most frequent of all diagnostic findings. [136]

Barnes et al. [123] observed halitosis in 84.4% of the NUG patients in their study. It was noted five times more frequently in NUG patients than in controls (Table 7), but was believed to be a consequence of poor oral hygiene in the affected area. Most importantly, they commented on the existence of a similar relationship between halitosis and poor oral hygiene in control patients. [123]

Manson [120] states that there may be a necrotic odour, but that it is not always present, nor is it characteristic of NUG.

Jiménez and Baer [113] described NUG in deprived South American children with poor oral hygiene, but observed the presence of halitosis in only 50% of cases (Table 8).

Collins [163] states that NUG may occur in two forms. In one, there is an abundance of fusospirochaetal organisms accompanied by halitosis; in the other vibrios predominate and there is no offensive odour. No documentation is provided, but the suggestion is made that the presence of halitosis should not be regarded as a requirement for a positive diagnosis.

Although a necrotic odour may be present, it is not necessarily characteristic of NUG, but is merely a sign of the presence of oral infection, or of necrotic tissue. [100, 122]

Halitosis may ultimately be present in all but the mildest of cases.[112, 128] It correlates with the duration of the lesion, the amount of haemorrhage and tissue destruction, and the state of oral hygiene which existed in the period preceding the examination.[116, 122, 123]

This halitosis is not necessarily pathognomic, nor characteristic of NUG[100, 120, 122, 123], and should never by itself be considered a definitive diagnostic sign.[122, 164] It may in some cases be altogether absent.[104, 113, 122]

TABLE 8 *Signs and Symptoms in 28 Children Affected by NUG Seen at the University of Antioquia School of Dentistry, Medellin, Colombia, South America*

Signs and Symptoms		Frequency	Total
Temperature	More than 99.5	19	
	Less than 99.5	3	
	Undetermined	6	28
Lymphadenopathies	Submaxillary	16	
	Submaxillary and cervicals	6	
	Absent	1	
	Undetermined	5	28
Sialorrea	Present	12	
	Absent	12	
	Undetermined	4	28
Halitosis	Present	14	
	Absent	11	
	Undetermined	3	28
Pain	Present	15	
	Absent	10	
	Undetermined	3	28
Gingival bleeding	Present	27	
	Absent		
	Undetermined	1	28
Tooth mobility	Present	13	
	Absent	5	
	Undetermined	10	28

From: Jiménez. M.L. and Baer. P.N. Necrotizing Ulcerative Gingivitis in Children: A 9 Year Clinical Study. J. Periodontol. 46:12, 715-720, Dec. 1975.

Pseudomembrane.

Pseudomembranous inflammation is the response of mucous surfaces to necrotizing agents. Destruction of the surface epithelium by ulceration allows irritants to penetrate the corium, where they increase vascular permeability. Plasma subsequently exudes on to the eroded surface where it coagulates, enclosing necrotic epithelium, debris and microorganisms in a fibrinous meshwork. This coagulum constitutes the false membrane from which this form of acute inflammation derives its name.

One typical example is the pseudomembrane of diptheria, which carries particular risk of respiratory obstruction. [165]

The presence of necrotic material generally excites an acute inflammatory reaction in the surrounding tissues, a feature which is well marked in infarction. This feature is also noted in NUG as a linear erythematous margin surrounding the ulcerated areas. [104, 127, 148, 166]

Goldhaber and Giddon [122] considered the presence of an adherent greyish pseudomembrane to be a good indicator of the acute phase of the disease.

Fitch et al. [166] stated that the ulcerations are commonly covered by a pseudomembrane, surrounded by an erythematous border. Goldberg [126] regarded gingival craters covered by a grey pseudomembranous slough, and surrounded by a pronounced linear erythema as the characteristic distinguishing lesion.

One study [123] reported the presence of a greyish white pseudomembrane in 73.4% of NUG cases. (Table 7). Its absence from the other subjects may have been accounted for by the fact that some incipient cases were included. In addition, this loosely adherent necrotic tissue is readily removed [103, 123], and may have been lost during

mastication or attempts at oral hygiene. The presence of pseudomembranous material was also reported in two control patients. This may have been due to misdiagnosis, or the presence of a similar appearing type of removable mucosal film.[123]

Thus the presence of a pseudomembrane may be regarded as a very frequent but somewhat inconsistent finding. Its removal exposes the painful underlying corium which has been denuded by the ulceration. (Plates 5 and 6).

Other clinical features are frequently described as being pathognomic or frequently encountered, but require very critical evaluation. They include lymphadenopathy, pyrexia, malaise (including anorexia, insomnia, tachycardia, mental depression, constipation, gastrointestinal disorders, headaches and restlessness), sialorrea, a wooden or wedge like feeling in the teeth, and a definite tendency for seasonal occurrence.

Unfortunately, many of these features continue to be described in the general literature, despite the fact that their significance is disputed by specific studies.

Although systemic manifestations may accompany NUG[167], some are readily explicable. Gastrointestinal symptoms could be attributed to the effects of swallowed blood and necrotic material. Pain could lead to food avoidance (misinterpreted as anorexia), and to restlessness or even insomnia.

Lymphadenopathy.

Since this feature may occur in many oral infections, it is not specific to NUG.[100] It is difficult to assess its significance, or the frequency with which it occurs in accurately diagnosed cases.

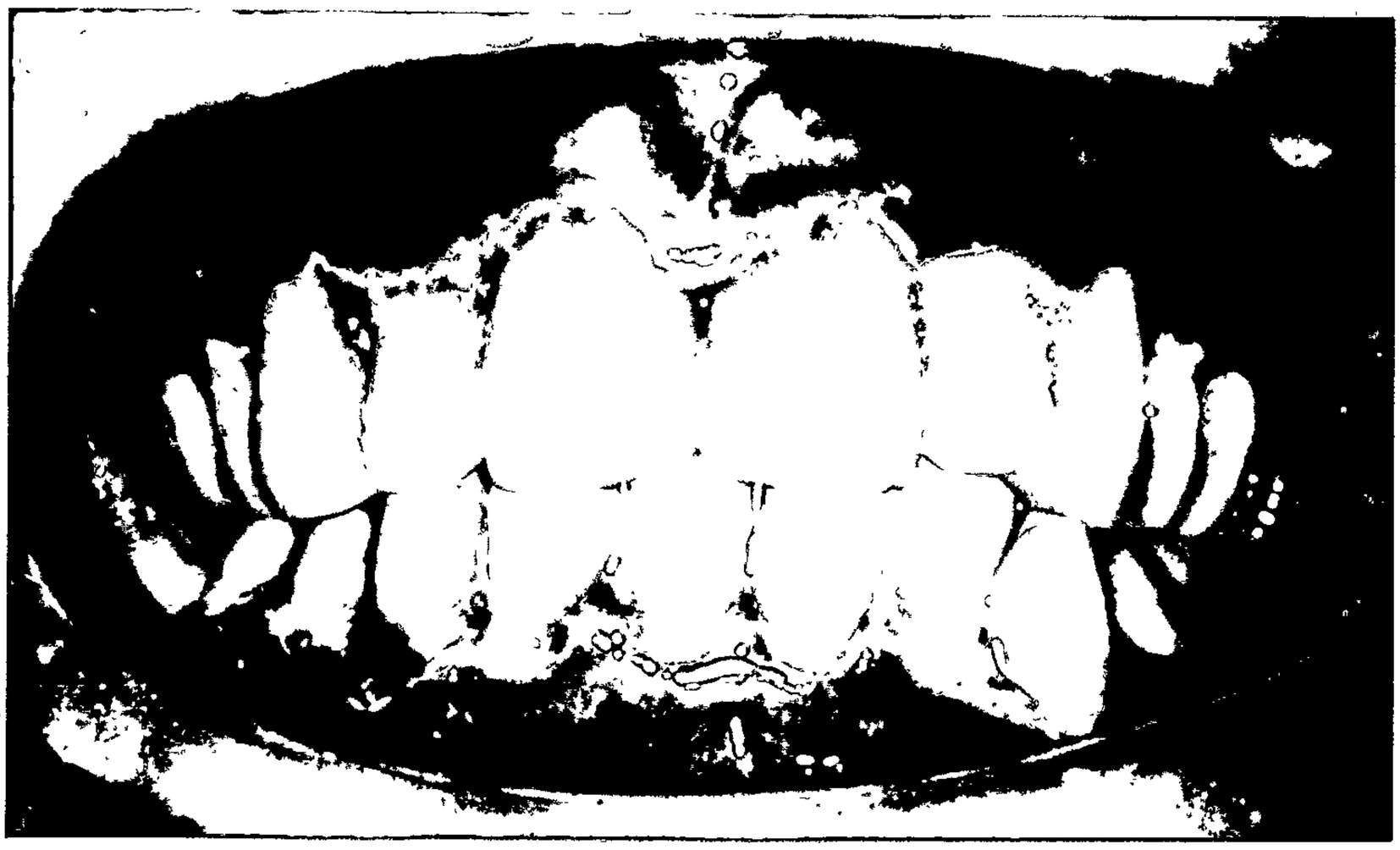


PLATE 5. Haemorrhagic corium exposed where pseudomembrane has been removed. Marginal and papillary involvement.

PLATE 6. Palatal papillary ulceration. Corium exposed after removal of pseudomembrane.

Many clinical descriptions list local submandibular or cervical lympadenitis as a common or routine finding.[109, 117, 124, 166] Others contend that it may occur, but usually only in severe advanced cases[99, 103, 122, 127] or as a consequence of simultaneous viral infection[120, 128] or secondary infection.[120]

Stammers[131] commented on the extreme variability in the incidence and severity of lymphadenopathy, and the lack of correlation with the apparent severity of the lesions. It was absent in some of the most severe cases, while others showed only mild enlargement or tenderness. Paradoxically, considerable pain and enlargement were reported in some cases of comparatively mild ulceration.[131]

Burket[119] stated that marked enlargement was an occasional finding, particularly in children. Although his diagnostic criteria are somewhat suspect, this contention is supported by the study of Jiménez and Baer[113], who found lymphadenopathy present in almost all of the children in whom they reported NUG. (Table 8).

