

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, CMI 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 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. ¹³³

Tissue damage resulting from the inflammatory response in CMG may contribute to cumulative vasoconstriction 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. ¹⁶⁴

Large amounts of bacterial endotoxin are known to be present in both the gingival environment and in the gingival tissues during NUG. ¹⁷⁵ Since large doses of endotoxin are known to be able to decrease phagocytic activity and resistance to infection 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 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.²⁶⁵ The lost biological responsiveness is regained some one or two weeks after cessation of administration of the endotoxin.²⁶⁵

Since NUG may undergo spontaneous remission without treatment^{103, 120}, but is notorious for its propensity to recur^{117, 267}, 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.¹⁷⁶ 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.¹⁰¹

These include alcoholism and liver cirrhosis ¹⁸⁵, 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 NUG. 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.

Stammers¹³¹ 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 infections⁹⁹ have been partly substantiated by objective observations. Grupe and Wilder¹²⁸ noted that many of the 870 patients in whom they observed NUG gave histories of recent URT infections. Skach et al.¹⁴³ 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.

Spouge¹⁰³ 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 H_2O_2 ¹⁷⁶ derived from large numbers of phagocytes such as PMNs, many of which disintegrate and release their contents which include H_2O_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 ¹²⁵ 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 ¹²² 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. ¹⁴²

The clinician should however be aware that NUG may occur superimposed on tissues affected by systemic diseases such as acute leukaemia ^{99, 103, 185}, heavy metal poisoning ^{104, 195}, and infectious mononucleosis. ¹⁸⁵ In the latter instance the coincidental presence of the two conditions may be purely fortuitous. ¹⁶⁹

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. ¹⁰³

Haematological examination may be indicated if the medical history proves non-contributory. ^{99, 104}

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 PNUG, 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 Schluger¹⁶⁷ 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.

Brown¹⁵⁹ 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 Stammers¹³¹ 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

Goldhaber¹²² 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.²⁶⁸

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 King²⁶⁹ 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 CMG, 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 mongloid 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 high²¹³, 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

Brown¹⁵⁹ noted that the greatest number of recorded recurrences in his study occurred in a mongloid 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 pathognomic of NUG.¹⁰⁴

Gram-negative anaerobes, filaments, fusiforms and spirochaetes are known to increase in numbers with the establishment of gingivitis

