Of the control patients, 13.9% were rated as having both excellent oral hygiene and no calculus.

This study supports the general impression in the literature that NUG is almost always associated with pre-existing CMG. 100, 109, 125, 164, 183 There may be relatively rare exceptions in which it may occur in patients with little or no other apparent gingival disease. 103, 120

Manson 120 states that it is in these latter cases that the underlying problem of environmental psychological stress is most obvious. MacPhee and Cowley 100 contend that lateral rather than interproximal ulceration is more likely to occur in those cases in which there is no pre-existing established periodontitis. Neither of these claims is supported by any documentation. It would be of interest to examine those patients with no obvious predisposing gingival disease in order to assess their cardiovascular status, adrenocortical activity, immunoglobulin patterns, CMH responses, and smoking habits.

Several authors claim that NUG does occur readily in clean mouths. 128, 260 Their classification appears to be based on overall subjective clinical impressions of the appearance of the gingiva and the teeth, or on the amount of obvious supragingival calculus.

These claims must therefore be regarded with suspicion, since the incidence of gingival disease in the community is high. They could only be substantiated if accurate and detailed periodontal examination had fortuitously and very recently preceded the onset of the disease.

Poor oral hygiene was consistently noted among African children in whom the incidence of NUG was high 150, 152, although its presence was considered insufficient alone to explain the high
incidence of the disease. Malberger\textsuperscript{152} made the observation that NUG hardly ever occurred in those children who had spaced dentitions, and who consequently did not develop chronic interproximal gingival inflammation.

There are several mechanisms whereby the presence of chronic marginal gingivitis could contribute to the pathogenesis of NUG. Opportunistic infection by fusospirochaetal organisms might be facilitated by the development of a local gingival environment which favours their selective development. Pre-existing gingival inflammation results in an increased flow of gingival fluid. This may provide essential serum products as metabolites for the more fastidious members of the anaerobic flora, as well as creating more optimum condition of pH and Eh.\textsuperscript{133}

Tissue damage resulting from the inflammatory response in CMG may contribute to cumulative vasoconstriction\textsuperscript{141}, or to vascular damage which could facilitate immune complex deposition. Damaged tissues are a frequent site for the opportunistic development of mixed fusospirochaetal infections.\textsuperscript{164}

Large amounts of bacterial endotoxin are known to be present in both the gingival environment and in the gingival tissues during NUG.\textsuperscript{175} Since large doses of endotoxin are known to be able to decrease phagocytic activity and resistance to infection\textsuperscript{265}, the onset of NUG could be interpreted as resulting from this form of non-specific suppression of the inflammatory and immune responses.

Endotoxin derived from the subgingival plaque associated with pre-existing gingivitis would increase capillary permeability\textsuperscript{265}, and possibly also activate complement by the alternate pathway.
The PMN response would occur as usual, but its effectiveness would be suppressed by the excess of endotoxin. It is also of interest to note that continued exposure to endotoxin results in a loss of responsiveness to its, and other endotoxins' biological actions. The lost biological responsiveness is regained some one or two weeks after cessation of administration of the endotoxin.

Since NUG may undergo spontaneous remission without treatment, but is notorious for its propensity to recur, a role could be postulated for endotoxin mediated fluctuations in non-specific immune competence which would influence remissions and exacerbations of the acute symptoms.

However, it has not been demonstrated whether the high levels of endotoxin present in the disease are in fact derived from pre-existing CMG prior to the establishment of the acute lesion. It is possible that they may be a secondary finding, subsequent to the opportunistic proliferation of Gram-negative anaerobic organisms within damaged tissues.

**Lowered physical resistance.**

It is generally agreed that NUG is an opportunistic infection, which occurs in susceptible hosts sufficiently debilitated to allow the disease to become established. The possible roles of smoking and of environmental stress in lowering both local and systemic resistance have already been presented. However, numerous other factors have been implicated as predisposing factors which may decrease host resistance.
These include alcoholism and liver cirrhosis, specific dietary deficiencies, fatigue and overwork, inadequate or monotonous diet, antecedent or intercurrent illness such as frequent upper respiratory tract infections, operations, pregnancy and physical disability. 101, 112, 118, 127, 164

There are few objective reports on the incidence, the importance, or the proposed physiological mechanisms of these predisposing factors. 122 Many of the descriptions occur in the earlier literature, and it is possible that oral mucosal lesions related to systemic conditions such as leukaemia, agranulocytosis, gross dietary deficiencies or some viral infections were misdiagnosed as primary or superimposed NUK. It is also possible that the advent of improved diagnostic techniques, and improved medical care, have reduced the incidence of the gross forms of predisposing disability formerly associated with many systemic diseases.

The widespread use of chemotherapy may be suppressing opportunistic fusospirochaetal infections.

Those predisposing factors described could exert a conditioning effect on the gingiva by systemic mechanisms. Their effects could also be explained in terms of accompanying increased psychological stress, neglect of oral hygiene by the ill patient, or in some cases increased tobacco consumption. 131 This does not exclude a systemic conditioning role, which could contribute to the severity of the presenting lesions or their actual initiation.

Schluger 167, 172 stressed the importance of physical disability and lowered general resistance on the basis of the finding that 7.5% of his cases occurred in patients undergoing
long periods of hospitalization for non-dental conditions. Others occurred following vigorous field exercises under poor living conditions. No data were presented regarding any previous history of the disease, the state of oral hygiene or the level of tobacco consumption.

Stammers placed great emphasis on the importance of local predisposing factors, particularly poor oral hygiene and excessive smoking. He stressed that the group which he studied would have been unlikely to be suffering major dietary deficiencies, and regarded any systemic factors as secondary to the local ones. It is not possible to determine whether those patients in whom both local and systemic predisposing factors were identified had more severe or more intractable lesions than those in whom no obvious systemic factor was found.

Reports that NUG frequently occurs following upper respiratory tract infections have been partly substantiated by objective observations. Grupe and Wilder noted that many of the 870 patients in whom they observed NUG gave histories of recent URT infections. Skash et al. found that 40% of their patients gave a history of recent common colds or of tonsillitis. They concluded that it was unlikely that vitamin C deficiency or poor nutrition were major aetiological factors, since the peak incidence of the disease occurred when the consumption of both fresh fruit and vegetables reached its maximum within the group studied.

Spouge commented that nutritional deficiencies had enjoyed several eras of popularity as predisposing factors. He noted that the only convincing established relationship was the occurrence of severe manifestations of the disease in grossly malnourished children.
In these cases the effects of malnutrition usually occur in synergism with debilitating febrile diseases or parasitic infestations. 238

Assessment of the role of dietary deficiencies is made difficult, as it is not known to what extent nutritional factors affect the pathogenesis of periodontal lesions. 239

Quantitative evaluations would be influenced by the extent of food avoidance caused by pain associated with the presence of NUG.

Catalase is known to be involved in host resistance to some types of oral ulceration, and Nicol et al. 176 attempted to implicate low catalase levels as a systemic factor in the production of NUG lesions.

They demonstrated lower levels in NUG patients than in controls, but noted that individual results overlapped considerably. Catalase levels in NUG patients at some times of the year were higher than those in control patients at other times. The conclusion drawn was that the reduction of catalase levels in the NUG patients was a consequence of the ulceration, rather than its cause. 176

It was also suggested that the NUG lesion might produce a diffusible inhibitor which would greatly inhibit local catalase levels, while producing slight systemic effects. Such an inhibitor would most probably be $\text{H}_2\text{O}_2$. 176 derived from large numbers of phagocytes such as PMNs, many of which disintegrate and release their contents which include $\text{H}_2\text{O}_2$. 67

The same study failed to demonstrate any statistically significant differences in haemoglobin values, packed cell volumes, erythrocyte sedimentation rates (ESRs) and leucocyte counts when comparing NUG and control patients. 176

The findings confirmed the earlier ones of Carter
and Ball who investigated possible indicators of systemic debility. They found all their NUG patients within normal limits for erythrocyte, leucocyte and differential blood counts, ESRs and haemoglobin values. NUG patients were shown to have slightly lower mean serum ascorbic acid levels than the controls. This finding was not considered significant, and is readily explained in terms of food avoidance by the NUG patients.

Goldhaber and Giddon concluded that the most conspicuous predisposing factors were tobacco smoking, pre-existing gingivitis, local trauma and particularly psychological disturbance. They stressed that these only contributed to the production of the disease in susceptible individuals.

Thus the role of lowered physical resistance in determining host susceptibility remains to be clarified, and is generally considered to be of lesser importance than that of local predisposing factors.

The clinician should however be aware that NUG may occur superimposed on tissues affected by systemic diseases such as acute leukaemia, heavy metal poisoning, and infectious mononucleosis. In the latter instance the coincidental presence of the two conditions may be purely fortuitous.

Necrotizing gingival lesions which do not respond readily to adequate conventional local or chemotherapeutic treatment should be regarded as a possible indication of underlying undiagnosed disease.

Haematological examination may be indicated if the medical history proves non-contributory.
Pericoronal flaps.

There has been an historical association between the presence of pericoronal flaps and the incidence of NUG. 132, 178 Such areas were described as stagnation or incubation zones, which due to their anaerobic environment specifically favoured the proliferation of fusospirochaetal organisms. 132, 172

This association is still frequently described 104, 109, 130, 135, despite the fact that there are few objective studies to support such claims. They appear difficult to substantiate in view of a recent study which demonstrated that posterior, and particularly mandibular posterior regions, are least often affected by NUG. 123

Recurrent NUG also occurs least frequently in the mandibular molar region. 267

Carter and Ball 125 observed the presence of erupting third molars in 20% of their NUG patients, but did not indicate whether the lesions actually involved the third molar regions. Another study noted "gum flaps" as predisposing factors in 20% of the patients studied. 142 It did not specify their location or define whether they were pericoronal flaps, gingival craters from previous episodes of NUG, or simply periodontal pockets with readily retractable walls.

In their study of local factors associated with RNUG, Manson and Rand 267 found that pericoronal flaps were implicated in less than 8% of the cases examined. They concluded that such areas may play an important role in individual cases, but do not appear to be of general significance.

Barnes et al. 123 commented on the unexpected finding that the molar areas were relatively infrequently involved, despite the fact that many of their patients had erupting third molars.
They concluded that any association between NUG and erupting third molars is a minor one.

Since the age of peak incidence of NUG is that at which the incidence of pericoronitis and third molar eruption are also most common \(^{186}\), it is perhaps surprising that no closer association has been demonstrated between them.

Shields \(^{101}\) asserts that NUG lesions are commonly found under the operculi of impacted third molars, adjacent to malposed teeth, in association with orthodontic bands and under the saddle areas of partial dentures.

The latter statement is based on undocumented "personal observation". \(^{101}\) Since only a single case has been reported elsewhere in the literature \(^{138}\), the claim must be regarded with some scepticism.
PRECIPITATING FACTORS.

Local trauma.

Local trauma, including beatings about the mouth, is frequently quoted as a contributing or precipitating factor in the aetiology of NUG. No mention of the possible mechanism of involvement is offered. 100, 109, 122, 127, 164

The evidence for this emphasis in the literature is not extensive, and the number of actual cases cited is low. In addition, the groups in whom the observations were made were those in whom a high incidence of the disease is known to occur, military personnel in wartime retarded individuals in institutions, and civilian industrial workers under wartime conditions.

Description of the role of actual physical beatings appears to be restricted to one paper by Schluger 167 in 1949, in which he quotes its occurrence in three of a total of 92 recorded cases. The patients were in a wartime military environment and the beatings were stated to be severe. Their effect could readily be explained in terms of the additional stress or anxiety which would presumably accompany them, or to neglected oral hygiene due to accompanying pain or trismus.

Brown 159 studied a total of 806 dentulous retarded individuals, and found a high incidence of NUG among them. He reported only one instance associated with repeated episodes of head punching, which he regarded as a contributing factor in the production of an extremely severe emotional disturbance.

The findings of Stammers 131 are used to support the argument for the role of local trauma as a precipitating factor in the aetiology of the disease. Investigation of these findings reveals:
(a) ... 83 patients of a total of 1017 presented with acute symptoms subsequent to recent dental extractions. This was the only form of local trauma identified.

(b) ... the group studied was the wartime civilian population of a large industrial city which was being subjected to months of intensive aerial attack. Oral hygiene was poor, working and sleeping conditions disturbed and in many cases substandard (shelter conditions), and smoking by both men and women was almost universal, and in many cases extremely heavy.