While some report that the presence of lymphadenopathy is an infrequent occurrence[125, 128], the concensus of opinion is that, although not a notable feature, it is most likely to occur in severe cases.[122, 127, 164, 165, 168]

Pyrexia and malaise.

There is little justification for some descriptions of NUG to continue to list systemic manifestations such as pyrexia[124, 169, 170] and malaise[124, 166, 169] as classical features of the disease.

They appear to be only occasional findings, whose occurrence is usually limited to very severe or advanced cases.[102, 103, 119, 127, 168] The claim that the systemic condition can override the local oral condition cannot be substantiated.[171] When elevation of temperature

does occur it is usually only slight [101, 135, 164, 172], and rarely exceeds 101°F (38.3°C). [103]

As early as 1944, Stammers [131] observed that the highest temperature recorded in his study of 1017 cases was 100.1°F (37.8°C). Many of these cases were extremely severe, yet in the most severe instance, which was accompanied by stomatitis and palatopharyngitis, the temperature was only 98.8°F (37.1°C).

Other detailed studies support the view that pyrexia and malaise are neither common nor consistent findings in NUG. When they do occur they are not necessarily severe, nor is their severity related to that of the lesions.

Grupe and Wilder [128] found that pyrexia, malaise and lympadenitis occurred in only some 2% of their cases. When pyrexia was present the temperature was rarely elevated more than one degree above normal.

Some studies [101, 122] concluded that generalized malaise was rare, and that moderate to high temperature elevation was not a symptom of NUG. They quoted findings which indicated that a moderate decrease in oral temperature was equally likely to occur.

This finding is of interest, as bacterial endotoxin, as well as producing pyrexia, may also produce a subsequent hypothermia [173], and temperature fluctuations. [174] High local levels of endotoxin are a feature of NUG [175], and some of the apparent variations in temperature recordings might be explained in terms of varying degrees of endotoxaemia.

It is also possible that stress induced release of endogenous steroids may exert an antipyretic effect. [122]

Brown [159] commented on the absence of systemic manifestiations in his study on the occurrence of NUG in mentally retarded individuals.

Barnes et al.[123] concluded that NUG patients exhibited no consistent or frequent elevations of temperature, and that any elevation which occurred was likely to be only slight. Control patients were used in this study, and there were considerable similarities between the temperature ranges for NUG and control groups. (Table 9).

TABLE 9.
Temperature range of patients with acute necrotizing ulcerative gingivitis and control patients*

Temperature	*ANUG subjects*		*Control patients*	
	Number	*Percentage*	*Number*	*Percentage*
97°-98°	9	4.1%	5	4.6%
98°-99°	143	65.6	81	75.0
99°-100°	59	27.1	22	20.4
100°-101°	7	3.2	0	0.0
Total	218	100.0	108	100.0

*Based upon a sample of 108 military and dependent subjects of equivalent age, sex, and race who do not have ANUG.

From: Barnes, G.P. Bowles. W.F. and Carter. H.G. Acute Necrotizing Ulcerative Gingivitis: A Survey of 218 Cases. J. Periodontol. 44:1, 35-42, Jan. 1973.

Jiménez and Baer[113] recorded pyrexia in many of their child patients, again indicating that systemic manifestations, when they do occur, may be more severe in debilitated younger patients. (Table 8). It would be difficult to assess the degree of temperature elevation attributable to the NUG, and that arising from the intercurrent illness or debility.

Graphic descriptions of malaise and pyrexia, consistently accompanied by lymphadenitis, still appear in some recent literature[124, 170, 171] and may lead to misdiagnosis.[169]

The presence of malaise and of marked elevation of temperature suggest the strong possibility of misdiagnosis [116, 122, 126, 164], or of incomplete diagnosis of concurrent and possibly predisposing illness or infection. [120] In at least one study, the absence of pyrexia was used to confirm differential diagnosis of NUG from primary herpetic gingivostomatitis. [176]

Unpleasant or metallic taste sensations.

Although not a consistent finding [103], alterations to taste sensations may be reported by some patients. [119, 126, 166]

Seidberg [130] states that the metallic taste is due to the liberation of iron salts from the haemoglobin of haemorrhagic (sic) blood. Some correlation with the amount of haemorrhage and necrosis would appear reasonable.

An objective study which included incipient and mild cases concluded that 40% of NUG patients were aware of a bad taste. No control patients made this complaint. [123] The study concluded that alteration of taste sensation was a symptom of little value. (Table 7).

Another study recorded a 50% incidence of recorded awareness of unpleasant taste. [142]

Attempts to assess clinical improvement on the basis of subjective improvement of taste sensation have yielded conflicting results. Some state that there is rapid improvement [129], while others concluded that a bad taste, if present, tends to persist. [177]

The production of similar taste sensations is one of the reported side effects of metronidazole therapy. (See page 229)

Sialorrea.

There are some reports of increased salivation during NUG [117, 126], variously described as profuse [119], excessive [103] and thick or pasty. [109]

Klotz [124] alone considers sialorrea to be a main clinical feature.

The only objective study was performed on debilitated young South American children, and sialorrea was noted in less than 50% of these cases. [113] (Table 8).

MacPhee and Cowley [100] point out that increased salivary flow may occur not only in NUG, but as a general sign of oral infection.

Wooden or wedge like sensations.

Wedge like sensations in the interproximal regions, wooden feeling teeth, or a form of paraesthesia have been reported to occur in some patients having NUG. [104, 119] Glickman [109] states that wooden peg like sensation in the teeth is characteristic of NUG.

This finding may be accounted for by an acute inflammatory involvement of the marginal region of the periodontal ligament. [103]

The phenomenon appears to be restricted to NUG, and does not occur in control patients; its incidence is reportedly as low as 44%. [123] It should therefore not be regarded as a significant diagnostic feature, but rather as a corroborative finding.

Seasonal occurrence.

The possibility of seasonal occurrence is widely discussed in the literature, with complete lack of agreement on the season in which the peak is stated to occur.

Those objective studies which have been conducted have produced conflicting results [109], a situation which is little changed since commented on by Miller and Greene in 1958. [178]

A European study [143] reported three periods of peak incidence, September-October, January and June. There was frequent correlation between the onset of NUG and a history of recent upper respiratory tract infection, but the peak periods reported showed no correlation with weather conditions. [143]

Pindborg [179] stated that the peak incidence in his study occurred from August to October.

Peak incidence in the United Kingdom is variously reported as occurring in Spring and Autumn [120] and in Winter. [102, 180] In the United States it has been described as occurring in the Autumn. [181, 182]

One South American report stated that seasonal variation showed peaks in Spring and Autumn [136], i.e. at similar times to those claimed for regions with entirely different extremes of seasonal climatic changes. [103]

Enwonwu [150] observed no seasonal variation in the incidence of NUG in debilitated Nigerian children.

In the U.K. Nicol et al. [176] attempted to correlate the occurrence of NUG with seasonal variations in erythrocyte catalase levels. They observed that the occurrence of NUG was sporadic and showed no marked seasonal variation.

Several studies related peaks in the incidence of NUG to alterations in lifestyles due to factors such as vacations from college, army leave or induction for military service. [122, 123, 125] Others relate peak incidence to scholastic stress. [183, 184]

It may well be that the incidence in closed communities such as military or scholastic groups, shows peaks which are related to stress provoking environmental influences. The incidence in the general population may vary due to fluctuations in climatic conditions, such as the severity of climatic alterations between seasons. The latter could be

related to the severity and the incidence of upper respiratory tract infections.

Consideration should be given to the possibility that climatic or other changes might predispose to greater severity of the lesions. In other seasons, mild or incipient cases may remain undiagnosed, giving a false impression of lower overall incidence.

DIAGNOSIS.

Careful evaluation of the foregoing criteria should enable accurate establishment of the diagnosis in most cases.

It is however necessary to consider some conditions which may, in certain circumstances, be mistaken for NUG. In addition, the clinician must remain aware that NUG may occur superimposed on, or concurrently with, other diseases. These may have oral or systemic manifestations, or both.

Those cases which are accompanied by marked systemic manifestations pronounced pyrexia, or which do not respond promptly to accepted treatments, must be re-evaluated for both the accuracy and the completeness of the diagnosis. [102, 103]

Repeated inexplicable recurrences must also receive similar re-evaluation. [120]

Conditions which may resemble NUG.

Acute non-specific gingivitis may be bacterial in origin [100], or due to thermal, chemical or mechanical trauma. [120] The lesions are frequently localized, and are diagnosed by careful evaluation of the case history, or the presence of obvious exciting factors such as food impaction.

Erythema, oedema and haemorrhage may be present [100], and traumatic lesions may have ragged edges of loose necrotic tissue which may resemble

a pseudomembrane. [120] The lesions are not preferentially restricted to the interdental gingiva.

Acute "streptococcal" stomatitis is regarded by some as an extremely rare infection which may occur secondarily to viral infection, [120], with which its clinical features are very similar. [102] A localized form, restricted to the gingiva, is also described [102, 109], but may be misdiagnosed primary herpetic gingivostomatitis in either the incipient or healing stage. [149]

Beefy, diffuse erythematous gingival enlargement is described, accompanied by pain, pyrexia, lymphadenitis, [102, 109, 120] and possibly haemorrhage. [100] The lesions frequently involve attached gingiva and oral mucosa, are not accompanied by necrosis or ulceration, and show a predominance of streptococcal forms in bacteriological smears. [100, 102]

Pericoronitis.

It is possible that conflicting descriptions of the symptoms of NUG may be based on misdiagnosis of acute or chronic pericoronitis as localized acute or "subacute" NUG. It is also possible that unrecognized pericoronitis was present coincidentally with but independently of NUG, and that the clinical description represented a composite of the presenting symptoms.

Classical descriptions of the so called systemic signs of NUG including marked lymphadenitis, malaise and pyrexia, closely resemble the features of acute pericoronitis. [118, 185, 186] Traumatic ulceration of the operculum could readily be mistaken for the characteristic ulceration of NUG localized to that region. Retromolar slough [186] could be mistaken for a pseudomembrane.