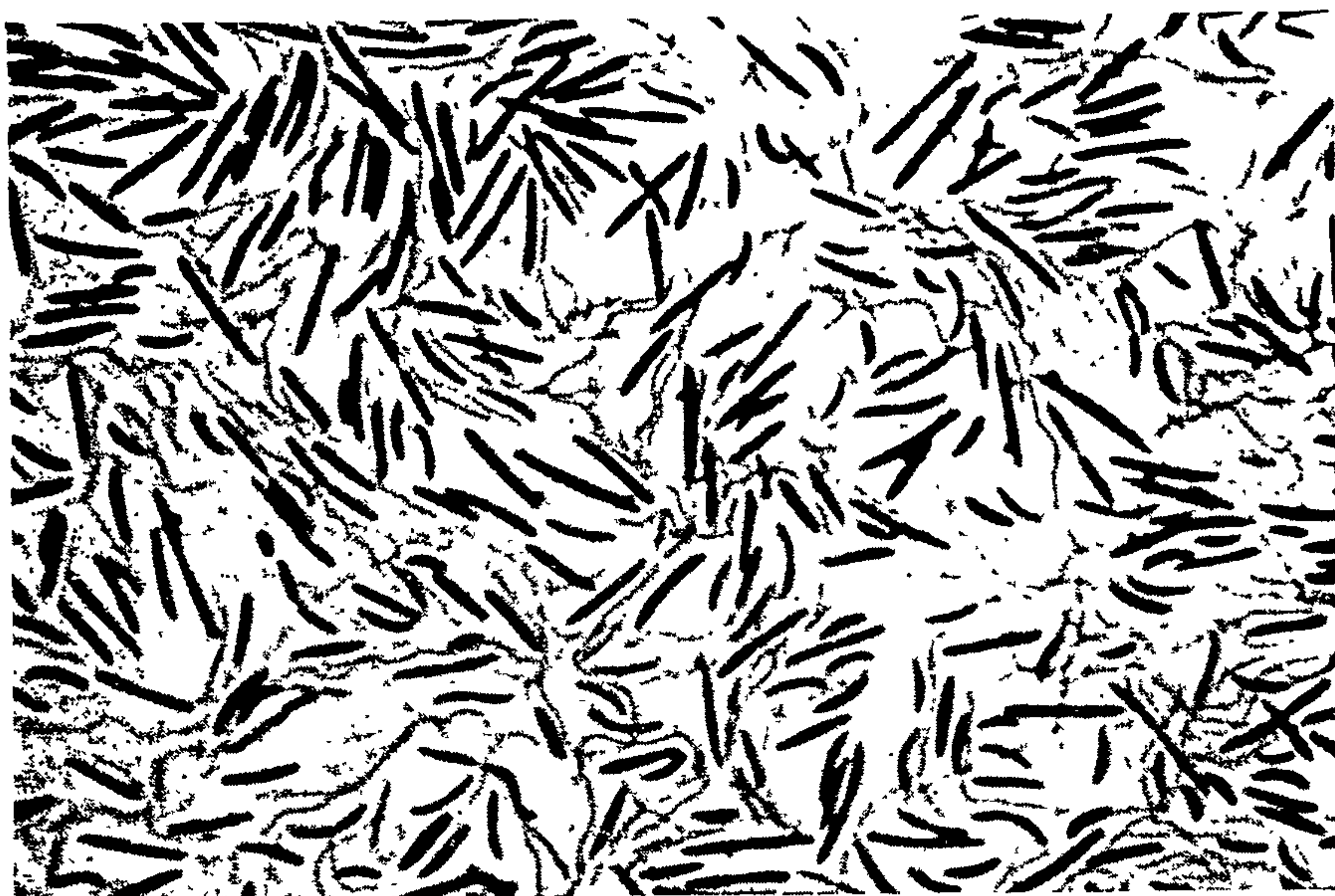


Fig. 22a Oral smear from a patient with ulcerative necrotizing gingivitis demonstrates spirochetes and fusiform microorganisms. (From the collection of Edgar D. Coolidge.)