What is most significant is that Stammers himself concluded from the case histories that many of the 83 cases constituted exacerbations of early or previously undiagnosed NUG, or recurrent attacks. He attributed any possible aetiological role to poor postoperative oral hygiene, rather than to physical trauma of the extractions per se. 131

Goldhaber 122 also refers to 2 patients with NUG who had recently had extractions, and in whom lesions appeared to spread from the extraction sites. These findings could be explained in the same way as those of Stammers. It is not possible to evaluate the degree of stress which may have been produced in any of these patients by the actual necessity to undergo extractions, or the effect of the vasoconstriction which would have accompanied the use of local anaesthesia. 263

In an attempt to transmit the disease experimentally in humans, deliberate gingival traumatization was employed in addition to the local inoculation of infected material from actual gingival lesions. These attempts were uniformly unsuccessful. 112 King 269 undertook a similar experiment in his own mouth, and failed in the first instance to produce a lesion. However, he subsequently became ill, and reported that a characteristic lesion then developed in the
experimentally traumatized area. Any inference drawn from this single case would support the argument for decreased host resistance rather than gingival trauma as an aetiological factor.

Glickman \(^{109}\) comments on the role of local trauma due to possible injury during dental prophylaxis. He also states that the disease frequently occurs at sites traumatized by opposing teeth in certain malocclusions (palatal gingiva of maxillary incisors and labial surfaces of mandibular incisors). However, these are areas of known predilection for the occurrence of the lesions. \(^{104, 123}\) No documentation supports these observations, which could be explained in terms of interference with the performance of oral hygiene measures.

Continued unqualified inclusion of trauma and beatings to the mouth as major aetiological factors in the aetiology of NUG appears to be unjustified.

**Ischaemic necrosis.**

MacPhee and Cowley \(^{100}\) suggest the possibility that ischaemic necrosis of the gingival epithelium may precede opportunistic fusospirochaetal infection in NUG. They attribute the ischaemia to the endotoxin enhancement of the vasoconstrictive effects of nicotine and of stress released endogenous catecholamines.

Kardachi and Clarke \(^{141}\) propose the hypothesis that the initial lesion of NUG is an aseptic necrosis which becomes secondarily infected by the proliferation of commensal anaerobic organisms in the already damaged tissues.

They describe the initial lesion as a purely vascular phenomenon, precipitated by a series of vasoconstrictive events:

(a) Stress induced peripheral vasoconstriction due to the central release of adrenalin, and autonomic (sympathetic) release of noradrenalin in the walls of the gingival arterioles.
(b) Gingival vascular stasis, due to the presence of the inflammatory response associated with the antecedent chronic marginal gingivitis.

(c) Additional vasoconstriction due to the effects of smoking. They describe this action as being both local and systemic, although the evidence favours a purely local effect due to the release of noradrenalin from adrenergic axon terminals within the tissues. 249,250

(d) Inadequate thermoregulatory mechanisms and possible use of the mouth for heat exchange. This would lead to peripheral vasoconstriction and augment other circulatory effects, particularly during the winter months.

The attractiveness of this hypothesis lies in the fact that it may explain the role of several of the commonly implicated predisposing factors, which may act synergistically. It also allows speculation on the role of endotoxin in further potentiating the vascular changes described, and on a role for immune complex deposition on vascular basement membranes as a result of ischaemia. 228

Although there is considerable evidence favouring the argument that cumulative vascular changes may be important aetiological factors, this particular hypothetical construction is based on certain unacceptable assumptions.

(a) The "Triad of inter-related predisposing factors", stress, smoking and CMM, is not present in all cases.

(b) The increased incidence of NUG in the winter months is not supported by the evidence on seasonal incidence.

(c) There is no conclusive evidence that the oral mucosa does, or indeed can participate in thermoregulatory functions. 30

(d) The description of the circulation to the col regions and the tips of the papillae is based on early reports by MacPhee and Beagrie 137 and Kindlova. 270
The former ignored the collateral contribution from the vessels of the periodontal ligament, and the latter failed to consider the contribution of the branches from the inter alveolar arteries.

These omissions were recognized and corrected in later published work by these authors. 100, 271

The interpretation placed on Kindlova's observations on the role of the glomerular capillaries is not only highly speculative, but actually at some variance with the findings which she reported. 270 Kindlova was unable to demonstrate that the glomerular capillaries were sphincter operated and could therefore be separated from the circulation, or that they represented arterio-venous anastomoses.

She also pointed out that the glomerular capillaries were a feature of the blood supply of the healthy periodontium, and disappeared in early periodontal disease. It could therefore be questioned whether they are present in the gingival tissues before the onset of NUG, which is nearly always preceded by CMG.

Subsequent descriptions of the gingival vasculature have indicated that arterio-venous shunts are probably absent from the oral regions in man. 30 Precapillary sphincters, although present, are apparently less responsive than those of skin, and gingival capillaries may remain open even when gingival arterioles participate in induced vasoconstriction. 30

The hypothesis also tends to ignore the other mechanisms whereby CMG, smoking and stress may affect gingival tissues (catecholamine potentiation of endotoxin activity, immunosuppression, chalone activity, lowering Eh and facilitating bacterial colonization etc.)
It cannot be used to explain the occurrence of NUG in very young children under certain circumstances, although argument is advanced that the absence of the disease in older age groups is attributable to a less dense and less active sympathetic network. 248

The high incidence of NUG in mongolid retarded individuals has been noted. 159 Since it occurs in these patients at a very early age (mean age 9.4 years), they presumably do not smoke.

However, it is of considerable interest that the incidence of cardiovascular defects in these patients is extremely high 213, and that this factor might predispose to the development of local ischaemia.

Peripheral circulation is stated to be poor, and acrocyanosis is frequently found to be present. 264

Brown 159 noted that the greatest number of recorded recurrences in his study occurred in a mongolid patient with severe congenital cardiac disease accompanied by cyanosis.

Endogenous infection.

Gram staining of smears taken from lesions clinically classified as NUG demonstrates a multiplicity of organisms, with a marked predominance of spirochaetes and fusiform bacilli. 102, 127, 199 (Figures 22a and 22b).

Although histological evidence of overwhelming numbers of these fusospirochaetal organisms is accepted by some as corroborative evidence of the presence of the disease 99, 156, 177, it is considered inconclusive in the absence of clinical symptoms, and cannot be regarded as pathognomonic of NUG. 104

Gram-negative anaerobes, filaments, fusiforms and spirochaetes are known to increase in numbers with the establishment of gingivitis
Fig. 22a Oral smear from a patient with ulcerative necrotizing gingivitis demonstrates spirochetes and fusiform microorganisms. (From the collection of Edgar D. Coolidge.)

Fig. 22b Electron photomicrograph of *Borrelia vincentii*. Shadowed preparation. (x11,000.) (Courtesy Edward G. Hampp, Bethesda, Md.)

and of chronic destructive periodontal disease. 199, 251, 272

Fusospirochaetal organisms are frequently found to appear as contaminants superimposed on lesions induced by other agents such as nutritional disturbances, radiation damage or viral infections. 164 Genital fusospirochaetosis is regarded as an endogenous infectious disease 119, which is usually only observed in individuals with low resistance, and frequently occurs secondarily to other lesions. Organisms are often demonstrable within the tissues. Spirochaetes predominate in the acute phase and are more numerous in the deeper necrotic layers of the lesion than on the surface. Penetration by spirochaetes into the tissues is also a feature of NUG. 197, 198, 273

"Vincent's type" organisms are also stated to appear in tropical ulcer, which occurs as a chronic lesion in debilitated patients. 274

The precise role of bacteria in the production of the NUG lesion has been a matter of intense speculation and research for many years, but remains undetermined. Nevertheless, NUG is frequently classified as an infection of the oral mucosa. 99, 102, 103, 104

There is little doubt that endogenous bacteria are implicated in the production of the clinical manifestations of the disease. Rapid remission of the acute symptoms is readily achieved by the administration either locally or systemically of a wide variety of both broad spectrum and also more specific chemotherapeutic agents. 275, 276

Selective local overgrowth of the indigenous species does not necessarily indicate a primary pathogenic function in the initiation of disease. It may simply represent opportunistic behaviour and relative displacement of other species from the affected area. However,
elimination of the local overgrowth of fusospirochaetal organisms by either mechanical or chemotherapeutic means is found to coincide with the palliation of symptoms and clinical remission of NUG. Fitch et al. treated 100 patients using mechanical (ultrasonic) debridement as the sole form of treatment. They obtained sequential bacteriological smears for 82 cases, which confirmed the clinical observation that elimination of identifiable fusospirochaetal overgrowth coincided with the remission of symptoms.

A similar finding was reported in a study on the effectiveness of metronidazole in the treatment of NUG. Clinical resolution was accompanied by rapid disappearance of spirochaetes, although fusiform organisms did persist somewhat longer.

Listgarten proposed that caution be exercised in assigning a pathogenic role to bacteria solely on the basis of their relative prevalence in the microbial flora. A strong immune response could suppress the growth of a certain microorganism so that it does not constitute a major component of the identifiable oral flora. However, the response induced in the host tissues as a consequence of this suppression could be an important factor in the pathogenesis of the lesion.

Historically, the two most frequently implicated organisms, identified by their gross morphology, are:

Fusobacterium fusiforme. A Gram-negative, strictly anaerobic bacillus, 0.5 to 1.0 microns in diameter. It is a slender curved organism with pointed ends, having a cigar shaped appearance and often occurring in pairs. (Figure 22a). Thomas points out that the bacteroides-fusiform group of organisms is large, heterogeneous and pleomorphic, and that the distinction between the two genera is as yet provisional.
Borellia vincentii is a Gram-negative, loosely wound, strictly anaerobic actively motile spirochaete. It is stated to be 0.3 to 0.5 microns in diameter and five to 10 microns long, with three to five open irregular curves. (Figure 22b).

Descriptions of its gross morphology vary further illustrating the difficulties of attempting to classify spirochaetes on morphological grounds alone. Identification is made more difficult by the fact that these two organisms occur in association with other similar organisms, and with other species including vibrios, facultative and obligate diphtheroids, streptococci, treponemes, bacteroides, coccobacilli, filamentous organisms and veillonella.

Thus there is a complex, mixed and predominantly obligate and facultative anaerobic flora. These organisms are all present to some degree in a high proportion of clinically normal mouths, and their numbers increase with the establishment of periodontal disease. Wet unstained smears examined by phase contrast microscopy reveal many of the fusiform organisms to be motile. In addition, motile amoebae can be demonstrated in 60% of cases, and motile trichomonads in 12%. Although direct smears demonstrate an apparently high proportion of spirochaetes, this appears to represent a localized concentration rather than a generalized proliferation. Examination of gingival debris following uniform dispersion by sonic oscillation reveals that spirochaetes comprise only 2% of the total microbial population in NUG. A similar percentage is present in cases of mild marginal gingivitis. Gibbons and van Houte concluded that the
approximate proportional distribution of spirochaetes in the gingival crevice was 2% of the total flora.

The principles of proof required to accept a particular microorganism as the cause of a disease are known as Koch's postulates.

(a) The organism must be found in all observed cases of a given disease, in pathological relationship to its symptoms and lesions.

(b) The organism must be isolated from such cases in pure culture on artificial media.

(c) This pure culture, when inoculated into a susceptible animal, must reproduce the disease (or, as later modified, engender production of specific antibodies in the new host).

(d) The organism must be isolated again in pure culture from such experimentally caused infections.

These ideal criteria are valuable in establishing pathogenicity, but they have limitations and are not always attainable in practice. Some organisms (including spirochaetes) are difficult or impossible to grown on artificial media in order to culture them in vitro. Others are pathogenic only to man.

Only the first two of Koch's postulates have been fulfilled for *Borrelia vincentii* or *Fusobacterium fusiforme*. 104
ANIMAL EXPERIMENTS.

Early attempts at experimental transmission of fusospirochaetal infections utilized rabbits or guinea pigs as experimental animals. Mixed anaerobic cultures were made of material obtained from unselected cases of gingival and periodontal disease, including NUG. These caused abscess formation when injected into guinea pig groins, and the lesion could be produced through several animal transfers. 280

Subcutaneous injection of single pure strains of cultured organisms failed to demonstrate pathogenicity. Attempts to produce lesions by utilizing various combinations of pure strains gave disappointing results. 280 Lesions were produced in some cases, but these were small and were not regarded as typical of fusospirochaetal infections. Exudates were transferred to fresh animals, and in those cases in which lesions were produced they were smaller and less characteristic. 280

The experimental method used may not have ensured collection of organisms from the deepest portions of the lesions of the original donor patients, or the subsequent survival of the more fastidious species. Organisms were not collected under strictly controlled anaerobic conditions, and it is doubtful whether the precise ecological conditions which occur in the human disease were reproduced. 99

In other experiments, abscesses were produced by the intracutaneous injection of both viable and heat killed pure strains of Borrelia vincentii and Borrelia buccalis. 281 Similar results were reported for viable and heat killed Fusobacterium nucleatum and Fusobacterium polymorphum. 282

The use of recombined or simultaneously cultured viable strains of spirochaetes and fusobacteria was shown to produce a synergistic effect. 282
It was observed that a cell free filtrate from an oral diptheroid potentiated the enhancement and extension of the spirochaetal lesions. This filtrate contained hyaluronidase and chondroitinase and was presumably capable of depolymerizing ground substance.