The age of eruption of the third molars coincides with the age of peak susceptibility to NUG. Oral manifestations which may be common to both conditions are pain, sialorrea, halitosis, unpleasant taste

sensations, discolouration of the gingival tissues, inflammation, oedema and the accumulation of debris due to forced avoidance of oral hygiene.[120] Diagnosis is further complicated by the fact that both conditions will respond to similar forms of treatment, and that both have been described as showing seasonal peaks of incidence in Autumn and Spring.[120, 186]

Accurate differentiation is therefore of major importance in considering any possible relationship between the presence of pericoronal flaps and the presence of NUG. This topic has received almost no attention in the literature.

The considerable similarities between the clinical features of acute pericoronitis and NUG localized to the third molar region have been described; the following features are useful in distinguishing between them.

(a) ... Systemic manifestations such as marked pyrexia and lymphadenitis occur very frequently in pericoronitis, but are extremely inconsistent findings in NUG.

(b) ... Acute pericoronitis is frequently accompanied by frank suppuration, which is not a feature of NUG.[100, 185, 186]

(c) ... Haemorrhage, which is a characteristic finding in NUG is not a feature of pericoronitis.

(d) ... Trismus and facial oedema may occur in acute pericoronitis, but are not characteristic of NUG.[100, 118, 185]

(e) ... The major organism demonstrated in bacterial smears of pericoronitis is Streptococcus viridans.[166]

Primary herpetic gingivostomatitis (PHG) is the oral manifestation of initial infection with Herpesvirus hominis type 1.[100] Occasional infections with the type 2 virus are also described.[190]

It is the most frequently encountered oral vesiculo-bullous lesion, and occurs most frequently in children aged six months to five or six years.[124, 187] Younger infants are rarely affected as they derive passively acquired immunity from circulating maternal antibodies.[100, 124] Adult onset does occur[102, 124, 188], and may be confused with NUG. It is also possible for both conditions to occur simultaneously.[122, 128] Later onset occurs in communities of high socio-economic status.[99]

There is a prodromal stage of several days accompanied by malaise, pyrexia and lymphadenitis.[102, 148] The temperature may reach 40°C.[149] Severe oral discomfort begins during this stage and may be accompanied by food refusal in children.[149, 187]

At a later stage the gingivae become red and painful and may be considerably enlarged.[102] Other regions of the oral mucosa are also involved. Numerous small vesicles subsequently appear, which may involve masticatory, specialized and lining mucosa[100] and even facial skin.[149] Lesions may occur on the soft palate, sublingual mucosa, tongue and pharynx.[148]

These vesicles are rarely seen intact.[124, 189] They macerate within a matter of hours[100], leaving small painful shallow ulcers with a yellowish membranous base surrounded by a halo-like elevated erythematous margin.[162, 187] Where these ulcers involve keratinized epithelium, they may be surrounded by loose desquamated epithelial remnants which may be mistaken for a pseudomembrane.[124, 149] Haemorrhage is not as common as in NUG.[162] (Table 10).

TABLE 10

Differentiation between NUG and PHG

NUG	PHG
Probably opportunistic endogenous infection in a susceptible host.	Primary exogenous infection with Herpesvirus hominis.
Not communicable.	Communicable.
Lesions confined to interdental and marginal gingivae.	Lesions diffusely distributed to all oral mucosal surfaces.
Deep ulcerations.	Superficial discrete ulcers following vesicular stage.
High rate of recurrence. No immunity develops.	Non-recurring in this form. Some degree of immunity.
Variable systemic involvement, frequently none at all.	Marked and consistent systemic involvement.
No prodromal stage.	Definite prodromal stage.
Extremely rare in children.	Highest incidence in infancy and childhood.
Frequently produces persistent gingival deformity.	Self limiting, no residual deformities.
Responds rapidly to treatment.	Clinical course unaffected by treatment although symptoms relieved.
Indefinite duration.	Duration approximately 10 days.
Interdental haemorrhage common.	Haemorrhage relatively uncommon.
Biopsy reveals non-specific inflammation and ulceration.	Biopsy reveals Lipshütz inclusion bodies and ballooning degeneration of epithelial cells.

Fortuitous localization of the ulceration to the gingivae could lead to a mistaken disgnosis of NUG. [149] It must be stressed that necrosis is not a feature of these lesions, nor are they preferentially restricted to the interdental regions. [122, 124] Gingival erythema persists for some days after the ulcers have healed. [148]

Sialorrea is a common feature in children [120], and drooling of infected saliva may cause skin lesions.

Primary herpetic gingivostomatitis is a self limiting disease which runs a course of 10–14 days, leaving no residual deformities. [149] There may be concurrent conjunctivitis [100] or paronychia [100, 188, 189] due to contact with infected saliva.

Dehydration may become a serious problem in children, and encephalitis is an occasional very severe complication. [189]

The condition is communicable, and the case history may reveal recent contact with another infected person. [100, 124]

Acute Leukaemia. In acute monocytic leukaemia in particular, leukaemic infiltration produces gingival enlargement and may eventually result in ulceration. [109, 190] This enlargement is not confined to the interdental or marginal gingivae, nor is the ulceration, when it does occur, restricted to these regions. [99]

Systemic symptoms such as weakness, lymphadenopathy and pyrexia may overshadow the oral findings. [119, 190]

NUG may occur superimposed on tissues already conditioned by leukaemia. [103, 120] In these cases generalized discolouration and enlargement of the attached gingiva may indicate the underlying condition [109], as may the presence of mucosal pallor or petechial haemorrhages. [190] Haematological examination will establish the diagnosis.

Agranulocytosis may be accompanied by oral ulceration. These ulcers are stated to be isolated necrotic patches, well differentiated from adjacent unaffected tissues, covered with a dark pseudomembrane.

The lesions do not have an erythematous periphery, and there is little evidence of an acute inflammatory response due to the lack of polymorphonuclear neutrophils.[109, 140, 190]

These lesions are sometimes described as NUG superimposed on agranulocytosis [103, 104], although the presence of one condition would appear by definition to exclude the possibility of the other .

Haematological examination and a possible contributory history of drug ingestion will facilitate diagnosis.[190]

Gonococcal lesions may occur within the oral cavity, usually in association with stomatitis, tonsillitis or pharyngitis.[191, 192] A gingival form has been described in which necrotic interdental papillae are present, covered by a yellowish pseudomembrane which when removed reveals a bleeding surface.[109, 192]

As the incidence of oral venereal disease is increasing [191], the clinician should be aware of this form which in many respects mimics NUG. Particular care should be exercised with drug addicts in whom NUG and venereal diseases may occur concurrently.[193, 194]

Acute pseudomembranous candidiasis occurs in children and in debilitated adults.[102, 120]

The lesions may affect all oral mucosal surfaces. They consist of slightly elevated creamy patches which when removed leave an erythematous and possibly bleeding base.[111]

If confined to the gingiva, the lesions may initially be mistaken for NUG. They are however frequently painless [111], are not associated with ulceration, not limited to the interdental gingivae, and positively identified by the presence of abundant hyphae on microscopic examination. [102, 111]

Heavy metal poisoning may, in rare instances, condition the gingiva and allow the superimposition of NUG. [103, 195]

PART 4.

HISTOPATHOLOGY.

The histological appearance of the NUG lesion is one of superficial non-specific necrosis and acute inflammation. [99, 113, 170] It is similar to that which may be produced by mechanical trauma or by thermal or chemical injuries. [110]

Although traditionally described as arising at the tip of the interdental papilla, bucco-lingual sections of affected tissues show that the initial ulceration is located interproximally in the region of the col. [103, 133, 134]

There is extensive surface ulceration of the gingival epithelium, with variable involvement of the subjacent papillary layer of the connective tissue. The ulceration is covered by a meshwork variably composed of microorganisms, fibrinous exudate, necrotic and desquamated epithelial cells, cellular debris, leucocytes and extravasated erythrocytes. It is this material which appears clinically as the pseudomembranous slough. [185] The epithelium at the margin of the lesion shows varying degrees of oedema and hydropic degeneration, and numerous inflammatory cells are contained in the intercellular spaces. [113]

Beneath the ulcerated surface there is a marked, diffuse, oedematous inflammatory reaction of the connective tissue. Polymorphonuclear leucocytes predominate in the early stages of the disease, together with some macrophages. Although larger numbers of chronic inflammatory cells are present in the deeper layers of the corium, their presence is attributed to pre-existing chronic gingival inflammation. [196]

Blood vessels proliferate, and there is considerable

capillary dilatation and engorgement. Vascular thrombosis is a common finding and may result in ischaemic necrosis.[185] The hyperaemia is responsible for the clinical appearance of a linear erythema beneath the pseudomembrane, and haemorrhage results from rupture of the blood vessels.

There is a local decrease in the number of fibroblasts[185], and considerable disruption and lysis of the collagen fibres and ground substance of the gingival connective tissue[110], accompanied by oedema.

In the healing phase, unaffected epithelium from the margins of the lesion proliferates beneath the necrotic surface, to cover the denuded connective tissue.[110]

Ultrastructural studies have confirmed that spirochaetes, and possibly some fusiform organisms, are capable of invading the apparently normal connective tissue in advance of the necrotic lesion. They may also be found within the intercellular spaces of pre-necrotic epithelium adjacent to the ulcer.[197, 198]

The ultrastructural features of the NUG lesion are described on pages 192 to 195.

Part 5.

IMMUNOLOGICAL CONSIDERATIONS.

Attempts have been made to explain the aetiology and pathogenesis of necrotizing ulcerative gingivitis as immunological reactions. However, research to correlate immune responses to plaque antigens with periodontal status has yielded conflicting information concerning both cell mediated immune responses and serum antibody titres. [91, 199, 200]

The complexity of the oral flora, the possibility of cross reactivity [59, 200], and the lack of definitive information on the microbial population responsible for the production of the NUG lesion makes interpretation of the results of immunological studies highly speculative.

Smoking and the immune response.

Smoking is very frequently implicated either as an aetiological or a predisposing factor in NUG. (See pages 148–153) Cigarette smoke has a demonstrable immunosuppressive effect on both primary and secondary humoral responses in mice, which is considered similar to the response which occurs in humans. [201, 202, 203]

Toxic effects of tobacco smoke include the irreversible inhibition of both the locomotive and phagocytic functions of oral PMNs [204], and of other immunocompetent cells. [205] Progressive suppression of both IgG and IgM has been recorded *in vitro* [205], and *in vivo* humoral suppression has also been demonstrated in humans. [206]

Kenney et al.[204] harvested PMNs from the mouths of smokers and non-smokers, and tested them for their ability to phagocytose latex spheres, and to exclude trypan blue.