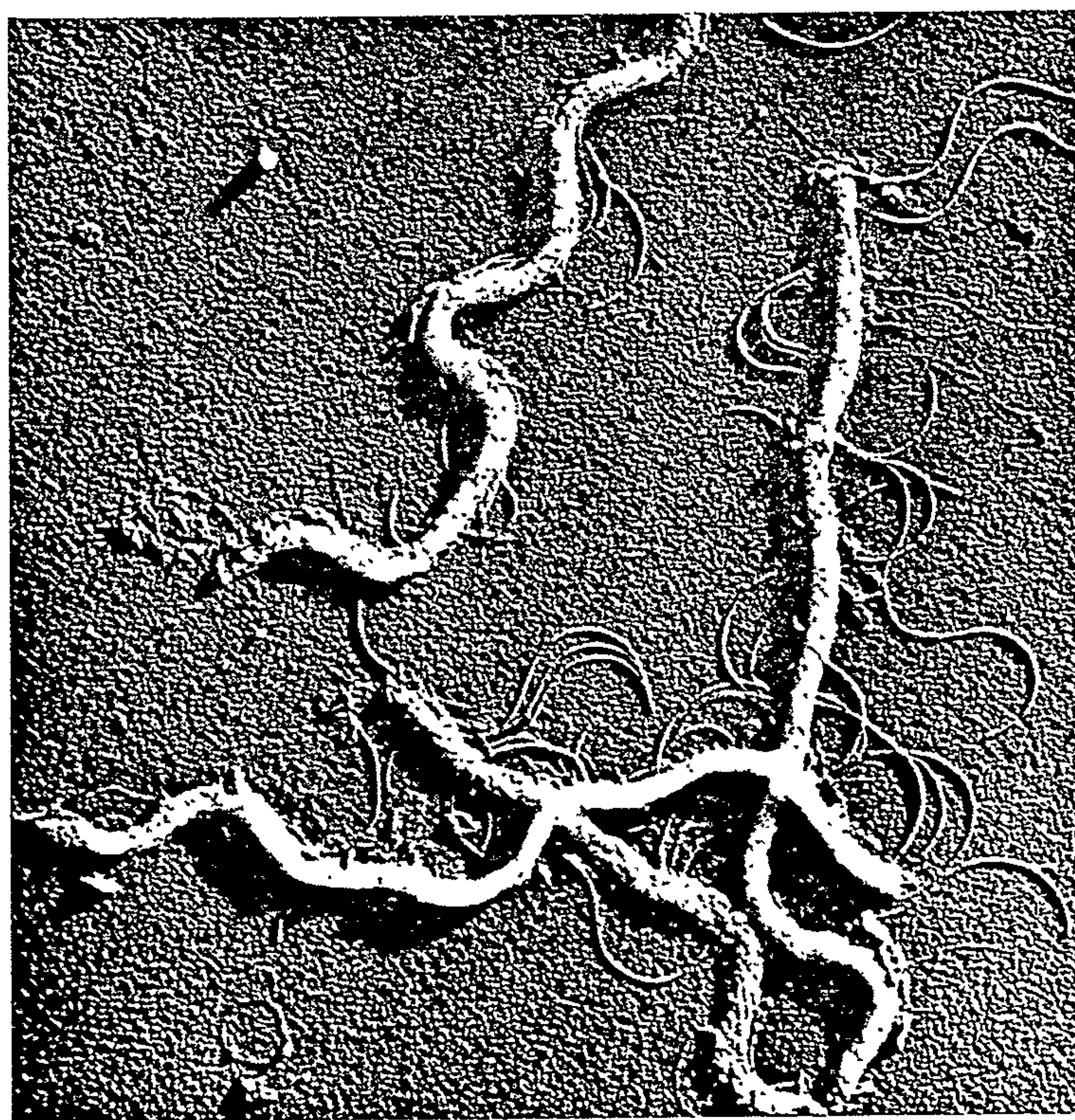


Fig. 22b Electron photomicrograph of *Borrelia vincentii*. Shadowed preparation. ($\times 11,000$.) (Courtesy Edward G. Hampp, Bethesda, Md.)

From: Grant, D.A. Stern, I.B. and Everett, F.G. Orban's Periodontics.
St. Louis. Mosby. 4th Edn. 1972.

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 disease¹¹⁹, 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 ^{127, 166} is found to coincide with the palliation of symptoms and clinical remission of NUG.

Fitch et al. ¹⁶⁶ 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. ¹⁵⁷

Listgarten ²⁷² 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. ²⁷²

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. ¹⁹⁸ It is a slender curved organism with pointed ends, having a cigar shaped appearance and often occurring in pairs. (Figure 22a). Thomas ²⁷⁷ 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 ¹⁹⁸ and five to 10 microns long, with three to five open irregular curves. ²⁷⁸ (Figure 22b).

Descriptions of its gross morphology vary ^{104, 112,} further illustrating the difficulties of attempting to classify spirochaetes on morphological grounds alone. ²⁶⁶

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 diptheroids, streptococci, treponemes, bacteroides, coccobacilli, filamentous organisms and veillonella. ^{198, 279}

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 ⁹⁹, and their numbers increase with the establishment of periodontal disease. ^{251, 272}

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%. ¹³³

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. ²⁷⁹ A similar percentage is present in cases of mild marginal gingivitis. ¹⁹⁹ Gibbons and van Houte ²³⁵ 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.²⁸¹ 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, 6×10^7 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 Gibbons²⁸⁵ 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.²⁸⁵

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.²⁸⁶

Kaufman et al.²⁸⁷ 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.²⁸⁸ 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.¹⁵⁹ 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. melanogenicus, 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.²⁸⁸

The role, if any, of bacterial collagenase in the pathogenesis of periodontal disease remains unclear.⁴⁸

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.²⁸⁹ No marked differences were observed in the virulence of the infectivity of the debris from any of the three groups.²⁸⁹

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:²⁹⁰

(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.²⁹¹ These lesions could be experimentally transferred to healthy dogs, but only after systemic administration of corticosteroids.²⁹²

The microbial flora described in association with lesions showed a preponderance of peptococci, corynebacteria, propionibacteria and fusobacteria. Spirochaetes were not described.²⁹³

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

The role of spirochaetes.