Very high doses of bacteria were required to produce these experimental lesions, $6 \times 10^7$ cells/ml in the case of both viable and heat killed organisms. In those cases where viable organisms were utilized they did not remain motile or survive for long within the lesions. It was therefore subsequently suggested that the lesions produced were not true infections, but rather foreign body reactions resulting from the size of the eliciting inoculation. 127, 283

Later studies showed that differing combinations of anaerobic organisms could produce "typical" fusospirochaetal lesions in experimental animals. The most striking finding was that these lesions could be produced in the absence of both spirochaetes and fusiform organisms. 284 A minimum combination of four organisms was required, two strains of bacteroides, one of which was Bacteroides melaninogenicus, a motile Gram-negative anaerobic rod and a facultative diptheroid. It was concluded that mixed anaerobic infections may be non-specific in the bacteriological sense, but that there is an ecological biochemical specificity which can be provided by various combinations of organisms. 284

Macdonald et al. 283 confirmed that the presence of B. melaninogenicus was essential for the experimental production of mixed anaerobic infections. They suggested that the role of the other organisms was the enhancement of the growth and metabolism of this key pathogen. Many strains of the organism showed this pathogenic potential. Some also exhibited independent pathogenicity, although most were non-pathogenic in pure culture.
Socransky and Gibbons concluded that *B. melaninogenicus* is an essential organism in many experimental mixed anaerobic infections.

They commented on its endotoxin content, its ability to hydrolyze collagen and other proteins, and the potential toxicity of many of its metabolites. No conclusion was reached on the role of the other organisms in these mixed infections, though it was suggested that one of their essential functions might be to satisfy the naphthoquinone requirement of most of the strains of *B. melaninogenicus*. They concluded that this organism came closer to being an overt pathogen than any other microorganism normally residing in high numbers on the mucous membranes of man.

It has been shown that many strains of *B. melaninogenicus* possess fimbria-like structures which may allow preferential attachment to mucous membranes, thus facilitating colonization of the gingival sulcus.

Kaufman et al. commented on the collagenolytic properties of *B. melaninogenicus*, and stated that it is one of the few organisms possessing this ability. They demonstrated that a sterile cell-free extract of the organism which retained collagenolytic activity was capable of enhancing experimental skin lesions produced in rabbits by a single strain of *Fusobacterium fusiforme*.

The filtrate which they utilized was not tested for other enzyme activity, and the experimental method may have inactivated other factors which could have had a contributory role in the pathogenic potential of the organism.

Loesche et al. investigated the *in vitro* collagenolytic activity of the dental plaque in mentally retarded institutionalized individuals, who are known to have a high level of periodontal disease.
and of NUG. The study did not indicate the percentage of patients with Down's syndrome, nor the number having NUG.

At least three species of organism were identified which appeared capable of degrading undenatured collagen. These were *B. melaninogenicus*, *Clostridium histolyticum* and a facultative, motile, Gram-positive rod present in large numbers, whose appearance was compatible with the description given for *Bacillus cereus*. Neither the clostridium nor the bacillus species had previously been demonstrated in human plaque.

The role, if any, of bacterial collagenase in the pathogenesis of periodontal disease remains unclear.

None of these experimentally produced lesions are comparable with those which occur in the disease in man. Indeed it has been shown that it is possible to produce transmissible localized infections in guinea pigs by subcutaneous injections of gingival crevice debris obtained from NUG patients, periodontitis patients and normal controls. No marked differences were observed in the virulence of the infectivity of the debris from any of the three groups.

Lack of a suitable animal model may be the reason for the scarcity of recent information concerning the role of bacteria in NUG.

A single animal experiment resulted in the production of transmissible oral lesions similar to those which occur in the disease in man. Assessment of this experiment reveals:

(a) The lesions were associated with massive hair impaction around orthodontic appliances.

(b) The clinical description of the lesions is of marginal periodontitis associated with gingival ulceration.

(c) Bacteriological examination revealed a basically spirochaetal flora with few fusiforms.
(d) Methods of transmission from one dog to another were not described.

(e) The cellular response was predominantly monocytic with only occasional PMNs.

It appears that these lesions were chronic marginal periodontitis, with associated trauma to the gingiva from orthodontic appliances and hair impaction.

Acute necrotizing gingival lesions, stated to resemble NUG, have recently been described occurring in beagle dogs. These lesions could be experimentally transferred to healthy dogs, but only after systemic administration of corticosteroids.

The microbial flora described in association with lesions showed a preponderance of peptococci, corynebacteria, propionibacteria and fusobacteria. Spirochaetes were not described.

It is not possible to assess whether the lesions described fulfil the criteria for NUG.

The role of spirochaetes.

Listgarten and Socransky demonstrated the presence of spirochaetes in almost pure culture within biopsy specimens of NUG lesions viewed by electron microscopy. Similar organisms in lesser concentration were found in the bacterial plaque from these patients. It was suggested that the organisms found differed from Treponema microdentium and from Borrelia vincentii, and most importantly, that they were not detected in the bacterial plaque of patients without NUG.

A subsequent ultrastructural study was used to establish a classification for oral spirochaetes. It was based on the diameter of the protoplasmic cylinder, the ultrastructure of the outer envelope, and the number of protoplasmic axial fibrils originating at each end of the cylinder. Small, intermediate and large forms of spirochaetes were identified. The size range of the different groups
of these organisms overlapped, demonstrating the difficulty of attempting to classify spirochaetes by their size alone.

Intermediate type spirochaetes predominate in the loose microbiota which is found on the surface of subgingival bacterial plaque. 251 Because of their preferential growth in close contact with gingival tissues, it is suggested that they may play an important role in the etiology of periodontal disease. However it is still not certain whether the organisms appear as a result of environmental changes or whether they are the cause of the changes. 251, 272

Pure cultures of Treponema microdentium and Borrelia vincentii are morphologically similar to small and intermediate type spirochaetes respectively. 266

A descriptive code was developed, based on the number of axial fibrils originating at each end of the protoplasmic cylinder, and the maximum number which could be counted where their free ends overlapped. (Figure 23).

As the number of axial fibrils increases, greater variation in their numbers occurs. The classification was found to be most accurate in those species having smaller numbers of axial fibrils.

The predominant small spirochaete found in patients with NUG has a cylinder diameter in the range of 0.1 to 0.25 microns. It was of the 2-4-2 type, whereas Treponema microdentium was shown to be a 1-2-1 type. 266

Intermediate size spirochaetes were in the size range of 0.2 to 0.5 microns in diameter. The most prevalent spirochaete in the gingival lesion of NUG was of intermediate size, but generally possessed more axial fibrils than cultivated strains of Borrelia vincentii.

It was suggested that more than one intermediate size spirochaete may be present in the gingival crevice area.

A very large spirochaete, 0.5 microns or more in diameter was occasionally demonstrated in NUG samples. It had a large number of axial fibrils, and a distinctive outer envelope in which was more
resistant to disruption than that possessed by the other spirochaetes. 266

Further investigation of the bacterial flora in NUG demonstrated the ability of the large and intermediate sized spirochaetes to invade non-necrotic gingival tissues in advance of the necrotic lesion. 197 Four distinct zones were demonstrated in gingival biopsies of typical NUG lesions; these revealed differences in the numbers and types of spirochaetes which they contained. (Figures 24 and 25).

<table>
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<tr>
<th>ORAL CAVITY</th>
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<tr>
<td><strong>1. Bacterial Zone</strong></td>
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<tr>
<td><strong>2. Neutrophil Rich Zone</strong></td>
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<td><strong>3. Necrotic Zone</strong></td>
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<tr>
<td><strong>4. Zone of Spirochaetal Infiltration</strong></td>
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Figure 24. The four zones of the NUG lesion.
Figure 25. Acute necrotizing ulcerative gingivitis.

Electron microscope photomicrograph illustrates the epithelium adjacent to ulcerated lesion. Neutrophiles (Ne), red blood cells (RBC), microorganisms and cellular debris cover the epithelium. Dense masses of large and medium spirochetes (S) and some neutrophiles (Ne) distend the space between the epithelial cells (Ep). Original magnification, x3500.


1. The Bacterial zone: A mixed flora covered the surface of the lesion, in which it was not readily possible to identify all species. Spirochaetes were recognized by their characteristic ultrastructural features. Some spirochaetes were present in the bacterial zone although they were not particularly numerous.

2. The Neutrophil Rich zone: This layer separated the bacterial layer from the underlying gingival tissue. It contained many leucocytes, with a preponderance of PMNs. Spirochaetes were demonstrated in this region, both within the cytoplasm of disintegrating cells, and also within mononuclear and occasionally PMN leucocytes.

Heylings 198 reported that he found PMN leucocytes in close contact with both spirochaetes and fusiform bacilli, but that they did not appear to be attempting to ingest the bacteria. These PMNs contained very few cytoplasmic organelles, which was interpreted as indicating that they were no longer viable.

3. The Necrotic zone: This was observed overlying the ulcerative tissue, and contained disintegrating tissue cells and large numbers of spirochaetes. A few other organisms were present which were stated to resemble fusiforms.

PMNs, mononuclear leucocytes and plasma cells were present, together with debris consisting of fibrillar material and disintegrating cells. The spirochaetes within this region were predominantly of the intermediate and large types. Heylings 198 found fusiform bacilli within the ulcerated tissues, and noted that their respective numbers decreased with the depth of tissue penetration.
4. The zone of Spirochaetal Infiltration: The only organisms found in the areas of deepest bacterial penetration were intermediate and large type spirochaetes. They were found within well preserved and apparently normal non-necrotic tissues, in advance of any other bacteria. They often appeared clumped together in large concentrations, frequently surrounded by an area of apparent lysis. Blake 133 described a zone of lysis in association with empty cyst forms and surrounded by a dense mass of spirochaetes; these were interpreted as drawing away from a germinal centre.

The zone of penetration was approximately 250 microns and never more than 300 microns beneath the surface of the ulcer. As well as being located within the connective tissue, spirochaetes were also demonstrated within the intercellular spaces of the normal epithelium adjacent to the ulcer. No fusiform organisms were demonstrated in the deepest zones of bacterial penetration. (Fig. 26).

Fig. 26. Zone of spirochaetal infiltration. Spirochetes, S, infiltrating the connective tissue beneath the ulcerated lesion. Collagen fibers are labeled col. (From Listgarten, M. A.: J. Periodont. 36:328, 1965.)

On morphological grounds it was suggested that the majority of the spirochaetes present in the deepest zones of the lesions were different to cultivated strains of *Borrelia vincentii*. Attempts to isolate these large and intermediate types of spirochaete have not been successful.

Later ultrastructural investigations by Heylings substantially confirmed Listgarten's findings, but there were certain apparently significant differences. He confirmed spirochaetal infiltration of non-necrotic epithelium, but observed relatively small numbers of fusiform bacilli as well.

The majority of the invading spirochaetes were described as differing from *Borrelia vincentii*. They were stated to be of only 0.2 microns diameter, in the same size range as the small spirochaete *Treponema microdentium*. This finding of a predominance of small type spirochaetes differs from that of Listgarten who demonstrated only intermediate and large type spirochaetes in the zone of infiltration.

Heylings used no criteria other than the size for classifying the spirochaetes. The organisms demonstrated were only half the width of the intermediate types, so it is not likely that they represented a strain from the lower limits of this size range.

Spirochaetes in the deeper areas were embedded in an electron dense amorphous substance. It appeared to be similar to a material demonstrated in the intercellular spaces, two to three cell layers below the ulcer floor, when thick sections were viewed by phase contrast microscopy. This was interpreted as evidence of considerable penetration of the epithelial tissues, and as a rationale for the use of systemic chemotherapy as the treatment of choice.
The discrepancies between these two studies could be partly explained by the fact that Heylings\textsuperscript{198} apparently limited his observations to the epithelial changes in early NUG. Listgarten\textsuperscript{197} used tissues from patients with established lesions, and included connective tissues in his sections. It is also apparent that the biopsy techniques differed, Heylings\textsuperscript{198} used a long narrow strip of marginal gingiva, while Listgarten\textsuperscript{197} excised whole interdental papillae by using buccal and lingual incisions.