Their investigations showed:

(a) ... the PMNs of smokers had impaired phagocytic capabilities when compared to the PMNs of non-smokers.

(b) ... fewer PMNs from smokers were able to exclude trypan blue.

(c) ... impairment of PMN function in smokers tended to be chronic.

(d) ... smoking a single cigarette produced an acute impairment of PMN function in non-smokers which persisted for at least 24 hours.

Impairment of function was estimated to be 75%, accompanied by a 20% reduction in cell vitality.[204]

Decreased PMN phagocytic function could reduce gingival defence against bacterial challenge.[204] In addition, impaired vitality could result in more rapid degranulation, and increased release of lysozonal enzymes capable of causing tissue damage.

Both nicotine and the water soluble fraction of tobacco smoke have immunosuppressive properties which are rapid in onset

and appear to affect the induction of the antibody response rather than antibody synthesis per se.[205] One possible mechanism which is suggested is interference with macrophage function by depression of enzyme activity.

Schwartz[207] confirmed that nicotine can interfere with the endocytic and exocytic functions of macrophages, and drew attention to the possibility of interaction with other amines. This provides a possible mechanism for cumulative effects by both stress and smoking in causing immunosuppression, or for interaction between nicotine and vasoactive amines released during the initial inflammatory response.

A role for local immunosuppression capable of affecting the oral mucosa could be postulated from the finding of a negative correlation between smoking and recurrent aphthous ulceration[208, 209]. This lesion is now accepted as having an autoimmune component in its aetiology.[210, 211, 212]

Down's syndrome and the immune response.

Patients with Down's syndrome are highly susceptible to severe recurrent respiratory infections, and to the development of acute leukaemia. Both NUG and RNUG are far more common in these patients than in non-mongoloid retarded individuals or in normal patients.[159, 213] There is speculation that altered immune responses may underly all of these phenomena.

Khan et al.[214] demonstrated reduced chemotactic migration of leucocytes in patients with Down's syndrome when compared with normal controls. They suggested that increased susceptibility to infection in these patients reflects immunological abnormalities, but that the exact effect of these defects on the pathogenesis of

infection is not understood.

Scully [213] states that the predisposing factor in the susceptibility to infection of these patients is a deficiency in cell mediated immunity. The studies which he cites described partial leucocyte dysfunction against staphylococci in 16 out of 88 children with Down's syndrome [215], humoral changes which only occurred in adult patients [216], and an *in vitro* decrease in the phagocytic ability of polymorphonuclear leucocytes. [216]

Goodman [217] and Brown [159] concluded that investigations into possible changes in the immune system in mongoloids had proved either negative or at best controversial.

More recent evidence indicates that a congenital T-lymphocyte immunodeficiency is an integral feature of Down's syndrome. [218]

The role of food antigens.

Thomas *et al.* [219] investigated the incidence of serum antibodies against food antigens in patients with both aphthous and non-aphthous oral ulcerations, including NUG.

They demonstrated an abnormally high incidence of antibodies against milk antigens and other food proteins in the sera of patients having different types of oral ulcerations.

The production of the antibodies was not interpreted as evidence of primary hypersensitivity to food antigens. It was regarded as a consequence of immunization caused by increased absorption of antigenic food protein molecules, as a result of increased mucosal permeability arising secondarily to the ulcerations. [219]

Immunoglobulin investigations.

Lehner and Clarry [220] performed quantitative immunofluorescent investigations on sera obtained from patients with acute and recurrent NUG, and controls. They failed to demonstrate any significant rise in antibody titre against single strains of Borrelia vincentii, Fusiformis fusiformis (now known as Fusobacterium fusiforme), or Bacteriodes melaninogenicus. No rising antibody titre was demonstrated in the convalescent phase in the NUG patients.

No difference was established in the antibody titres when comparing NUG, RNUG and control patients, either to individual strains or in combined titres to all three organisms. The latter might have indicated the possibility of a synergistic effect.

It is possible that a basal level of serum antibody had previously been established by these commensal bacteria, but an anamnestic rise in the level would have been expected with the development of pathogenic behaviour.

The study did not support a primary pathogenic role for any of the three organisms studied in the aetiology of NUG, but did not exclude a secondary function. [220]

These findings should be interpreted with caution. Gilmour and Nisengard [200] subsequently stressed that antibody titres to a selected strain of microorganism cannot be considered as representative for the species, as synergism or inhibition may occur between intra-species strains.

In an attempt to determine aetiological factors and immune features, Lehner [221] investigated serum immunoglobulin patterns in patients with NUG, RNUG and controls.

He demonstrated an immunoglobulin pattern which he stated appeared to be specific to ulcerative gingivitis.

(a) Early in the course of NUG, serum IgG is significantly depressed. This is more marked in patients with RNUG, but the level rises to normal during the course of the disease.

(b) IgM is significantly raised in both NUG and RNUG, and this raised level is maintained.

(c) IgA is unchanged in NUG, but somewhat depressed in RNUG, rising again during convalescence. (Figure 19)

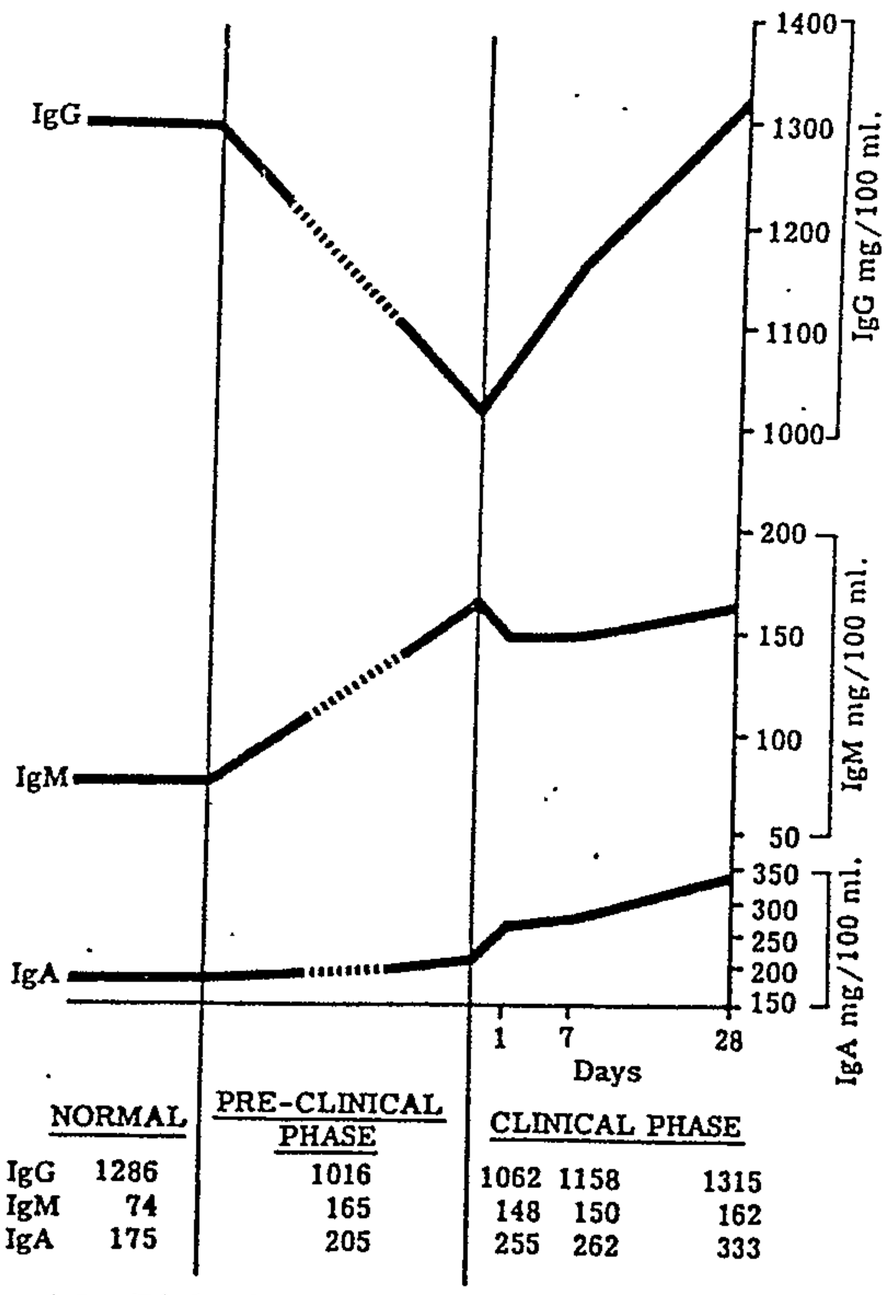


FIG. 19 –Biphasic immunoglobulin changes in acute ulcerative gingivitis.

From: Lehner. T. Immunoglobulin Abnormalities in Ulcerative Gingivitis. Br. Dent. J. 127:165–169, August, 1969

No significant changes were determined in C3 levels.

On the basis of these findings an immune hypothesis was proposed for the development of NUG. (Figure 20).

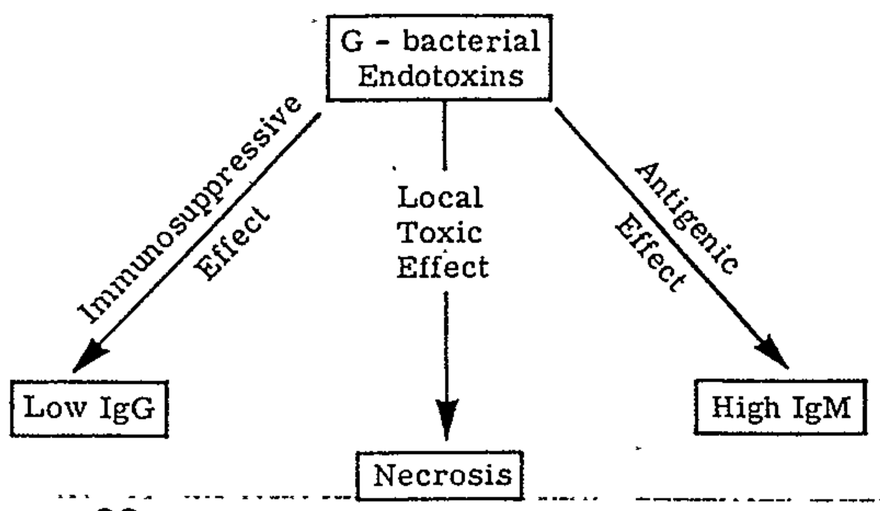


FIG. 20 -Immune hypothesis in ulcerative gingivitis.