Listgarten and Socransky²⁹⁴ 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 study²⁶⁶ 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 aetiology 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.

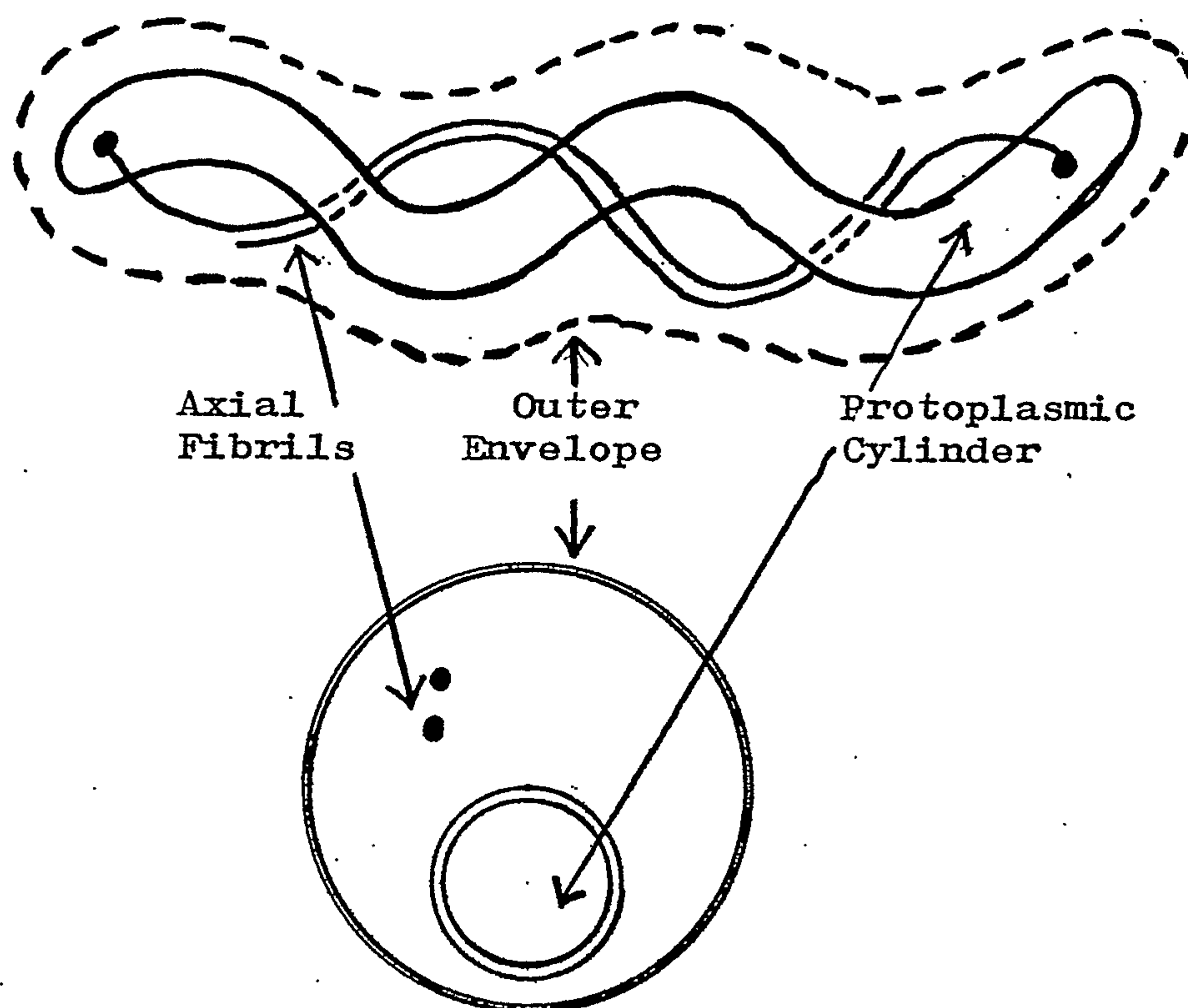


Figure 23. Diagrammatic representation of the main structural components of a 1-2-1 oral spirochaete. After: Listgarten M.A. Electron Microscopic Observations on the Bacterial Flora of Acute Necrotizing Ulcerative Gingivitis. J.Periodontol 36:4. 328-329. 1965.

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).

ORAL CAVITY

1. Bacterial Zone	Mixed flora, including fusiforms. Small, intermediate and large type spirochaetes in small numbers.	Surface Material
2. Neutrophil Rich Zone	Abundant PMNs. Some fusiforms. Increased numbers of various types of spirochaetes.	
3. Necrotic Zone	Abundant spirochaetes, predominantly intermediate and large types. Few fusiforms. Virtually no other organisms.	Gingival Tissues
4. Zone of Spirochaetal Infiltration	Approximately 250 microns in depth, does not exceed 300 microns. Intermediate type spirochaetes, predominantly ≥ 7 type. No fusiforms. Occasional very large spirochaetes.	

Figure 24. The four zones of the NUG lesion.