Listgarten and Lewis\textsuperscript{296} studied the distribution of spirochaetes in NUG lesions. Pooled superficial and deep scrapings from established lesions revealed the following distribution:

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<th>% of Total Spirochaetes</th>
<th>Median %</th>
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<tr>
<td>Small</td>
<td>7% to 39%</td>
<td>28%</td>
</tr>
<tr>
<td>Intermediate</td>
<td>43.9% to 90%</td>
<td>72%</td>
</tr>
<tr>
<td>Large</td>
<td>0% to 20%</td>
<td>3%</td>
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In deep samples, intermediate types having more than seven axial fibrils originating at each end (\(\geq 7\)), predominated over those having less than six (\(\leq 6\)). Pooled superficial and deep scrapings showed that the type \(\geq 7\) occurred more frequently than the type \(\leq 6\) in 10 of 11 patients.

\textit{Borrelia vincentii} is an intermediate type spirochaete of the \(\leq 6\) variety. The findings indicated that the type \(\geq 7\) type spirochaetes tend to outnumber \textit{Borrelia vincentii} in pooled scrapings, and are found in higher percentages in the deeper portions of NUG lesions.
These studies on spirochaetes may be summarized as follows:

(a) Unlike chronic forms of periodontal disease, bacterial penetration of the gingival tissues occurs in NUG.

(b) The invading organisms are predominantly, if not exclusively, spirochaetes, morphologically different from *Borrelia vincentii*. Although in the same size range, they differ from those found in the plaque of individuals with chronic marginal gingivitis.

(c) Spirochaetes penetrate viable tissues in advance of the necrotic lesion. This may indicate pathogenicity, but could be opportunistic behaviour by a highly motile organism following depolymerization of ground substance, or degradation of collagen, by enzymes released by other organisms. 283

(d) Elimination of spirochaetal (and fusiform) predominance coincides with the clinical remission of symptoms.

A chance observation by Listgarten 297 was the appearance of large numbers of *typical* spirochaetes in a patient who had been selected as a normal control, and who developed NUG within two weeks of this observation. Such an isolated finding would be difficult to repeat, but could imply a primary pathogenic role for spirochaetes.

There is evidence that spirochaetes are late colonizers of the oral cavity in Western populations residing in temperate zones.

Spirochaetes do not occur in the mouths of endentulous infants, but the incidence of their occurrence increases with age until they are ubiquitously found in dentulous adults. 298

Gibbons and van Houte 235 state that for unknown reasons, oral spirochaetes and *Bacteroides melaninogenicus* do not colonize the gingival sulcus area until approximately the age of puberty.
Kelstrup \(^{299}\) demonstrated that the incidence of the presence of *B. melaninogenicus* in the gingival sulci of children was only approximately 20% in the age group five to 13 years, after which a rise in prevalence was observed. These observations are consistent with the clinical finding that NUG rarely if ever affects young children in these geographical regions.

NUG is a common finding in even extremely young children of low socio-economic background in tropical and subtropical regions.

Sheihah \(^{151}\) reported an 11% incidence of NUG in children aged two to six years within a randomly selected Nigerian population. He stated that bacteriological smears were made from samples taken from affected papillae in diagnosed cases, but did not report the findings. These would presumably have revealed the presence of spirochaetes and fusiform organisms.

Emslie \(^{152}\) reported a high incidence of cancrum oris and NUG in Nigerian children, and concluded that cancrum oris always develops as an extension of NUG. Smears were taken from these patients and revealed a mixed flora including spirochaetes and *B. melaninogenicus*. These bacteriological findings are in agreement with those of Tempest. \(^{232}\)

Malberger \(^{152}\) reported a similarly high incidence of both NUG and chronic periodontal disease in young Gambian children. Although he did not take bacterial smears from those patients with acute periodontal conditions, smears from those with moderate to severe chronic periodontal disease showed "large amounts of Vincent's organisms". Only 20% of the children with no obvious gingivitis were shown to have these organisms.

Jiménez et al. \(^{156}\) and Jiménez and Baer \(^{113}\) reported on cases of NUG in undernourished socially deprived Colombian children.
Spirochaetes were demonstrated in those cases in which bacteriological studies were performed.

Abundant spirochaetes were demonstrated in gingival lesions which occurred in a 15 months old Aboriginal child. 300

While it may be said that colonization of the oral cavity by spirochaetes and other strict anaerobes such as B. melaninogenicus appears to coincide with the age of onset of NUG, this cannot by itself be interpreted as evidence of primary pathogenicity. Differing combinations of predisposing factors may occur at an earlier age in undernourished, deprived children in tropical climates, than in affluent communities in temperate climates. Thus in both instances the fusospirochaetal overgrowth could be secondary to tissue damage from other causes.

A causative role for spirochaetes and fusiform organisms has been suggested 100, 301 on the basis of their sensitivity to the 5-nitroimidazoles (Metronidazole, Nimorazole). This was based on the obvious clinical effectiveness of these agents in the treatment of the disease, and their apparently limited spectrum of activity. The contention can no longer be supported, as it has been shown that the 5-nitroimidazoles are active against a wide range of organisms. 302 Metronidazole in particular is highly effective against many clinically important species of both Gram-negative and Gram-positive anaerobic bacteria 302, including B. melaninogenicus. 303

The role of fusiform organisms.

There is no generally accepted method for classification of the fusobacteria or the related bacteroides species. 304 Those methods which are recommended are very time consuming and difficult,
and identifications based on morphological grounds alone should be interpreted with some caution.

Heylings\(^{198}\) provided some evidence of infiltration by relatively few fusiform organisms between still viable epithelial cells. The proportion of fusiforms to spirochaetes became less as the bacterial penetration extended into deeper tissues. The organisms described were approximately 0.3 microns in cross section, more than twice the size described for Fusobacterium fusiforme but within the size range of Fusobacterium polymorphum.\(^{198}\)

Small numbers of fusiform organisms were present within the necrotic zone described by Listgarten\(^{197}\), who stated that the deepest zone of bacterial penetration contained no organisms other than spirochaetes.

Hadi and Russell\(^{305}\) demonstrated a real increase in the number of viable fusiform organisms present in the saliva of patients with NUG when compared with controls. They obtained limited evidence that the count fell again to normal with regression of the symptoms. The predominant organism was found to be Fusobacterium nucleatum. These findings were not interpreted as evidence of primary pathogenicity, but the possibility of using selective cultural methods in confirming diagnosis was proposed.

An apparently disproportionate increase in the numbers of Leptothricia buccalis B was noted within the reported total increase, but no conclusions were drawn from this finding.\(^{305}\) A subsequent study of gingival material from NUG patients failed to confirm the apparent selective increase in numbers of L. buccalis B, but the predominance of F. nucleatum was confirmed.\(^{306}\)

Of greater interest in this study was the finding that when
material from cases of advanced chronic periodontal disease (ACP) was included, the demonstrated increase in the count of viable fusobacteria applied to both the NUG and the ACPD groups. There was no significant difference between the two, although in both groups the mean count was significantly higher than in normal individuals. Findings were expressed as the actual concentration of fusiform organisms per gram of gingival debris, excluding the possibility of an apparent increase due to the greater amounts of debris present in established periodontal disease.

Conclusions were guarded; no attempt was made to implicate fusiform organisms as primary pathogens in NUG. The findings confirmed that the presence of periodontal disease is characterized by an increase in the Gram-negative flora, either as a contributing agent or as an indicator of disease.

Significantly greater cell mediated immunity against *F. fusiforme* has been demonstrated when comparing NUG patients to those with CMG. As the CMI activity against other Gram-negative bacteria was similar in both groups, it was proposed that *F. fusiforme* might be implicated in the change from pre-existing CMG to the acute disease.

**PERPETUATING FACTORS.**

The acute symptoms of NUG may undergo apparently spontaneous remission without treatment or resolve very rapidly when treated in a variety of ways. Such symptomatic remission is frequently only temporary, and should not be misinterpreted as a definitive cure.
No specific chronic phase of NUG can be demonstrated either clinically or histologically, but the predictable frequency with which the acute phase is known to recur has been well documented. Smitt studied the incidence of NUG in Dutch naval personnel, and reported a 25% rate of recurrence within the first six months following an acute episode of NUG. It is important to note that these patients apparently did not receive any form of gingival surgery. Smitt relied on restoration of normal gingival contour as a result of regeneration of destroyed papillary tissue over a period of several months. The recurrences can therefore be explained in terms of persistence of the gingival deformities resulting from tissue destruction by the initial acute lesion. Surgical recontouring is now practiced in cases where papillary regrowth is delayed for such long periods as described by Smitt.

Giddon et al. recorded that 30% of the NUG patients within the student population they studied gave a history of previous attacks.

Recurrences have been described as occurring in a manner suggesting that the gingival tissues in some way become sensitized to some local agent. Lehner suggested that an underlying idiopathic IgG hypogammaglobulinaemia might be responsible.

Factors which perpetuate the disease by facilitating recurrence include all those local factors which predisposed to the initial episode but were not effectively eliminated. Predisposing factors such as smoking and psychological stress which are not readily amenable to modification will also influence recurrence.

Inadequate management of the residual condition following palliation of the acute symptoms results in the perpetuation of the
disease due to the persistence of gingival deformities.

Destruction of the papillae, and subsequent proliferation of repair tissue, results in saucer shaped interdental deformities. These are surrounded by shelf-like ledges of thickened marginal tissue which favour food retention and impaction. 120

Such gingival defects become more exaggerated with repeated acute attacks, developing into deep interdental craters whose walls are formed by loose aprons of tissue labially and lingually. 162 Further ulceration then occurs at the base of these craters.

Inverted or reverse gingival architecture results when destruction of the interdental gingiva, and possibly septal bone, is severe, while the labial and lingual marginal gingiva is either unaffected or enlarged by the inflammatory reaction. 104

Since NUG most frequently occurs and recurs in the mandibular anterior region where the interdental septa are extremely thin 123, 125, 267, rapid bone loss may be associated with repeated recurrence. This results in permanent deformity 99, reverse architecture and chronic periodontitis.

Manson 120 describes the permanent gingival deformities of NUG as so characteristic that previous acute episodes of the disease may be diagnosed in patients in whom there have been no exacerbations for many years. This view is supported by Schluger. 172 (Plates 7 and 8).

Stammers 131 noted that recurrences occurred far more frequently in patients who had failed to complete definitive treatment, than in those in whom periodontal pockets and other morphological and iatrogenic predisposing factors had been eliminated. Recurrence was observed in 27.6% of those who failed to complete treatment.

PLATE 8. Recurrent necrotizing ulcerative gingivitis.
Manson and Rand 267 investigated the incidence and the aetiology of RNUG, and commented on the frequency with which it occurred. They recorded the incidence of associated local perpetuating factors, and noted that 82% of recurrences were associated with poor gingival contour arising from failure to correct the gingival deformities caused by the first acute attack. 39% were associated with food impaction which would be facilitated by the presence of gingival craters and also contribute to their persistence.

Goldhaber and Giddon 122 recommended the elimination of all local predisposing factors, particularly any interproximal gingival craters.

MacPhee and Beagrie 137 stressed that interdental ulceration produced vertical tissue loss within the col region. This resulted in a loss of functional morphology due to the development of interdental cratering.

They confirmed the importance of a rehabilitation phase following palliation of acute symptoms. The treatment plan consisted of a short initial phase devoted to the alleviation of acute symptoms and establishment of oral hygiene procedures. This was followed by elimination of those iatrogenic and morphological defects which initially predisposed to the development of gingival inflammation, and finally, surgical restoration of functional gingival form.

To be effective in preventing the recurrence of NUG, this treatment and rehabilitation phase must be completed within a reasonable period of time. 137 Pritchard 162 states that early and effective local treatment which prevents tissue destruction may be followed by a return to normal gingival architectural form. He stresses the frequency with which the disease recurs if suppression of the local acute symptoms is not followed by adequate treatment, including
surgical recontouring to restore normal anatomical relationships.

Attention has been drawn to the difficulty in achieving these treatment aims in many cases, because of the underlying psychological problems which are characteristic of these patients. The effect of this psychological factor on the achievement of definitive treatment is typified by the observation attributed to Waltzer, "patients with NUG never complete their treatment and never pay their bills".

Spouge states that there is an increased tendency for recurrent attacks to be precipitated during exposure to debilitating conditions such as exhaustion, stress or upper respiratory tract infections.