From: Lehner, T. Immunoglobulin Abnormalities in Ulcerative Gingivitis. Brit. Dent. J. 127: 165-169, August 1969.

The lowered level of IgG was attributed either to a pre-existing idiopathic deficiency, which might also explain the high rate of reported recurrences [117], or to a selective immunosuppressive effect by bacterial endotoxin in the pre-clinical or early clinical stages of the disease. Consideration should now be given to considering the possible immunosuppressive effects of smoking; the study did not differentiate between smokers and non-smokers.

Raised levels of IgM were attributed either to the antigenic effects of Gram-negative organisms such as veillonella, fusobacteria, bacteriodes and spirochaetes, or to a possible response

to protozoal infection. The demonstration of large numbers of trichomonads and amoebae in smears of NUG material when viewed with phase contrast microscopy [133] could support this interpretation.

Subsequent rises to near normal levels of IgG during the convalescent phase were attributed to resolution of the disease and the cessation of endotoxin induced immunosuppression.

Lehner [221] considered that these findings constituted an immunoglobulin pattern unique to NUG. He suggested that the role of decreased host resistance could be in establishing the early manifestation of lowered IgG.

A similar pattern was subsequently demonstrated in the early stages of an acute clinical condition which had some features of infectious mononucleosis. [222]

A later study included both humoral and cellular immune responses, again in patients with NUG, RNUG and controls. [223]

Antibodies were found against bacterial antigens from Odontomyces (Actinomyces) viscosus, Fusobacterium fusiforme, Veillonella alcalescens and Bacteroides melaningenicus. The findings parallelled the earlier ones of Lehner and Clarry [220], and demonstrated no significant differences in antibody titre to any of the antigens used.

Sequential antibody estimations at seven and 28 days in the NUG patients also failed to show any significant differences in titres during the course of the disease or during convalescence.

No difference was found in either salivary or serum IgA levels when comparing NUG patients with the controls, thus confirming earlier findings on serum IgA levels in NUG. [221]

Cell mediated immune activity was measured by the lymphocyte transformation test, and significant differences were observed between patients and controls. The cell mediated response to several of the Gram-negative organisms was similar to that reported to occur in chronic marginal gingivitis, but the response against Fusobacterium fusiforme was significantly greater in those patients with NUG. [223]

The interpretation placed on these findings was that none of the Gram-negative anaerobes investigated has a primary role in NUG. The similarity of the cell mediated immune responses may indicate that NUG is superimposed on an existing chronic marginal gingivitis (CMG). The greater response to Fusobacterium fusiforme suggested that this organism might be implicated in the change from CMG to NUG. However, the effects of spirochaetes, other bacteria and purified endotoxins also require evaluation.

Shwartzman reaction.

A hypothesis was developed, based on the presence of an initial CMG, with subsequent relative overgrowth of Gram-negative organisms. This follows a disturbance in the balance of the local gingival environment, presumably due to altered host resistance. The resultant increase in the quantity of endotoxin would lead to the production of the characteristic lesion, either by direct local necrotic effect, or by the induction of a localized Shwartzman reaction. [223]

No attempt was made to explain the mechanism for providing the intravenous eliciting injection which is required to induce the

reaction. This could presumably be attributed to toxaemia or bacteraemia from local trauma due to mastication or toothbrushing, or the trauma of dental procedures [131] or beatings to the mouth. [167] These are still frequently, although with little apparent justification, stated to be predisposing or precipitating factors in the production of NUG. (See pages 174-176).

A further hypothesis was put forward by Shapiro et al. [224] They demonstrated that the localized Shwartzman reaction did not occur in rabbits in which a generalized chemical sympathectomy had been produced by treatment with 6-OH dopamine. They commented on potentiation of local Shwartzman reactions by the addition of catecholamines to the provoking dose of endotoxin, and speculated that high level of endogenous stress released catecholamines, together with high endotoxin levels, might be of importance in the pathogenesis of the lesion of NUG in humans. [224]

Goldhaber and Giddon [122] state that both the local Shwartzman reaction and the Arthus phenomenon may have significance in the aetiology of NUG. They limit themselves to brief descriptions of both phenomena, and to speculation that steroid suppression of the reticulo-endothelial system may facilitate the production of lesions having the appearance of the Shwartzman reaction.

Rizzo and Mergenhagen [225] investigated the responses of the oral mucosa of rabbits to the local inoculation of endotoxin, and suggested a role for the Shwartzman reaction in the pathogenesis of periodontal disease. They noted the production of regional lymphadenopathy, and that small quantities of endotoxin resulted in the production of pyrexia. [226] It was suggested that these findings implicated endotoxin in the production of pyrexia in NUG. The argument is not convincing, as pyrexia is at best a very inconsistent finding in NUG [122], and the rabbit is the animal used for demonstration

of the Shwartzman phenomenon.

Turk and Edwards [55] stress that there is no evidence to suggest that the Shwartzman reaction is a distinct immunological hypersensitivity reaction. There is no satisfactory experimental model to prove that it may be involved in the pathogenesis of NUG.

Although it is widely used as a serological test to confirm the presence of endotoxin, there is no evidence to show that the Shwartzman reaction occurs in disease in man. [73]

Arthus reaction.

The histological features of the lesion of NUG are superficially similar in appearance to those of local Type 111 immediate hypersensitivity (Arthus type) reactions, localized acute necrotizing vasculitis accompanied by an intense polymorphonuclear infiltrate. [227]

In the Arthus reaction, the maximum PMN infiltration occurs within the first four hours. Replacement is rapid, and by 24 hours mononuclear cells may comprise 50% of the cellular infiltrate. [228]

This is unlike the cellular response in NUG. Here the PMN infiltration persists much longer, so that it remains a feature in histological examination of established lesions. [197]

However, cutaneous vasculitis in man is stated to resemble an Arthus reaction, despite a prolonged PMN response which may persist for three to four days. This extended response is thought to be due to prolonged deposition of immune complexes, or possibly to a superimposed Shwartzman reaction. [228]

Immune complex deposition is stated to be dependent on the anatomy of the local vasculature. Regions which have a high blood flow

per unit of tissue mass have the potential to trap large quantities of immune complexes.[228] The anatomical arrangement of the gingival vasculature appears to fulfil these requirements. Complexes are stated to localize in the sub-endothelial layer of venules[228, 229], and attention has been drawn to the high proportion of post-capillary venules present in the marginal plexus beneath the junctional epithelium and the col.[3, 43]

Local immune complex formation is due to the diffusion of antigen through the tissues, and its combination with circulating antibody within the vessel walls. It is claimed that in man this is unequivocally seen only after subcutaneous or intradermal inoculation.[228]

No single laboratory technique will accurately demonstrate the presence of immune complexes in all clinical situations, nor will it demonstrate the actual pathogenicity of the complex.[228] The criteria for detection of immune complexes in tissues are[228]:

(a) ... Immunoglobulin and complement (ideally, specific Ag and Ab) may be demonstrated by immunofluorescence or by isotopically labelled specific antisera.

(b) ... The use of selective elution techniques.

(c) ... Ultrastructural demonstration of electron dense deposits which are stated to be typical.

Turk and Edwards[55] observe that some features of NUG are reminiscent of an Arthus type reaction. However they argue that the large numbers of organisms present could result in local antigen excess. This does not preclude an Arthus type reactivity, which Dolby[230] and others[86] point out may occur in situations of moderate antigen excess.

Gell and Coombs[86] stress the importance of the observation the Ag-Ab complexes formed in moderate antigen excess may not precipitate, but are locally toxic to tissue despite the fact that they remain soluble.

Argument against Arthus type involvement advanced by Turk and Edwards [55] stressed that immunofluorescent demonstration of deposits of complement components and immunoglobulin in the vessel walls is not necessarily evidence of immune complex disease. The fluorescent material in biopsies from NUG patients lacked the typical"lumpy" distribution, and was rapidly dispersed by saline elution. Similar features may be demonstrated in vascular lesions of different aetiology. They stated that failure to demonstrate immune complexes does not necessarily exclude their involvement, as they may disappear rapidly from the lesion, but concluded that the findings added to the evidence against the role for complex mediated hypersensitivity in NUG. [55]

Dolby [230] stresses that the vasculature and the tissues have only a limited variety of possible responses to injury. Widely different forms of injury may produce lesions with similar histological features.

He examined biopsy specimens from the ulcerated interdental papillae of NUG patients. Fluorescent microscopy techniques demonstrated fluorescence in 8 out of 20 specimens, and that:

(a) ... the distribution of IgG and complement was similar to that found in chronically inflamed gingiva (Brandtzaeg [78] found both C3 and IgG in extracts of inflamed gingiva, but their incidence was low and he argued against describing them as immune complexes).

(b) ... the material detected was reduced more by washing with phosphate buffered saline, than by acid buffer which is specifically employed to dissociate immune complexes, and

(c) ... the material remaining after elution did not have the granular appearance of immune complexes produced in laboratory animals.

He concluded that immune complex formation does not play a part in the pathogenesis of NUG. [230]

The production of the Arthus type reaction is dependent on a high level of IgG [87], and its intensity varies with the serum concentration of antibody. [231] A further argument against its possible role in the aetiology of NUG is the significant relative IgG hypogammaglobulinaemia which Lehner [221] demonstrated exists within one to five days of the onset of disease.

Immunological phenomena in the debilitated host.