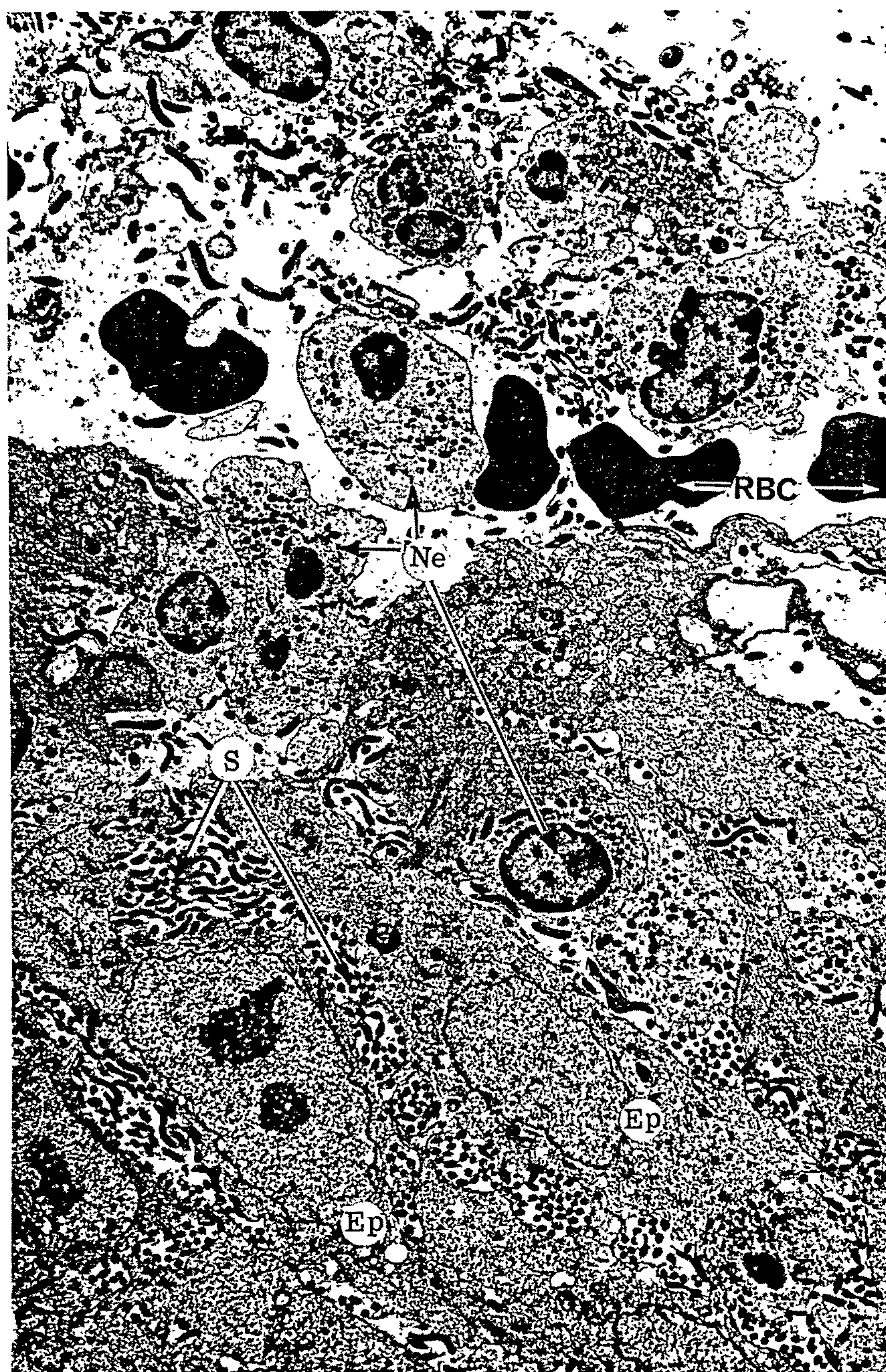


Figure 25 . *Acute necrotizing ulcerative gingivitis.*

Electron microscope photomicrograph illustrates the epithelium adjacent to ulcerated lesion. Neutrophils (*Ne*), red blood cells (*RBC*), microorganisms and cellular debris cover the epithelium. Dense masses of large and medium spirochetes (*S*) and some neutrophils (*Ne*) distend the space between the epithelial cells (*Ep*). Original magnification, $\times 3500$.

From: Listgarten, M.A. Electron Microscopic Observations
of the Bacterial Flora of Acute Necrotizing Ulcerative
Gingivitis. *J. Periodontol.* 36:4, 328-329.
July - Aug. 1965.

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).