Underlying undiagnosed systemic diseases, e.g. blood dyscrasias may occasionally be perpetuating factors in NUG. Patients in whom predisposing factors appear to be minimal, but who exhibit frequent, inexplicable or recalcitrant recurrences of NUG should undergo haematological examination.
Part 7.

INCIDENCE and COMMUNICABILITY.

Most epidemiological studies of NUG have utilized readily accessible but select communities such as military personnel or student populations.

The incidence of NUG in the total civilian community has rarely been studied. Results obtained from military or student populations must be interpreted in the knowledge that the age groupings of these subjects correspond very closely with the age group of peak incidence of NUG. 123, 143 In addition, these groups are usually subject to physical, academic, emotional and social environmental stresses which may contribute to the systemic and psychological aetiological components of NUG.

Clinical impressions expressed in the literature 99, 119 indicate that the incidence of NUG may be decreasing in some communities.

During World War I the disease occurred in pseudoepidemic proportions, from which the common description of "trench mouth" derives. 103, 112 Although at that time considered a communicable disease, it is now believed that this widespread occurrence was due to shared environmental predisposing factors. These included prolonged exhaustion, gross physical debility, monotonous and inadequate diet, frequent URT infections, extremely poor hygiene, unremitting intense psychological stress and heavy tobacco consumption.

Methods of treatment and their availability were necessarily inadequate, so the incidence of recurrence was presumably high.

It is stated that German forces remained relatively unaffected. 109, 112 Although difficult to confirm, this could be explained by the fact that their disposition was usually defensive, resulting in better rations, accommodation and hygiene, considerably less physical exhaustion, and less anxiety than that which occurred in attacking troops.

Comparative figures for tobacco consumption are not available.
During World War II both military and some civilian populations were affected, although apparently not as severely as in the previous conflict.

This could reflect a rise in standards of oral health, hygiene, nutrition and living conditions, as well as improved methods of treatment. It is also noteworthy that civilian and military morale received considerable attention in order to maintain psychological competence.

Statistics for the Vietnam conflict have not been published. They would be of considerable interest in view of the reputedly high level of drug abuse and its reported association with NUG.

Pindborg studied the incidence of NUG in military personnel during 1945 to 1948, and reported an incidence of 6.9% among newly conscripted sailors. The incidence in serving personnel was as high as 20%. He commented on the very poor living conditions of these men, and stated that there was an increase in NUG at the end of the war which decreased with the passing of time.

It should be noted that Pindborg classified NUG as incipient (pre-Vincent's), acute, subacute and chronic. The incidence of actual acute NUG was 1.2%. Pindborg classified NUG as incipient (pre-Vincent's), acute, subacute and chronic. The incidence of actual acute NUG was 1.2%.

Grupe and Wilder examined over 2000 recently inducted military trainees, and noted that 2.2% had NUG.

Smitt studied inductees and serving personnel in the years 1958 to 1959. 2.1% of prospective conscripts were found to have NUG, while the incidence on board naval vessels was much higher. He concluded that an incidence of 2.5% should be regarded as normal in camp or on board ship.

Comparable civilian figures are provided by Giddon et al. who reported a 2.5% incidence of NUG in students entering college, while a further 1.2% gave histories compatible with previous NUG.
Other students subsequently developed the disease, and at the completion of their first year in college 6.7% of students had been affected.

It was later assumed that approximately 10% of this class would have been affected by the time they completed their studies, and an even higher percentage by the time they reached the age of 30. This assumption remains unsubstantiated. In the most recent study, Barnes et al. reported an incidence between 0.11% to 0.15% in newly inducted soldiers, and an incidence of 0.47% in serving soldiers. These figures, lower than those reported in earlier studies, are comparable with those of a large scale civilian study conducted in Europe during the decade 1958 to 1967.

The clinical impression of a reduction in the incidence of NUG could be influenced by any of the following factors.

(a) Return to normal civilian levels following high incidence during wartime.

(b) Improvements in diagnostic criteria, eliminating previous overestimates based on misdiagnosis.

(c) Improvements in nutrition and health care, thus reducing debilitating predisposing systemic factors.

(d) Abortion of symptoms due to the widespread use of self administered or medically prescribed chemotherapy. Were this the case, an eventual increase in the number of characteristic residual gingival deformities could be anticipated.

(e) In some communities, improved oral hygiene including interdental cleaning may have reduced the incidence of severe predisposing gingivitis in the susceptible age group. Concurrently, there could be a reduction in iatrogenic predisposing factors following improved restorative and preventive techniques.

(f) There may be fewer recurrences, as a consequence of more effective comprehensive treatment.
(g) Diminution in the severity of presenting symptoms, and earlier attendance for treatment. This could result in incipient cases being managed as non-specific acute or chronic marginal gingivitis, and remaining undiagnosed as NUG. There has been some diminution in the severity of the presenting lesions since the disease was first described by Vincent. 165

(h) There may be an actual temporal variation in the incidence or the severity of the disease.

**Communicability.**

Until World War II, NUG was regarded as a communicable infectious disease. Transmission by direct contact or via shared eating utensils was described, and isolation of the patient and the use and sterilization of separate eating utensils was recommended. 117 Such recommendations occasionally persist in the more recent literature. 309

There appears to be little value, other than the aesthetic consideration, in advising patients to avoid kissing children 119, as they are not usually affected by the disease.

Findborg 114 originally considered the disease to be communicable, but now states that its communicability has been "exaggerated". 160

Studies during World War II provided convincing evidence of the non-communicable nature of NUG. 167 Stammers 131 commented on the astonishing lack of evidence of its epidemic origin. These observations are further supported by the failure of efforts at direct transmission of NUG.

The extremely fastidious aetiological requirements of the commonly implicated bacteria makes the possibility of their transmission by any of the usual methods extremely unlikely.
Jiménez et al. 156 reported the familial occurrence of NUG in socio-economically deprived children in Colombia.

They speculated that NUG might in certain circumstances become contagious, but stressed that the observed familial occurrence could have been a fortuitous finding attributable to shared adverse environmental factors including malnutrition, stress and poor hygiene.

There is now general agreement that the disease is not communicable 99, 103, 104, 118, 126, 130, 167, and that if its aetiology is in fact primarily infectious, then it is the endogenous bacterial microflora which is implicated.

**Sex Distribution.**

There is no agreement on the effect, if any, of sex on the distribution of NUG.

Various studies have indicated:

(a) ... an equal distribution between men and women 120, 131, 156, 307, 308

(b) ... a higher prevalence in women 146, 177, 183

(c) ... a higher prevalence in men 123, 142, 143, 147, 267

One study involved both mongoloid and non-mongoloid retarded patients. There was no significant difference between the proportions of men and women among affected mongoloids. In the non-mongoloid group, more women than men were affected. 159

Skach et al. 143 reported that the maximum prevalence was approximately the same in men as in women. The age of maximum susceptibility persists longer in men so that the total number affected exceeds that of women. This difference was attributed to ill defined hormonal factors related to development and the attainment of maturity. 143
Many of the other studies were short term and conducted on small groups, so their accuracy may be questioned. The actual distribution of the sexes within the community studied is not often recorded.\textsuperscript{123} Other variables such as differences in oral hygiene performance and in smoking habits have rarely, if ever, been considered.

Stammers\textsuperscript{131} noted an equal distribution of NUG between men and women. He attributed this to a shared industrial environment under wartime conditions, and the increased consumption of tobacco by women.

Barnes et al.\textsuperscript{123} recorded a higher incidence of NUG in men, which could not be wholly explained in terms of their numbers within the community studied, nor their utilization of available dental services.

It is suggested that further study of this factor is required.\textsuperscript{123}
PART 8.

TREATMENT.

NUJ is stated to respond rapidly to prompt and effective treatment, but there is continuing controversy over which forms of treatment should be regarded as adequate.\textsuperscript{104, 122} Uncertainty over the exact etiology of the disease is reflected in the fact that treatment continues to be largely empirical.

Difficulties are encountered in evaluating the relative effectiveness of different forms of treatment. Sequential quantitative bacteriological assessments have been shown to be of dubious value in measuring the degree of improvement.\textsuperscript{310, 311} At best, they appear to offer no greater accuracy than careful objective clinical assessments.\textsuperscript{147}

Patient assessment of subjective improvement appears to be consistently more favourable than that determined by objective assessment, bacteriological assessment, or a combination of both methods.\textsuperscript{146, 147, 311} Successful comprehensive treatment is therefore based on the understanding by both the clinician and the patient that the suppression of symptoms alone does not constitute adequate treatment.

The use of an ulcer improvement index has been proposed as a method of objectively assessing improvement during the course of clinical trials.\textsuperscript{310} The index is determined by expressing the number of ulcers which resolve between the initial and the second visits as a percentage of the initial ulcer score.\textsuperscript{310} Since determination of the index itself depends on clinical assessment of improvement in ulceration, it appears to offer little advantage
over other forms of clinical assessment. 311

There is a possibility of a gradual decrease in acute manifestations without treatment, and of actual spontaneous remission of symptoms. 103, 120 One study drew attention to the fact that some placebo treated patients reported symptomatic improvement, and some were assessed as clinically improved. 145 It was suggested that whenever the results of clinical trials into the effects of drug treatment were being considered, it should be borne in mind that a percentage of patients who have not had treatment may show improvement. However, no steps were taken to determine whether the placebo treated patients had obtained concurrent treatment elsewhere. 145

When considering NUG it is usual to describe a two stage treatment plan:

(a) Rapid resolution of the necrotizing process, to minimize the amount of irreversible tissue destruction and to promote symptomatic relief. 120

(b) Restoration of gingival health by complete treatment of any residual gingival deformity or residual chronic disease. 120

The best treatment is the minimum treatment consistent with the return to health of the affected tissues and the prevention of recurrence. Those forms of treatment which simultaneously fulfill all these criteria should be employed wherever practicable.

Treatment of the Acute Phase.

Historically, more than 100 drugs have been used in the treatment of NUG. 178

There is now general agreement that the formerly popular use of topically applied chromic acid, with or without hydrogen
peroxide, is obsolete. 116, 267, 312 The effectiveness of this treatment was based on its caustic properties, rather than any effect on anaerobic bacteria by the release of nascent oxygen.

Relief of pain was achieved by the destruction of superficial nerve endings within the interdental gingiva 267, and the control of haemorrhage by the formation of a surface eschar of precipitated protein. 137

The risks which accompany the application of caustic drugs to lesions of the oral mucosa are still occasionally overlooked. 313

Those forms of treatment which are now most frequently employed, either singly or in combination are:

(a) ... debridement of necrotic material, accompanied by interproximal and subgingival scaling and early resumption of home care.

(b) ... chemotherapy, either local or systemic.

(c) ... use of mouthwashes for mechanical or therapeutic effect.

Systemic supportive measures may also be recommended in some specific instances.

Debridement.

Prompt and meticulous removal of all necrotic surface material, and of interproximal and subgingival calculus and plaque is an indispensable aspect of the treatment of NUG. 99, 116, 117, 162, 164, 168

The earliest possible resumption of effective plaque control by the patient is also an essential feature of any treatment plan. 100, 118, 120, 267

Proponents of other techniques consistently stress that these, used by themselves, are doomed to failure. Their use is intended to
ameliorate the acute symptoms to a level at which debridement and home care may be performed without causing undue patient discomfort. 122, 129, 135, 301, 314, 315

It must be stressed that the argument favouring debridement as the primary form of treatment is almost wholly based on assertion derived from clinical impressions, rather than controlled studies.

Schluger 167, 172 stated that he treated all cases by deep, immediate and thorough subgingival curettage. This was supplemented by mouthwashes of dilute hydrogen peroxide or warm water used for their mechanical flushing action. The term subgingival scaling is probably a more accurate description of the technique used. 162

He stated that pain was not a serious factor in this form of treatment, if fine slender curettes were used to perform careful instrumentation with minimal tissue manipulation. Pain was stated to be consistently within easy control, and rapid resolution of pain, inflammation and swelling were observed. 172

Stammers 131 observed that careful removal of calculus at the first visit was well tolerated by the patient, and that healing was accelerated irrespective of the type of medicament subsequently employed. Topical anaesthesia was occasionally used with success in very sensitive cases. 131

Oliver and Fletcher 312 employed repeated debridement as the only form of local treatment for all the patients in their study. Chemotherapy was reserved for those patients requiring chemoprophylaxis against infective bacterial endocarditis, or for those initially presenting with severe toxaemia. In these cases, scaling was commenced on the day following the commencement of chemotherapy.
Topical anaesthesia was occasionally used, but it was possible to treat most cases without causing severe discomfort. Pain, bleeding and swelling were all reduced following one treatment, and the smaller ulcers had healed following the second treatment. They concluded that healing was more rapid than that following the use of medicaments alone.