A high incidence of NUG and cancrum oris is reported to occur in children in underdeveloped countries [113, 150, 151, 152, 153, 154, 158] It is frequently associated with antecedent or concurrent debilitating infectious diseases or parasitic infestations. [150, 152, 158, 232] Other major predisposing factors appear to be severe protein calorie malnutrition (PCM) [150, 153, 154] or kwashiorkor. [151, 153]

The role of immunological mechanisms in the pathogenesis of this type of NUG is undetermined.

Jiménez and Baer [113] state that the immunoglobulin levels in malnourished patients remain within normal limits. Emslie [158] demonstrated normal levels of total immunoglobulins in patients suffering from cancrum oris, which he classified as a direct extension of NUG.

Ehwonwu [150] reported low serum albumin and elevated serum globulin in debilitated village children in whom the incidence of NUG

was high. A similar finding had been reported earlier in a case of cancrum oris which occurred in a debilitated alcoholic patient. [233]

Such findings on the levels of total serum immunoglobulins would not necessarily exclude the existence of the biphasic immunoglobulin pattern which was demonstrated by Lehner. [221]

It has now been shown that patients with severe PCM exhibit a low serum albumin, and serum immunoglobulin levels which are either within normal limits or slightly elevated. [234]

Reddy et al.[234] have also demonstrated significantly reduced concentrations of secretory IgA in such patients, and propose that the immunological functions are affected with the development of severe malnutrition. They suggest that this selective deficiency of secretory IgA might play an important role in the pathogenesis of mucosal infections in children suffering from severe PCM. One mechanism could be the facilitation of bacterial adherence to epithelial cells, due to the loss of the protective blocking action of secretory IgA. [82, 235]

Among the microorganisms which may colonize the mucosa by direct adherence to epithelial cells are fusobacteria [236], which might thus be enabled to colonize the gingival sulcus at an earlier age.

It should be stressed that although this deficiency of secretory IgA is present in severe PCM, a study in higher socio-economic group compared NUG patients and controls, and failed to demonstrate any significant difference in secretory IgA levels. [223]

A single extremely refractory case of NUG has been reported in a patient who was suffering from IgA deficiency. [237] The 19 year old patient was an habitual mouthbreather, probably as a result of associated recurrent nasopharyngeal infection. This may have been a predisposing factor in the development of the gingivitis. [237]

The impairment of various aspects of the immune system in PCM has been confirmed. [49, 238, 239] Despite normal or even elevated total serum immunoglobulins, defects in specific antibody responses have been demonstrated, and the relative deficiency of secretory IgA has been confirmed. [238]

Thymic and tonsillar lymphoid tissues are depleted in malnourished children in tropical regions, and decreased CMI has been demonstrated. [238] This finding may be of importance, as cell mediated immune responses may be implicated in the change from chronic marginal gingivitis to NUG. [223]

Leucocytes from children with PCM showed significantly decreased intracellular levels of adenosine triphosphate, pyruvate, lactate and oxaloacetate, and it is suggested that energy dependent leucocyte functions would be abrogated in PCM. [238]

The occurrence of measles in undernourished children has been implicated in the development of cancrum oris from earlier NUG [150, 232] It is suggested that there is depression of CMI activity due to a synergistic effect between PCM and measles. [238]

Thus progression from NUG to cancrum oris in the very young host might result from a state of immunological unresponsiveness or hyporeactivity known as anergy. [67] The immature immune mechanisms would be rapidly suppressed by the synergistic immunosuppressive effects of severe PCM, measles, or possibly other infectious disease or parasitic infestation.

Stress and the immune response.

Physical, and particularly psychological stress are regarded as important predisposing or precipitating factors in the

development of NUG. Until recently, it has been difficult to explain the physiological basis for this relationship.

Recent evidence indicates that stress may result in impaired immunological reactivity by at least two mechanisms.

(a) ... Activation of the hypothalamo-hypophyseo-adrenal axis by circulating catecholamines stimulates secretion of ACTH, and thereby the production by the adrenal cortex of corticosteroids. One effect of these steroids is immunosuppression.[240]

(b) ... Severe psychological stress has been shown to depress T-lymphocyte function significantly, without any change in immunoglobulin levels or T and B lymphocyte numbers. This abnormality of the immune function is apparently distinct from and independent of hormonally induced changes.[241]

Part 6.

AETIOLOGY.

While there is general agreement that the onset and the aggressiveness of the acute inflammatory symptoms of NUG are directly associated with opportunistic endogenous bacterial infection, no direct causal relationship has ever been established.

It is widely believed that the disease will not occur in the absence of various local or systemic predisposing or conditioning factors. These alter the balance of the host-parasite relationship, allowing previously symbiotic organisms to become pathogenic in susceptible individuals. [99, 100, 127]

For the purposes of orderly review and classification, aetiological factors will be considered in three major groupings:

(a) Predisposing factors, which alone, or more probably in varying combinations, influence host susceptibility.

(b) Precipitating factors, which actually initiate the disease process.

(c) Perpetuating factors, which influence recurrence of the disease.

Since different combinations of these factors may result in the production of the clinical lesion, it should be stressed that considerable overlapping occurs between the groupings in this classification.

PREDISPOSING FACTORS.

Smoking. Numerous studies have shown a positive correlation between smoking and either the incidence or the severity of NUG.

Stammers [131] noted that smoking was almost universal in the subjects in his study. In heavy smokers (those who smoked more than 30 cigarettes per day), more severe lesions occurred in the gingiva adjacent to the area where the cigarette was habitually held. [131]

Pindborg [242] reported that there was a significant correlation between smoking and NUG. This association was greater than that which could be explained in terms of increased calculus deposition or more severe gingivitis due to smoking. It was also noted that the increase in the incidence of NUG rose with the increase in the amount of tobacco used.

Smitt [117] showed that the incidence of NUG was five times higher in those using more than 50 gms of tobacco per week, than in moderate or non-smokers. 50 gms of tobacco is the equivalent of 62 cigarettes.

In a study of college students, Giddon et al. [183] showed that 63% of the NUG group smoked, whereas less than a third of the unaffected group smoked. Of the smokers, 13.3% of the unaffected group and 28.6% of the NUG group smoked at least 20 cigarettes per day.

Goldhaber and Giddon [122] reported that only 3% of their group of 61 NUG patients were non-smokers, and that 41% smoked more than 20 cigarettes per day. In the control group 25% were non-smokers and 5% smoked more than 20 cigarettes per day.

There is some doubt whether the association between smoking and NUG is a direct cause and effect relationship, or whether smoking should simply be regarded as a symptom of underlying emotional stress. [116, 122, 243]

It has also been stated that differences in the incidence of NUG between smokers and non-smokers can be explained on the basis of differences in the levels of oral hygiene between the two groups. [244, 245]

Bastiaan [245] asserts that the predominant factor is the oral hygiene status of the patient, and not smoking habits. This argument is based on older studies which were concerned with chronic periodontal disease and alveolar bone loss, and a more recent study by Sheiham. [246] However in Shieham's study less than 30% of the patients were in the age group in which NUG commonly occurs, and very few smoked more than 20 cigarettes per day. This study was one on chronic destructive periodontal disease and did not record the incidence, if any, of NUG. [246]

MECHANISMS WHEREBY SMOKING MIGHT DIRECTLY AFFECT THE DEVELOPMENT OF NUG.

Alteration in the composition of the microbial flora.

Colman et al. [247] have demonstrated differences in the oral microbial flora of smokers and non-smokers. Neisseriae were more numerous on the tongues and palates of non-smokers, while smokers showed a tendency towards higher numbers of anerobes such as veillonella and bacteroides. This study did not find any statistically significant differences in the ecology of supragingival plaque between the two groups. Subgingival samples were apparently not included in the study. The observed differences were attributed to more anaerobic conditions prevailing in the mouths of smokers, and possible selective toxicity of some tobacco smoke products for neisseriae.

This study demonstrated the potential of tobacco smoke to influence at least some oral bacteria, whose suppression might create more optimal conditions for the selective proliferation of other microorganisms. [133]

Immunosuppression.

Evidence concerning the immunosuppressive effects of tobacco smoking has already been presented, and mention has been made of a mechanism which might be capable of potentiating this effect due to the release of amines by either stress or inflammation. (see Pages 131-133).

Vascular Phenomena.

Nicotine is capable of exerting vasodynamic pharmacological effects on the gingival microcirculation. These have been attributed to:

(a) Increased plasma levels of adrenaline, due to the effectiveness of nicotine in causing its central release. This would result in powerful sympathomimetic effects, including lowered skin temperature, increased pulse rate and elevated blood pressure. [122, 141]

(b) The local release of noradrenaline from sympathetic nerve endings which are located in or close to the gingival blood vessels [248], resulting in peripheral vasoconstriction.

There is considerable evidence to show that these effects are primarily due to the local release of the sympathetic neurotransmitter noradrenaline, rather than to increases in the levels of circulating catecholamines. [249, 250] However the cumulative effects of increased concentrations of plasma catecholamines due to both stress and smoking, combined with the local effect of noradrenaline release, might be capable of producing an even greater degree of vasoconstriction.

Effects on Anaerobiosis

Blake [133] stressed that the onset of NUG might be dependent on the development of a gingival environment which favoured the selective growth and development of certain key organisms. One

condition which he stated was essential for the growth of spirochaetes and other strict anaerobes was a low oxidation-reduction potential (Eh).[133]

Others have confirmed that the highest oral concentrations of strictly anaerobic bacteria occur in areas of very low Eh such as the gingival sulcus or periodontal pockets.[251] Periodontal pockets have a much lower Eh than healthy gingival sulci, thus favouring the development of anaerobic organisms.[252]

Kenney et al.[253] studied the effect of cigarette smoking on Eh, and concluded:

(a) There is evidence of strong reducing capacity of cigarette smoking. The smoking of one cigarette led to a dramatic fall in the Eh of the gingival region in both smokers and non-smokers.

(b) There was no statistical difference in the proportion of anaerobic bacteria in the 14 day old plaques of smokers and non-smokers.

The study did not record the time lapse between the reported fall in Eh and the return to resting levels, nor the effect of heavy smoking in maintaining low Eh levels for long periods of time. The experimental method did not specify the exact region from which the plaque samples were obtained, and no attempt was made to determine the relative proportions of anaerobic bacteria detected.[253]

It does not therefore exclude a role for smoking in establishing a low Eh which would favour the proliferation of certain key organisms.