Early debridement reduced total treatment time, and tended to prevent the development of permanent gingival deformities (described as chronic recurrent NUG). Manson and Rand support the view that immediate debridement results in rapid relief of pain and enhanced healing, as do Schluger et al.

Fitch et al. reported on the treatment of 100 patients using ultrasonic instrumentation as the only form of treatment. Some of these patients had systemic involvements including malaise, lymphadenopathy and pyrexia. Two were hospitalized because of systemic toxicity and the severity of the oral symptoms.

It was stated that in most cases initial irrigation and gentle soft tissue debridement dramatically reduced the pain present within minutes. Following subgingival instrumentation, all patients reported relief of their acute symptoms at the conclusion of the first treatment.

Malaise, pyrexia and lymphadenopathy, where present at the first visit, were stated to have resolved or to be only slightly evident within 24 hours of the first treatment.

Ulceration, gingival enlargement and erythema were stated to be absent or reduced following this first treatment, and spontaneous
gingival haemorrhage had ceased. Persistence of ulceration was attributed to failure to remove all calculus at the first visit.  

The criteria for cure employed in this study did not include the restoration of normal gingival morphology, and the condition achieved is more accurately described as complete resolution of all acute signs and symptoms.  

20% of patients were so classified following one treatment, a further 52% following two treatments, and 21% required three treatments. These results were stated to be more rapidly achieved than when debridement was performed by hand instruments.  

Ultrasonic instrumentation is stated to offer the following advantages over other forms of treatment:

(a) Effective removal of surface slough, necrotic material and accumulated debris is facilitated by the irrigation and the flushing action of the instrument. 104, 118, 120, 316  

(b) The treatment is well tolerated by patients 317, 318 and leads to rapid diminution of symptoms during the initial visit.  

(c) Operator visibility is improved by the continuous lavage, if efficient aspiration is provided. Thus treatment may proceed despite induced haemorrhage.  

(d) Healing of the ulcerated tissues appears to be more rapid than when other forms of treatment are employed. 104, 166, 316  

(e) Effective interproximal and subgingival debridement may be performed for the first visit, thus fulfilling the criteria for an ideal form of treatment.  

(f) The disadvantages which may accompany the use of chemotherapy are avoided.
Some sources continue to caution against the early use of subgingival instrumentation during an acute phase, because of the alleged risk of spreading the infection or producing a dangerous bacteraemia. 119, 309

There are no reports in the literature to substantiate this claim. 164, 172, 312

Patients at risk of infective endocarditis because of congenital or acquired endocardial defects or cardiovascular prosthesis should receive prophylaxis with antibiotics as for any other dental procedure which may result in bacteraemia.

Chemotherapy.

Antibiotics.

Many antibiotics, administered either locally or systemically, will produce rapid clinical improvement of the symptoms of NUG. 276, 315, 319.

The indications for their use in treatment of NUG have been greatly reduced since the advent of the 5-nitroimidazoles. These have fewer general applications and fewer, less severe side effects than most antibiotics. 100, 102, 177

Chemotherapy should only be used as an adjunct to therapy in certain specific circumstances:

(a) When chemoprophylaxis is essential due to intercurrent medication or disease. 276

(b) In severe cases, or those with evidence of systemic involvement such as marked lymphadenitis or malaise. 122, 276, 314, 319
(c) In those cases which are highly resistant to local treatment. Careful review of the diagnosis is also necessary in these circumstances. 168, 276, 314

Penicillin.

Systemically administered penicillin is the antibiotic of choice for the treatment of NUG in the unsensitized patient. Topical use of this agent, advocated by Emslie 307 as late as 1971, is now universally condemned because of the risk of sensitization of the patient. Other risks include the development of resistant strains of organisms 276, 320, and the development of penicillin sore mouth or of candidiasis. 147

Oral administration has the advantages of convenience and lowered risk of sensitization. Treatment consists of 250 mgs of phenoxyethylpenicillin (Penicillin V) taken four times daily. 120, 135, 168, 308 For maximum effectiveness these doses are taken at least one hour before a meal and at least two hours after the preceding meal. To prevent the emergence of resistant strains of microorganisms, treatment should be continued for five days. 321

Symptomatic recovery is rapid, usually within 48 hours, 308, 310 thus allowing commencement of debridement.

If the patient has a history of hypersensitivity to penicillin, then erythromycin 118, 124, 276 and the tetracyclines 124, 276 are effective alternative antibiotics.

Chlortetracycline is also effective when applied topically. 128

Mouthwashes of this agent are used in the treatment of primary herpetic gingivostomatitis 163, and the use of penicillin in diseases of known viral origin is contraindicated. 104, 162 Chlortetracycline mouthwashes may therefore be the treatment of choice where NUG and PHG occur concurrently.
Vancomycin.

Several reports describe the use of topical applications of vancomycin in the treatment of NUG. 163, 307, 315, 322

Vancomycin hydrochloride is applied as an adhesive ointment or paste. Dosage varies from three to five mgs once daily 315 to 10 mgs applied five times daily. 307 Both symptomatic and objective improvement are stated to occur within 48 hours. 315

The effect of the drug is stated to be due to its ability to inhibit and disperse bacterial plaque. 315, 322 Two reports describe a reduction in the amount of materia alba 163, 315, for which the use of antibiotics is totally unjustified.

The use of vancomycin for topical application is stated to be safe, since it is poorly absorbed from the oral or gastric mucosa 163, and readily destroyed in the stomach. 315

Ototoxicity has been reported at the high dosage used parenterally, but side effects from the small amounts used topically are stated to be minimal. There are no reports of the development of resistant strains of organisms. 315

Holroyd 276 stresses that there are still parenteral uses for vancomycin, and that objections to its local use, or to routine use of any antibiotic in the treatment of NUG, remain valid.

The 5-nitroimidazoles are imidazole derivatives which are effective against a wide range of Gram-positive and Gram-negative anaerobic bacteria. 323

Metronidazole (Flagyl-May and Baker) 1-β-hydroxyethyl-2-methyl-5-nitroimidazole, is an effective systemic antiprotozoal agent, used in the treatment of urogenital trichomoniasis,
amoebiasis and other parasitoses. 324

Its effectiveness in the symptomatic treatment of NUG was first reported in 1962. Resolution of NUG symptoms was noted in a patient who was receiving metronidazole therapy for the treatment of trichomonal vaginitis. 157

The drug was originally thought to have an extremely limited spectrum of antibacterial and antiprotozoal activity. This impression tends to persist in the more recent literature. 99, 324 However metronidazole has been shown to be effective against a wide range of microorganisms 323, although claims that it is effective against all the clinically important species of Gram-positive and Gram-negative anaerobic bacteria 302 are still controversial. 325

It has been described as being universally bactericidal against obligate anaerobes. 326 More recent studies have suggested the need for in vitro sensitivity tests, as considerable variations in susceptibility have been observed among different genera and species. 325

Known susceptible organisms include fusobacteria which are apparently the most susceptible group. 325, bacteroides species 327, 328, leptothricia 329, clostridia and veillonella. 325, 329 Evidence of its in vitro effectiveness against bacteroides species was reported in early studies on its dental use. 157 Bacteroides fragilis appears to be particularly susceptible 325, 328, 329, and some strains of B. melaninogenicus have also been shown to be susceptible. 325, 326

It is stated to be absolutely inactive against aerobic bacteria. 330
Although the effectiveness of metronidazole against spirochaetes and fusiform organisms is unquestioned, there is disagreement regarding which of these genera is the first to be eliminated in the treatment of mixed infections.

Metronidazole is readily absorbed from the gastrointestinal tract, and maximum serum concentrations are reached within one to two hours. A serum concentration of four to five micrograms/ml, is attained one hour after the oral administration of 200 mgs of the drug. This level appears to have a rapid effect in suppressing spirochaetal activity.

It appears much more slowly and in lower concentrations in the saliva. A level of two micrograms/ml. is attained within four or five hours following a single 200 mgs oral dose, and much higher levels are achieved with subsequent doses. The salivary levels achieved with even a single dose exceed those required for the in vitro inhibition of spirochaetes.

Serum concentrations following a single dose exceed the minimum inhibitory concentration (MIC) and the minimum bactericidal concentration (MBC) required against some bacteroides species. Similar salivary concentrations would be attained within the first 24 hours of treatment. The MIC and MBC against strictly obligate anaerobes are regarded as being equivalent.

It is not known whether the pharmacological action of metronidazole is due to its presence in the serum, in the saliva or in both. It is most likely that the combined effect is that which occurs in vivo.

Evidence favouring an effect from the salivary component is strengthened by the finding that metronidazole when applied topically
is effective in the treatment of NUG. 144, 307

Numerous reports support the clinical effectiveness of metronidazole in the symptomatic treatment of NUG. 129, 142, 145, 157, 310

There is some disagreement on the rationale for its use, although the major factors influencing its popularity appear to be the simplicity of the treatment and the rapid achievement of subjective improvement. 142, 145

Results of two clinical studies indicated that the use of metronidazole might result in fewer recurrences than when other forms of chemotherapy are used. 142, 310 These tentative early observations have never been substantiated, and their uncritical acceptance 139 cannot be justified.

Others claim that the rapid elimination of spirochaetal and other organisms will minimize the extent of irreversible tissue destruction. 100, 145 A similar claim may be made for all forms of early and effective treatment, and comparative findings would be very difficult to assess.

Quayle 304 has drawn attention to the fact that rapid destruction of Gram-negative organisms could lead to the very rapid release of large amounts of endotoxin into the surrounding tissues. He mentions the possibility of the development of a degree of endotoxin shock. There is already a very high level of endotoxin in saliva, plaque, gingival fluid and gingival tissue during NUG 175, and its effects may be potentiated by stress released catecholamines. 175, 224 The presence of ulceration facilitates the entry of this endotoxin into the tissues.
Although metronidazole would eliminate the spirochaetes which are actually present within the normal tissues in advance of the necrotic lesion, debridement and lavage to displace the flush away the majority of microorganisms and the endotoxin from the site of the lesion may have certain theoretical advantages.

The local effect on the tissues from high levels of endotoxin released following rapid bactericidal action has not been studied, but should be borne in mind when considering the potential of various forms of treatment to minimize tissue damage.

Suggestions that this or any chemotherapy should be used to treat the early stages of the disease to avoid the possibility of pain from tissue manipulation 142, 295, or to postpone time consuming treatment 102, 142, 331 cannot be given unqualified support.

Therapeutic judgement dictates that analgesia and topical anaesthesia, in conjunction with sedation where necessary, are the methods of choice for pain control. More importantly, rapid relief accompanies gentle and effective debridement and lavage.

Chemotherapy may be the only effective initial form of treatment available or indicated for the severely handicapped or debilitated patient, e.g. those with Down's syndrome. It is also indicated in the emergency situation where immediate debridement cannot be performed for any reason, or when the presenting lesions are no longer confined to the gingiva, i.e. when mucositis or pharyngitis are present. 140

Its use is certainly justified in severe cases which are stated to respond extremely rapidly 142, but debridement should not be delayed and should preferably be commenced concurrently with chemotherapy.
Dosage.

Initial reports recommended a regimen of 200 mgs administered orally three times daily for seven days 145, 157, and this recommendation is still repeated in the current literature. 168, 171

Clinical effectiveness is achieved by the oral administration of 200 mgs three times daily for only two 177, 275, 310 or occasionally three days. 100 It should be noted that the manufacturer's recommended total dose for dental use has been reduced from 4.2 gms over seven days to 1.8 gms over three days. 331 Since there are no reports of the development of resistant strains, or of patient sensitization, treatment may be terminated as soon as clinical improvement has been achieved, thus minimizing the total dose. There are no reports that acquired resistance occurs in vivo or in vitro. 330

Toxic effects.

Metronidazole is regarded as having relatively few, infrequent and usually transient side effects. 177, 326, 332 Chemically it is an imidazole, bearing the nitro group which has been associated with the occurrence of some blood dyscrasias. 295 Its use is therefore contraindicated in patients with evidence or history of blood dyscrasia. 120, 324

Neutropaenia has been reported in some patients during administration of the drug, and transient moderate leucopaenia may occur. 324, 332 It is recommended that regular blood counts be performed during prolonged use, or if it is administered in high dosage. 324

The relationship between alcoholism and NUG has been described. 185
Metronidazole exerts an alcohol intolerance effect in man similar to that produced by disulfiram (Antabuse). Patients who are using the drug should be cautioned to avoid the concurrent use of alcohol as toxic psychosis, nausea, or headache may be induced.

Like disulfiram, it has been shown to elevate the circulating blood levels of sodium warfarin, and to potentiate warfarin-induced hypoproteibinaemia. These effects occur at doses similar to those proposed for the treatment of NCU, and systemic use of metronidazole for patients undergoing this form of anticoagulant treatment should be avoided.

Concurrent use of hydantoin anticonvulsants and disulfiram is contraindicated because of the possibility of hydantoin toxicity. A similar precaution should be observed with those 5-nitroimidazoles which have disulfiram-like effects. The only available report on the concurrent use of both drugs does not indicate whether any toxic effects were observed.

Production of transient hypotension has been reported, and the manufacturer suggests that it may be advisable to lower the dosage of the concurrently administered antihypertensive drug. Substitution of another drug for metronidazole appears more logical.

Its use is contraindicated in patients with active established lesions of the central nervous system. Neurotoxicity has been observed following prolonged administration. Although this peripheral neuropathy is stated to be completely reversible, at least two cases of persistent sensory neuropathy have been reported after treatment with large doses, 30.6 gms and 114 gms respectively.
Other reported side effects include gastrointestinal discomfort, nausea, unpleasant metallic taste sensations, anorexia, vomiting, urticaria, headaches and occasionally vertigo.

Urine colour changes may occur, due to the formation of water soluble pigments, azoxy hydrochlorides. This dark reddish-brown discolouration may be misdiagnosed as haematuria, but is an infrequent and apparently inconsequential side effect. The practitioner should be aware of its possible occurrence, so that the patient may be reassured that the discolouration is harmless and will disappear when the drug is withdrawn.

Recent reports have drawn attention to the fact that metronidazole in high dosage is oncogenic in rodents, mutagenic in bacteria, and therefore potentially dangerous in humans. Many agents which are mutagenic in bacteria are carcinogenic in animals and may also be teratogenic.

Metronidazole is the only drug, other than oncostatic chemotherapeutic agents, which exhibits mutagenic properties at concentrations equivalent to those reached in the body fluids during treatment with recommended doses.

To date, no carcinogenic effects have been observed in man as a result of the use of metronidazole.

The claim that the patient will only be subjected to a once in a lifetime exposure to the drug cannot be substantiated. Its effectiveness against anaerobic organisms has led to its use in high concentrations as a therapeutic or a prophylactic measure in abdominal and gynaecological surgery. Large doses are
used for antimicrobial prophylaxis of endogenously derived infection by non-sporing anaerobes.\textsuperscript{330}

A divided dose regimen of 200 mgs twice daily for six weeks (total dose 16.8 grams) has been recommended for the treatment of rosacea.\textsuperscript{335} Long term therapy is employed in the treatment of Crohn’s disease.\textsuperscript{337}

In addition, there is a possibility of repeated administration of divided doses for the treatment of actual or misdiagnosed NUG and RNUG. Loesche\textsuperscript{295} has advocated long term metronidazole treatment for periodontitis.

Its use has been recently advocated for the treatment of non-specific oral infections including pericoronitis and periapical abscess.\textsuperscript{334, 342} It is stated to be at least as effective as parenteral penicillin in such cases, and doses of up to 10.4 gms have been used.\textsuperscript{334}

All these uses are additional to its original application in the treatment of urogenital trichomoniasis, amoebiasis and giardiasis.\textsuperscript{331}

The manufacturers state that no embryopathic effects have been reported, and that it may be used in the first trimester of pregnancy if considered essential, and if short high dosage regimens are avoided. These claims are open to some question.\textsuperscript{332}

Metronidazole diffuses across the placenta, passes freely into the foetal circulation\textsuperscript{332}, and is found in the breast milk of nursing mothers in concentrations equivalent to those found in the serum. It is not known whether it can be injurious to the newborn infant.

There is agreement that metronidazole should not be used during the first trimester\textsuperscript{100, 120, 332, 341}, while some suggest
avoiding its use at any time during pregnancy and during breast feeding.

It must be stressed that metronidazole has fewer, less severe and more transient side effects than many other commonly used chemotherapeutic agents. The data presented suggest that it be used with some caution, in minimum effective dosage, and in combination with debridement and definitive treatment. Thus the initial dosage is kept to a minimum, and the possibility of recurrences and the necessity for repeated use is avoided.

Topical application.

Emslie claimed effectiveness for topical application of metronidazole in a chewing gum vehicle. 10 mgs of metronidazole were incorporated into a piece of gum of one gram weight. The patient was given eight pieces of gum, and instructed to chew each one continuously for four hours. No controls were used, so it is not possible to assess the amount of improvement attributable to physical cleansing and increased salivary flow.

This method has the major disadvantages that it requires considerable patient cooperation, and only allows pharmacological action during waking hours while the gum is in use. Patients reported occasional nausea, disliked the bitter taste, and might well discontinue treatment for these or for aesthetic reasons, or because of pain due to mastication.

In a later study, Emslie and Ashley used topical applications of metronidazole in paste form. They noted that it was effective in the treatment of NUG, although objection to the taste was again reported and doubts were expressed regarding patient compliance.
If metronidazole is the drug selected, then systemic administration by the oral route is the method of choice.

Nitromidazole. (Nitrimidazine, Naxogin - Carlo Erba)

1-N-β-ethylmorpholine-5-nitroimidazole has systemic trichomonacidal activity similar to that of metronidazole. 177 It is also effective against Gram-negative anaerobic organisms, although less active than metronidazole. An in vitro MIC of 1.05 micrograms/ml is required, compared with 0.34 micrograms/ml for metronidazole. 302

However it possesses superior pharmacokinetics to metronidazole, being more readily absorbed and reaching therapeutic serum levels very rapidly. 302 In an in vitro study of blood samples, its trichomonacidal activity was more rapid than that of metronidazole 177, and this therapeutic activity appears to be retained by its principle metabolites. 177

Reported side effects appear to be less than those for metronidazole. It possesses the disulfiram like effect 177, and there are occasional reports of mild and transient nausea or heartburn. 177

In a double blind controlled clinical trial, nimorazole was shown to be as effective as metronidazole in achieving remission of ulceration in NUG. The dosage employed was 250 mgs orally three times daily for two days. It was suggested that it might be possible to achieve comparable results with the same daily dose over an even shorter period of time. 177

Further clinical studies would be required to clarify aspects of the safety, mode of action, spectrum of activity and optimum dosage of this drug. 177, 302
Tinidazole. (Fasigyn-Pfizer), 1-2-ethylsulphonethyl-2-methyl-5-nitroimidazole has similar trichomonacidal properties, and is equally or more effective than either metronidazole or nimosazole against some Gram-negative anaerobic bacteria. 302, 327, 343

Its most common form of administration is a single two gram statim dose, a method which has certain advantages in ensuring patient compliance. 343 It is better absorbed than metronidazole, has a longer half life, and is therapeutically effective when given at about half the daily dose of metronidazole. 323

Side effects are uncommon and usually transient, the most frequent effects being on the gastrointestinal tract. It crosses the placenta and also appears in breast milk. Tinidazole should therefore not be used during the first trimester of pregnancy or by nursing mothers, although no dysmorphogenetic effects have yet been observed in rodent trials. 343

Attention has recently been drawn to the fact that both nimosazole and tinidazole share the mutagenic potential of metronidazole. 344

The effectiveness of tinidazole in the treatment of NUG remains to be evaluated, and its use in Australia is approved only for the treatment of urogenital trichomoniasis.
Mouthwashes.

The vigorous and frequent use of warm mouthwashes is often recommended as a form of treatment, or an adjunct to treatment, in the early stages of NUG. 104, 162, 164

Many claim that the effectiveness of mouthwashes is due to bacterial dilution and the mechanical removal of surface debris and necrotic material. It is therefore immaterial whether such lavage is provided by warm water 104, 164, 267 normal or hypertonic saline 137, 312 or a 3% solution of hydrogen peroxide diluted with an equal part of water. 172, 345

Such adjunctive use of mouthwashes is used in conjunction with immediate debridement, and is continued until the patient is able to resume effective plaque control measures.

Others claim actual therapeutic benefit from the use of oxygenating mouthwashes, and recommend their use to alleviate acute symptoms before attempting to perform subgingival scaling. It is presumed that the liberation of oxygen creates aerobic conditions which will suppress the overgrowth of the fusiforms, spirochaetal flora 146 but this has never been substantiated.

Both dilute hydrogen peroxide 146 and a solution of sodium peroxyborate monohydrate buffered with sodium bitartrate 146, 147, 308, 311 have been shown to be effective in treating the acute symptoms of NUG, when used as mouthwashes three times daily.

Wade and Mirza 146 concluded that the sodium peroxyborate preparation appeared slightly more effective than the hydrogen peroxide, but that the difference observed was not statistically
significant. They proposed that either preparation could be recommended as an alternative to antibiotic therapy.

No control patients were used in this study. It should be noted that the concentration of hydrogen peroxide used was lower than that which is most frequently recommended, i.e. 1.5% obtained by diluting 3% hydrogen peroxide with an equal quantity of water.

Wade et al. concluded that there was no statistical significance between the effectiveness of metronidazole taken orally three times daily, and the use of the sodium peroxyborate mouth wash three times daily.

Their figures did however reveal a trend to more rapid improvement in the metronidazole treated group, of whom 65% were rated in the highest category of improvement after 48 hours, compared with 43.5% of the group treated by mouthwashes.

A more recent study concluded that sodium peroxyborate was not as effective as either penicillin or metronidazole in the treatment of MUG.

The use of oxygenating agents may produce mucositis, glossitis, or with prolonged use the decalcification of tooth structure and damage to epithelial cells.

No studies have been undertaken to determine whether the symptomatic improvement attributed to oxygenating agents is due to the effect of the oxygen, or simply the detergent action of the vigorous lavage accompanied by effervescence.
Chlorhexidine.

A single report proposes the use twice daily of mouthrinses of 10 mls of a 0.2% aqueous solution of chlorhexidine digluconate in the early stages of treatment of NUG.\textsuperscript{347}

Pain is stated to decrease sufficiently within 48 hours to allow the patient to practice toothbrushing, and thorough scaling is stated to be possible within one week. No assessments of objective improvement are described, and the subjective improvement appears to occur more slowly than with other forms of treatment.

Another clinical report describes the use of chlorhexidine and cetrimide as a mouthwash for the treatment of NUG, but it is not possible to determine the amount or concentration of the agents used.\textsuperscript{348}

Since chlorhexidine apparently has no effect on subgingival plaque\textsuperscript{349}, its use alone in the absence of debridement appears unjustified.

However, following debridement and the removal of subgingival plaque, the use of chlorhexidine can prevent bacterial recolonization of the tooth surface\textsuperscript{347}, and significantly reduce gingival inflammation, provided the depth of the existing periodontal pockets does not exceed 3 mms.\textsuperscript{349}

The benefits of the procedure appear to be:

(a) ... the mechanical effect of lavage.

(b) ... removal of residual accessible uncalcified dental plaque.\textsuperscript{350}

(c) ... chemical inhibition of the development of dental plaque during the time that the patient is unable to perform effective oral hygiene.\textsuperscript{349, 350}
In vivo studies suggest that chlorhexidine may facilitate the healing of gingival wounds, presumably by its plaque inhibitory effect. However, recent experimental evidence shows that chlorhexidine, in the concentrations used clinically, can produce profound cytotoxic effects when it comes into contact with connective tissue cells or cells not covered with intact epithelium. Epithelial destruction and exposure of connective tissues are features of NUG.

Cellular toxicity has been demonstrated against human gingival cells and human newborn fibroblasts, and this cytotoxicity may be a factor in the delayed healing of certain types of wounds. These findings may not apply in the clinical situation where chlorhexidine becomes bound to salivary proteins, tooth pellicles, and existing dental plaque. However, they do suggest that the use of chlorhexidine in the treatment of NUG requires further critical evaluation.

Local toxic effects, although infrequently encountered, include development of glossitis, mucositis, and interference with taste sensation. The bitter taste of the compound may be a deterrent to patient compliance. Longer use may result in discolouration of the tongue, teeth, or tooth coloured dental restorations. There are occasional reports of the development of parotitis during treatment with chlorhexidine; these may be coincidental.
Systemic supportive treatment.

NUG responds well to purely local treatment capable of eliminating anaerobic organisms with specialized aetiological requirements and little invasive potential. 122, 135, 312

It is accepted that the onset of the disease, and either primary or secondary bacterial infection, result from an alteration in the host-parasite relationship. This is due to factors such as systemic illness, exhaustion, smoking, URT infections or environmental stress. 100, 140 Thus the gingival tissues are first conditioned by debilitation of the host, and necrotizing lesions supervene. 101

The disease itself may produce systemic symptoms, some of which may be due to food avoidance, loss of sleep 162 and the swallowing of blood and necrotic material. It may also be accompanied by varying degrees of lymphadenitis, malaise and temperature fluctuations.