Upper Respiratory Tract Infections.

The onset of NUG has been linked to recent episodes of upper respiratory tract infections.[99, 143] Since these infections occur more commonly in smokers[203, 206], their occurrence could provide an indirect link by which smoking predisposes to NUG.

The identification of these specific mechanisms which might directly affect the gingival environment suggest that the relationship between smoking and NUG is more than circumstantial. It is unlikely that the only role of smoking is as an indicator of a stress prone personality, or that its association with the lesion can be explained in terms of levels of oral hygiene alone.

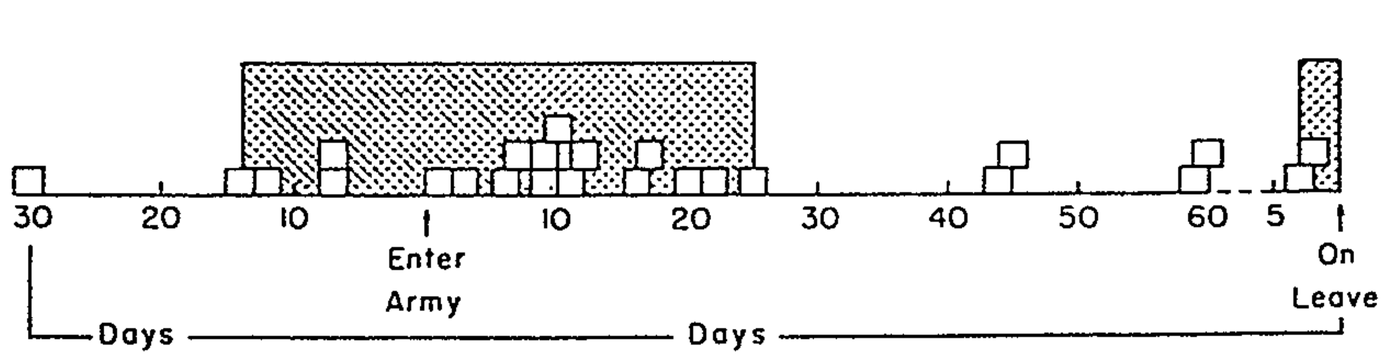
It should be noted that pooled data from the quoted studies indicate that there may be a critical level of tobacco consumption at which these effects become important in the pathogenesis of the disease. This level appears to be the use of 20 or more cigarettes per day.

Stress.

Tension, anxiety and environmental psychological stress have been described as important predisposing factors in NUG [122, 254], often in synergism with other factors. [243] These include academic stress such as entering college or taking examinations [184], and the stresses of adapting to or from a military environment. [128, 167, 179] NUG has been described as occurring in relation to scholastic, romantic or marital difficulties. [185]

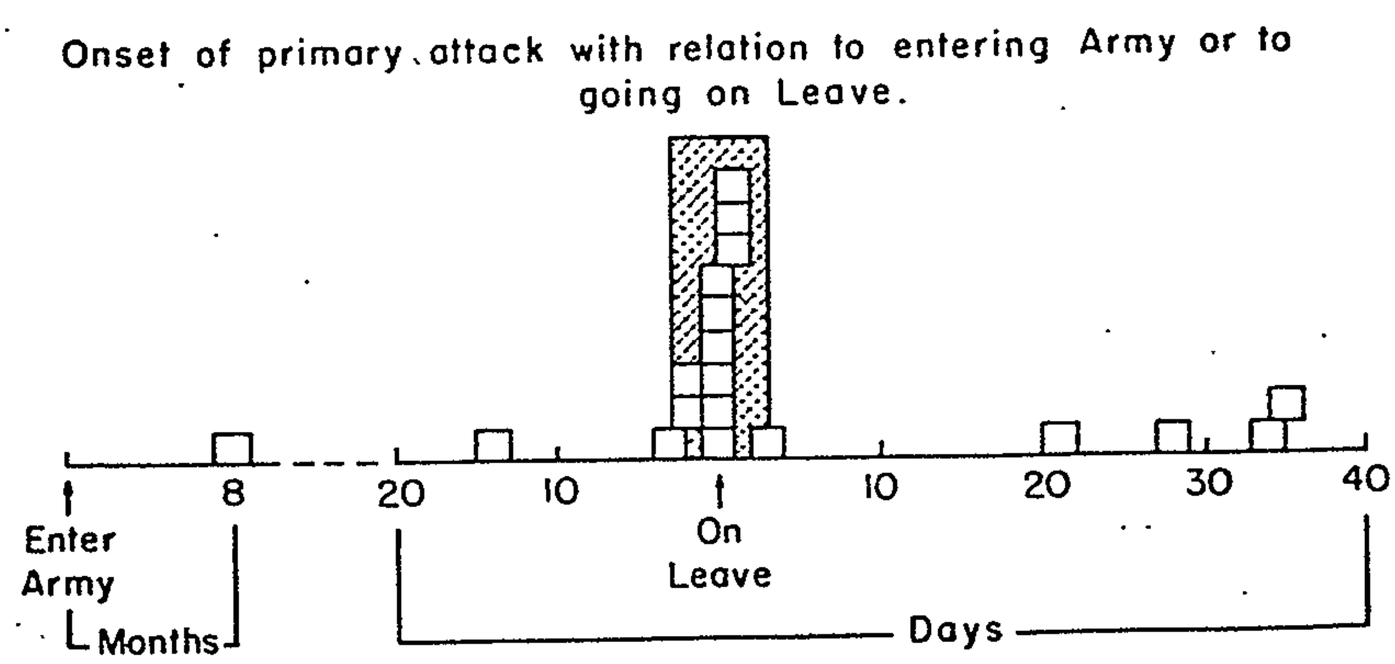
Goldhaber and Giddon [122] drew attention to the high incidence of NUG in military personnel, either at the time of induction into the army, or when going on leave even after years of adaption to the stresses of military service. (Figure 21).

TRAINEES — PRIMARY ATTACK (25 cases)



Onset of primary attack of ANUG in Trainees-primary attack group. Each box represents one case. End of time-scale (going on leave) represents about 119 days after entering army. Note that there is a break in the time-scale between 60 days and 5 days before going on leave. during which time no cases occurred. The shaded areas represent the cases occurring during the two most significant periods, around the time of entering the army or going on leave.

NON-TRAINEES — PRIMARY ATTACK (19 cases)



Onset of primary attack of ANUG in the Non-trainees-primary attack group. Note the concentration of cases about the time of going on leave (shaded area).

Figure 21.

From: Goldhaber, P. and Giddon, D.B. Present Concepts Concerning the Etiology and Treatment of Acute Necrotizing Ulcerative Gingivitis. Int. Dent. J. 14:4 468–496. 1964.

Grupe and Wilder [128] stated that a psychosomatic factor was the likely predisposing factor in the occurrence of NUG in military personnel. They suggested that stress acted "primarily on the papillary arterioles which resemble end arteries". Although the anatomical description is no longer regarded as accurate, the vasodynamic effects of stress are considered to be of major importance.

Fitch et al. [166] commented on the high incidence of NUG in newly inducted military trainees. This was attributed to psychological stress. Other studies have implicated a psychological component in the aetiology of NUG on the basis of observations of academic behaviour.

Giddon et al. [184] stated that the incidence of NUG appeared to bear some relation to examinations and also to vacation periods. It was higher in the junior college class who would presumably be subjected to more stress than would seniors who had adjusted to the academic environment.

NUG patients have been shown to have a statistically greater number of withdrawals from college than do the general unaffected student population. [183] Among students, approximately three times as many NUG patients sought psychiatric help than did a randomly selected group of dental patients. [183]

More students from the NUG group expressed an intention to major in psychology; this was interpreted as evidence of the presence of an underlying psychological difficulty in this group. [183]

These studies provide evidence that there may be NUG prone personalities in whom drastic alterations in lifestyles may provoke sufficient stress to predispose to, or actually precipitate, acute or recurrent attacks of necrotizing ulcerative gingivitis.

The presence of stress may be difficult to diagnose, and host responses to it may be even more difficult to identify or evaluate. Attention had been drawn to the fact that patients may tend to withold information concerning personal problems, and to the subsequent importance of detailed and sympathetic history taking. [122]

Williams [255] cautions against overemphasis on any single precipitating factor, and comments on the importance of cumulative stress in precipitating psychological decompensation. He also states that certain acute infections, particularly viral infections, may on a metabolic basis predispose to the emergence of anxiety, or by psychogenic mechanisms enhance the tendency to anxiety. [255]

This provides a possible synergistic mechanism between two of the factors stated to predispose to NUG, stress and recent illness, often of a viral (upper respiratory tract) nature.

Roth and Stone [256] described one intractable case of NUG in a patient who was overworked and in a state of prolonged tension. Marked improvement occurred with resolution of the psychological stress, and was attributed to the fact that the patient became more amenable to advice on oral hygiene.

Moulton et al. [257] concluded that NUG was precipitated by acute anxiety arising from conflict about dependency or sexual needs. They reported that local predisposing factors were minimal.

Goldberg et al. [258] reported that 41% of the NUG patients studied gave a history of moderate or severe psychological stress. They were unable to demonstrate any significant differences in personality between NUG patients and controls with other forms of periodontal disease, and explained the effects of stress in terms of a general adaption syndrome.

A more recent personality study was performed on naval aviation students subjected to psychological, academic and physical stress during their training. NUG patients differed significantly from controls in two respects;their personalities showed a positive correlation with dominance, and,not unexpectedly, a negative correlation with the trait of absement. It was proposed that the possession of these characteristics indicated an NUG prone personality. [259]

The onset of NUG has been associated with the abstinence syndrome which accompanies withdrawal from addiction to narcotic drugs, [193], and has been explained in terms of the acute psychological stress which is precipitated by drug withdrawal. It should be borne in mind that other predisposing factors occur concurrently in such patients, most of whom are in the age group of maximum susceptibility to NUG. [194] These factors include severe pre-existing gingivitis due to personal neglect and drug induced xerostomia [194], nutritional deficiencies, and systemic diseases such as serum hepatitis and venereal disease. [193, 194]

Attempts have been made at objective assessment of the correlation between the presence of stress and the incidence of NUG. The experimental method used was the measurement of the urinary excretion rate of 17-hydroxycorticosteroid (17-OHCS), on the basis that stress stimuli result in an increased output of adrenocortical hormones which is reflected in their level in the body fluids.