Supportive treatment is indicated where there is evidence of distress or disability from these factors which is not improved by initial local treatment or by chemotherapy. 162, 166, 309 Such treatment is adjunctive, and intended to improve the comfort of the anxious or debilitated patient. There is no evidence that it will affect the clinical course of NUG, and it must be accompanied by effective mechanical or pharmacological treatment. 162

It is of importance in the less frequently encountered more extensive forms of necrotizing mucositis, palatopharyngitis or cancrum oris. These are often associated with intercurrent debilitating disease. 140

Since the advent of rapidly effective forms of treatment such as ultrasonic debridement and chemotherapy, the role of supportive treatment in NUG is minimal.
Bed rest is sometimes recommended for severe cases accompanied by toxaemia. 104, 120, 309

These cases are most probably severe mucositis, or lesions occurring concurrently with other illnesses, rather than uncomplicated NUG.

**Analgesics.**

Mild analgesics may be required when initial debridement must be delayed 309, e.g. if awaiting the results of chemotherapy.

**Dietary advice.**

To minimize pain, avoidance of hard or highly spiced food is indicated until the ulcers have healed. 168 Vitamin supplementation is sometimes recommended. 104, 124, 168 It may be indicated for debilitated patients such as alcoholics, drug addicts or those recovering from febrile diseases, or if there has been prolonged food avoidance because of pain. Any effect is on the symptoms of the actual dietary deficiency, rather than on the clinical course of the NUG. 103, 131, 309

**Smoking.**

Smoking is a major predisposing factor, and should be avoided or reduced during the course of the disease. 124

Difficulties may be encountered in achieving patient compliance. 309

**Alcohol.**

Abstinence from alcohol is sometimes recommended. 124, 309

The rationale for this advice is not clear, although it appears that alcohol consumption is regarded as debilitating and capable of lowering tissue resistance. 104

Metronidazole produces alcohol intolerance effects, and patients receiving this drug for the treatment of NUG should avoid the use of alcohol. 333
Psychiatric counselling.

Psychiatric counselling has been suggested in situations where stress is a major predisposing factor in intractable cases with frequent recurrences. 103, 124

TREATMENT OF THE RESIDUAL CONDITION. (Rehabilitation phase).

Resolution of the acute symptoms of NUG is the first phase of comprehensive treatment, which cannot be considered complete while gingival deformities, or factors capable of causing them, remain. 135, 309

The most common error in management of NUG is the premature discontinuation of treatment following the alleviation of acute symptoms. 122, 267 Persistence of gingival deformities as a result of inadequate treatment is the most frequent cause of recurrent NUG. 122, 131

Patient assessment of improvement is frequently more favourable than objective clinical assessment 147, 311, and the psychological problems which contributed to the production of the lesions may also result in poor patient co-operation. 131, 162

It is therefore important that patients be made aware of the objectives of treatment, and of the importance of the rehabilitation phase in effecting a cure and minimizing recurrence. 124, 353

Mild cases of NUG, or those in which ulceration is confined to and evenly distributed within the marginal gingiva may heal with little or no residual deformity. Such cases are stated to occur where there is little evidence of predisposing periodontal disease. 137 Environmental stress may be the major predisposing factor in the development of this type of lesion. 120
Repeated scaling, curetage and oral hygiene instruction may be the only form of periodontal treatment required to restore normal papillary morphology in these cases. 104, 122, 137 To be effective, such treatment must be commenced early. 162, 312

Factors which predispose to plaque accumulation should also be eliminated. Necessary conservative treatment should be performed, deficient restorations replaced, overhanging margins removed, and third molar opercula treated where necessary. 120, 124, 137

Papillary regeneration occurs much more slowly where deep interdental ulceration has occurred. 137 These lesions are most frequently associated with pre-existing chronic gingival or periodontal disease, and may be accompanied by interdental bone loss. 137

Recurrent disease most frequently arises in association with residual gingival cratering (i.e. reverse gingival architecture) associated with delay or failure to eliminate these craters and restore functional gingival contours. 102, 137, 267

Smit 117 relied on restoration of normal contours by papillary regeneration alone. The recurrence rate for these patients was 25% within the first six months. Regeneration of destroyed papillary tissue was stated to take place over several months. The clinical description of this regenerated tissue more closely resembles that found in chronic fibrotic gingivitis than in normal gingiva. 117

Grupe and Wilder 128 confirmed that the histological appearance of such apparently healed interdental papillae was not normal, but resembled that present in chronic marginal gingivitis.
The development of this type of persistent gingival crater can be minimized by early and effective treatment. This may be achieved by debridement alone 104, 135, 312, or in more severe cases debridement in combination with chemotherapy. 137

Drug treatment alone, particularly the use of topically applied drugs such as caustics, results in slower healing and a greater incidence of persistent deformity. 131, 267, 312

When restoration of gingival health and normal morphology is delayed, surgical recontouring is indicated.

The extent of such surgery will depend on the nature of the residual lesion. It may be limited to gingivoplasty, or, where bone loss and pocketing are present, the complete surgical elimination of such periodontal pockets is necessary.

Although some advocate that definitive surgery be delayed for some weeks following resolution of acute symptoms 309, others have noted accelerated healing following excision biopsy of severe lesions. 125

MacPhee and Beagrie 137 advocated a two week resting phase to allow gingival inflammation to subside following initial treatment. The rationale for this delay is not made clear. Some delay may be indicated if osseous or flap surgery is contemplated. Scaling and oral hygiene should be continued during this period as complete healing of less extensive lesions may occur.

Uncertainty over the aetiology of NUG, and the high rate of recurrence, makes necessary extended reassessment of treated cases. A minimum period of six months is recommended. 117, 120
Since many of the known predisposing factors are not readily eliminated, the risk of recurrence remains high even in definitively treated cases. 164

Summary of treatment of NUG.

ACUTE PHASE.

A. Medical history. Diagnosis. Recognition of intercurrent or predisposing disease.

B. Immediate debridement and subgingival scaling.
   Ultrasonic instrumentation preferable.
   Repeat as often as required.

C. Vigorous use of mouthwashes. Adjunctive.
   Effect primarily from mechanical flushing.
   Some therapeutic benefit may be obtained from oxygenating agents or chlorhexidine digluconate.
   Patient commences oral hygiene as soon as possible.

D. Chemotherapy.
   (i) When medically required for chemoprophylaxis.
   (ii) To minimize tissue destruction when gingival involvement is extensive, or response to other treatment slow.
   (iii) Where systemic manifestations are present.
   (iv) When local measures must be delayed because the patient is extremely handicapped or debilitated.
   (v) If NUG is accompanied by necrotizing ulcerative stomatitis.
Choice of drug: (a) Metronidazole has least side effects.
(b) Penicillin is an effective alternative in the unsensitized patient.

Choice based on medical history and possibility of drug interactions.

Chemotherapy is used concurrently with debridement, mouthwashes and oral hygiene. Where this is not immediately possible, these measures must be commenced as soon as practicable.

E. Supportive treatment. Must be accompanied by other measures as outlined above.

**REHABILITATION PHASE.**

A. Continued scaling, curettage, oral hygiene instruction.

B. Treatment of dental predisposing factors.

C. Identification of systemic predisposing factors (exhaustion, stress, smoking etc.) Provide appropriate advice. Reassess tissue morphology – if still unsatisfactory.

D. Gingival recontouring (gingivoplasty) or other periodontal surgery depending on the extent of the residual lesions.

E. Regular reassessment for possibility of recurrence. Minimum period of six months.
CONCLUSION

Necrotizing ulcerative gingivitis is an acute, specific gingival disease which may be infectious in origin but is not communicable. It now occurs less frequently, and usually with less severity, than during wartime. Necrotizing ulcerative stomatitis and cancrum oris occur even less frequently in affluent societies, and are rarely if ever encountered by the general practitioner.

Strict application of the outlined clinical diagnostic criteria will ensure accurate diagnosis of uncomplicated NUG. Explanations have been advanced for some of the apparent inconsistencies in clinical descriptions. These are historically derived from severe manifestations of the disease in grossly debilitated patients, or they reflect the concurrent presence of other conditions such as primary herpetic gingivostomatitis or pericoronitis. In addition, varying degrees of endotoxaemia may be responsible for temperature fluctuations or variations in the extent of lymphadenopathy.

The dangers of either misdiagnosis or incomplete diagnosis which may affect either the patient or the practitioner have been stressed.

The aetiology of NUG remains unclear. A clinical manifestation of acute vasculonecrotic gingival lesions may represent a tissue response common to several differing combinations of aetiological factors.

What is clear from review of existing studies is that many local and systemic predisposing factors, formerly regarded
as inexplicably unrelated exert remarkably similar physiological effects. Many of these factors may act cumulatively or synergistically. They may also influence the development of other aetiological factors, e.g. acute viral infections can predispose to the emergence of anxiety states and psychological stress.

It is therefore possible to explain the roles of smoking, pre-existing gingivitis, Down's syndrome, febrile diseases, protein calorie malnutrition, upper respiratory tract infections and psychological stress in terms of common or closely related physiological phenomena.

The effects of these diverse environmental influences have been explained as varying degrees of vascular stasis, suppression of innate and acquired immune responses, and interference with epithelial cell mitosis. These effects may be cumulative.

Large quantities of endotoxin derived from the associated mixed Gram-negative anaerobic bacterial flora may play a role by causing further immunosuppression. Endotoxin also produces vascular lesions, and its effects are potentiated by amines released by stress, smoking and the acute inflammatory response, either alone or in combination.

Although the mechanisms have not been demonstrated to be similar in every case, this review has revealed that some form of immunodeficiency is a common factor in those groups in whom the incidence of the disease is high. There is some evidence that this immune defect may interfere with the phagocytic capacity of polymorphonuclear leucocytes.

Immunosuppressive phenomena have been described occurring in smokers, in patients subjected to psychological stress, in Down's syndrome and in severe protein calorie malnutrition.
Endotoxin induced immunosuppression has also been described. The production of the gingival lesion most probably occurs when the combined effect of these factors reaches a critical point. Apparently paradoxical absence of one or more of the commonly described predisposing factors is thus readily explained by the presence in greater severity of another factor which produces similar physiological effects.

Remissions and recurrences have been enigmatic features of the natural history of NUG. It is now possible to partly explain them in terms of alterations in host immune responsiveness to the biological effects of bacterial endotoxin.

It is still not certain whether the role of microorganisms is primarily pathogenic, or as secondary contaminants of another lesion such as an aseptic necrosis. There is an apparent overgrowth of fusospirochaetal bacteria, which represents a selective local concentration rather than a generalized proliferation.

The proportion of these organisms within the mixed flora is the same as that found in other forms of periodontal disease. However, they are preferentially located within the necrotic surface layers, rather than within the gingival sulcus or the periodontal pocket.

Spirochaetal invasion of the tissue occurs. The invading organisms appear to be unique to NUG, and are ultrastructurally different to Borrelia vincentii. They are not found in normal mouths, or in other forms of periodontal disease. In addition, Fusobacterium nucleatum and Bacteroides melaninogenicus may be of importance.
What is certain is that clinical manifestations of the disease coincide with the apparent fusospirochaetal overgrowth, and that clinical remission accompanies treatment directed at the elimination of organisms with fastidious ecological requirements and limited invasive potential.

Because of the uncertainty over the aetiology, aspects of the treatment of NUG remain empirical. The understanding that the many systemic predisposing factors simply condition the tissues for the development of the local gingival lesion, suggests that treatment directed at this local lesion should be successful.

This is borne out in clinical practice, if the treatment is based on sound surgical and pharmacological principles.

A graded sequential treatment plan has been proposed which:

(a) ... ensures rapid relief of pain and other symptoms, irrespective of the severity of the presenting lesions.

(b) ... rapidly eliminates the ulcerative process, thus ensuring that there will be minimal gingival deformity.

(c) ... recognises the potential risks of various forms of chemotherapy and establishes a rationale for their use.

(d) ... minimizes the risk of recurrence.

Attention has been drawn to some of the less well known but potentially dangerous side effects and drug interactions of the 5-nitroimidazoles. A recent addition to the range of these agents may be worthy of clinical trial.
The clinician is therefore enabled to diagnose confidently and to treat effectively. As with the more common forms of chronic gingival and periodontal disease, this clinical expertise is regrettably not matched by a similarly complete understanding of the biological phenomena which underly the development of the lesions.
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