One study [254] showed that the mean excretion rate of 17-OHCS for the NUG group was higher than that of normal controls or those with other forms of periodontal disease. Due to the large variance in the measurements, and the small numbers of patients involved, the

finding was not considered to be statistically significant. The conclusion drawn was that the study demonstrated an objective indication of increased adrenocortical activity in the presence of NUG. The authors suggested that the adrenal release may have been due to the febrile state of the patients [254], but body temperatures were not recorded, and would have been unlikely to show any consistent or significant pyrexia. [122]

A later study confirmed that patients with NUG had elevated urinary 17-OHCS levels during the course of the disease, and that these levels decreased when symptoms resolved following treatment. [260] Only a small number of patients completed this study. Although it confirmed the findings of the previous investigation, neither study demonstrated which was the first to occur, the NUG or the increased urinary 17-OHCS output.

It is possible to explain these findings in terms of the stress induced by the pain and anxiety associated with the actual presence of the disease.

Manhold et al. [261] demonstrated that the tissues of animals subjected to social stress utilized less oxygen than those of control animals. They speculated that failure to meet oxygen requirements could contribute to breakdown of the periodontal tissues. Stress mechanisms could be implicated in this failure by two mechanisms:

(a) ... by interference with the requirement for an increase in total blood flow, as a result of sympathomimetic vasoconstrictive effects.

(b) ... by preventing the maintenance of an elevated oxygen pressure gradient between the tissues and the intracapillary plasma.

Although they provided no documentation to support the possible role of stress in the second of these two mechanisms, they concluded that extreme or long continued social stress lowered the ability of the tissues to utilize oxygen.[261]

Giddon[243] and Giddon, Clarke and Varni[262] proposed that a peripheral vasomotor defect may be present in NUG patients. They drew attention to the fact that the cardiovascular effects of prolonged stress may include changes in capillary morphology and abnormal peripheral vasomotor responses.

Evidence was advanced that NUG patients in remission actively avoided stressful situations which could stimulate strong sympathomimetic autonomic responses, which would induce cutaneous vasoconstriction. When unable to avoid such situations, they demonstrated digital vasomotor hypotonicity and elevation of digital temperatures.[262]

These findings were developed by Clarke and Giddon.[263] In a study of body geometry, patients who had recurrent attacks of NUG were shown to have an apparently statistically significant surface area deficiency. They suggested that this might result in a lowered cooling capacity for the body, and unusual thermoregulatory behaviour in NUG susceptible persons.[263]

They also hypothesized that the mucosal surfaces of the oral cavity might consequently become involved in the heat exchange functionbetween the body and the environment. The development of skin like vascular responses in the peripheral gingival microcirculation would result in extreme vasoconstrictive responses during periods of emotional stress.

This argument was supported by the finding that NUG patients

have subnormal oral temperatures during the remission phase.[262] It was subsequently incorporated into another hypothetical explanation of the aetiology of NUG.[141]

It is therefore important to stress that the argument for any thermoregulatory function by the gingival vasculature remains highly speculative. Oral mucosa has a thermoregulatory function in panting animals, but this has not been demonstrated in man.[30]

The reportedly low oral temperatures in the remission phase of NUG were not significantly less than those of the control patients.[262] Although the sublingual temperatures did contrast with the recorded digital temperatures, it should be noted that all of the NUG patients smoked and drank coffee in excess of the controls.

The apparent temperature differential is readily explained in terms of generalized vasodilatation due to caffeine, with concurrent local vasoconstriction in the oral mucosa due to the local (sympathetic) effects of nicotine.[249, 250]

There is as yet no conclusive evidence that stress related thermoregulatory abnormalities affect the gingival tissues of NUG susceptible patients.

Several physiological mechanisms offer hypothetical explanations for the role of stress in influencing the host-parasite relationship in favour of the development of NUG:

(a) Steroid release: Goldhaber and Giddon [122] noted that large doses of corticosteroids could depress both innate and acquired immune mechanisms. They provided no evidence that the levels of endogenous steroids released in NUG patients were capable of exerting similar immunosuppressive influences, but commented that the absence of pyrexia in NUG patients might be attributable to the antipyretic

effect of stress released steroids. This lack of fever may also be explained in terms of some degree of endotoxaemia. [173]

Enwonwu [150] has drawn attention to the fact that one of the consequences of protein calorie malnutrition is adrenal hyperfunction. He states that plasma cortisol levels in undernourished children may be more than double those of well fed children, and that febrile infections, also common in these children, can enhance adrenocortical secretion. He compares the occurrence of NUG in such patients with its occurrence in others in whom stress may have produced increased plasma cortisol levels.

Mechanisms whereby steroid levels may be implicated in the pathogenesis of the lesion are given as [150, 239]:

(a) decreased mitotic activity of epithelial tissues.

(b) reduced synthesis of collagen and ground substance allied to the inhibition of the proliferation and migration of fibroblasts.

(c) elevated levels of serum hyaluronidase.

(d) suppression of the immune responses.

No evidence is given that the effect of endogenous steroids is comparable <u>in vivo</u> to that demonstrated in studies utilizing large amounts of exogenous hormones. It should be noted that there is an extremely wide range of levels of circulating steroids within the range of normal. [254]

Combined release of endogenous steroids and catacholamines can result in depression of epithelial cell turnover and renewal, by increasing the activity of chalones. [1]

(b) Vasopressor effects: Induced emotional stress may result in a sustained drop in the peripheral blood flow. These peripheral changes may predispose to, aggravate or perpetuate physical, chemical or infective dermatological lesions. Either emotional or physical factors are capable of producing identical cutaneous reactions in different patients, or even in the same patient at different times. [264]

Stress induces the central release of adrenaline and the local release of noradrenaline; both are capable of producing profound vasoconstrictive effects. These may be enhanced by corticosteroids [122], and similar effects are produced by smoking. The role of the sympathetic neurotransmitter noradrenaline may be of particular significance, as there is experimental evidence of apparent sympathetic dominance in the autonomic nervous systems of NUG patients. [243]

Endotoxin can enhance the vasoconstrictive effects of adrenaline and probably noradrenaline, and their combined presence can result in the production of vasculonecrotic lesions. [122] Thus powerful synergistic mechanisms exist for the production of profound and sustained vasoconstriction in patients who are subjected to severe or prolonged stress.

(c) Salivary changes: Although it has been suggested that changes in salivary flow may result from stress stimuli [122], the occurrence of sialorrea in many cases of NUG should be noted. Any effect of stress on the saliva would therefore necessarily have to be attributed to changes in its composition or its pH. Possible factors could be a decrease in the amount of salivary lysosomal enzymes, or depression of salivary immunoglobulin levels.

The latter has as yet only been demonstrated in one group of susceptible subjects, young children suffering from severe protein calorie malnutrition. [234]

(d) Immunosuppression: Attention has been drawn of defects of T-lymphocyte function which occur under severe stress, and are independent of hormonally induced immunosuppression. [241]

(e) Indirect effects: Severe stress may result in increased tobacco consumption and neglect of oral hygiene, thus influencing the severity of the effects of smoking and of existing chronic gingival disease.

Pre-existing chronic marginal gingivitis and poor oral hygiene.

There is considerable disagreement over the role, if any, of poor oral hygiene and pre-existing gingivitis in the aetiology of NUG. Since the disease is accompanied by pain which makes effective oral hygiene difficult or impossible, it is possible to gain an inaccurate clinical impression of the level of oral hygiene and of gingival inflammation which existed before the onset of the acute symptoms.

Stammers [131] concluded that NUG occurred superimposed on existing gingival lesions, but stressed that these might be located interproximally and therefore be difficult to diagnose.

Schluger [172] also stressed that the most important single factor in the aetiology of NUG was a low standard of oral hygiene. This view was supported by the findings of Pindborg [179], who noted that in 91 cases of NUG, 87 developed from pre-existing CMG, while only four cases developed in patients with previously healthy gingiva.

Barnes et al. [123] attempted an objective assessment by recording the OHI and the amount of calculus present for the 218

patients in their study. They compared these findings to those in control patients. While the presence of calculus is an indicator of long standing continuing plaque accumulation, the OHI is of questionable significance in NUG patients who may have avoided oral hygiene procedures because of pain.

Findings were expressed as oral hygiene classifications ranging from excellent to poor, and calculus formation ratings from none to heavy. (Table 10). Unfortunately, no information is given on the basis for grading the subjects into these classifications.

The conclusions drawn were that the evidence supported the claim that poor oral hygiene and the presence of calculus are generally associated with an increased incidence of NUG. This association is not necessarily present in every case. [123]

It is of interest to note that only one (0.5%) of the NUG subjects had no calculus present, and that only two (0.0%) received the oral hygiene classification of excellent. [123]

TABLE 10

Oral hygiene classification of patients with acute necrotizing ulcerative gingivitis and control patients*

Oral hygiene	*ANUG subjects*		*Control patients*	
	Number	*Percentage*	*Number*	*Percentage*
Excellent	2	0.9%	15	13.9%
Good	26	11.9	49	45.4
Fair	87	39.9	27	25.0
Poor	103	47.3	17	15.7
Total	218	100.0	108	100.0

*Based upon a sample of 108 military and dependent subjects of equivalent age, sex, and race who do not have ANUG.

TABLE 5.

Presence and extent of calculus formation in patients with acute necrotizing ulcerative gingivitis and in control patients*

Calculus	*ANUG subjects*		*Control patients*	
	Number	*Percentage*	*Number*	*Percentage*
None	1	0.5%	15	13.9%
Slight	63	28.9	62	57.4
Moderate	97	44.5	24	22.2
Heavy	57	26.1	7	6.5
Total	218	100.0	108	100.0

From: Barnes. G.P. Bowles. W.F. and Carter. H.G. Acute Necrotizing Ulcerative Gingivitis: A Survey of 218 Cases. J.Periodondol. 44:1 35-42. Jan. 1973.