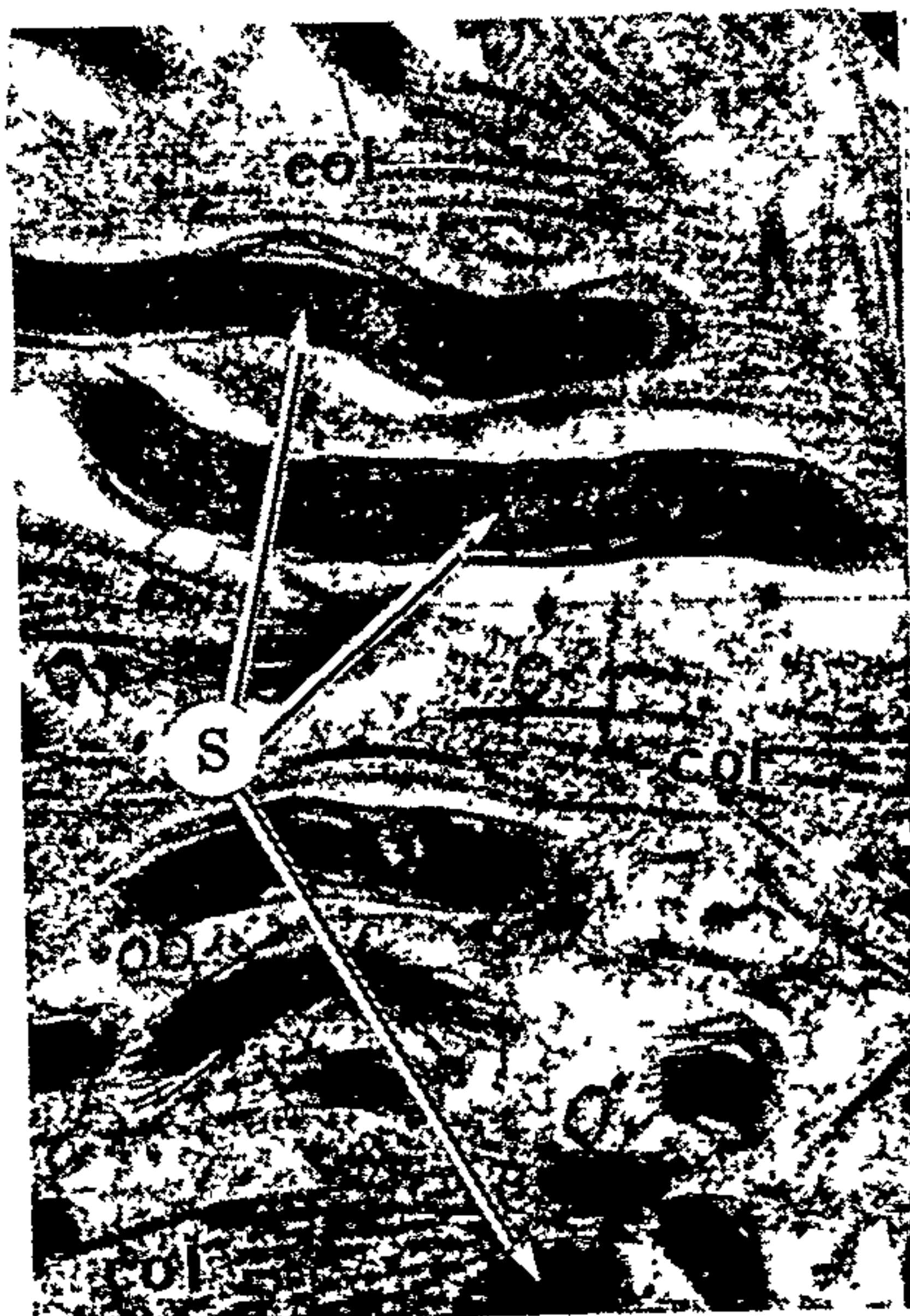


Fig. 26 . Zone of spirochaetal infiltration. Spirochetes, S, infiltrating the connective tissue beneath the ulcerated lesion. Collagen fibers are labeled col. (From Listgarten, M. A.: J. Periodont. 36:328, 1965.)

From: Grant. D.A.. Stern. I.B. and Everett. F.G. Orban's
Periodontics. St. Louis. Mosby. 4th Edn. 1972

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.¹⁹⁷

Attempts to isolate these large and intermediate types of spirochaete have not been successful.²⁹⁵

Later ultrastructural investigations by Heylings¹⁹⁸ 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.

Heylings¹⁹⁸ 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.¹⁹⁸

The discrepancies between these two studies could be partly explained by the fact that Heylings¹⁹⁸ apparently limited his observations to the epithelial changes in early NUG. Listgarten¹⁹⁷ used tissues from patients with established lesions, and included connective tissues in his sections. It is also apparent that the biopsy techniques differed, Heylings¹⁹⁸ used a long narrow strip of marginal gingiva, while Listgarten¹⁹⁷ excised whole interdental papillae by using buccal and lingual incisions.

Listgarten and Lewis²⁹⁶ studied the distribution of spirochaetes in NUG lesions. Pooled superficial and deep scrapings from established lesions revealed the following distribution:-

	<u>% OF TOTAL SPIROCHAETES</u>	<u>MEDIAN %</u>
Small	7% to 39%	28%
Intermediate	43.9% to 90%	72%
Large	0% to 20%	3%

In deep samples, intermediate types having more than seven axial fibrils originating at each end (≥ 7), predominated over those having less than six (≤ 6). Pooled superficial and deep scrapings showed that the type ≥ 7 occurred more frequently than the type ≤ 6 in 10 of 11 patients.

Borrelia vincentii is an intermediate type spirochaete of the ≤ 6 variety. The findings indicated that the type ≥ 7 type spirochaetes tend to outnumber 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 edentulous 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. melaningenicus 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.

Sheiham 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 ¹⁵⁸ 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 bacteria³⁰², 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.

Heylings¹⁹⁸ 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 Listgarten¹⁹⁷, who stated that the deepest zone of bacterial penetration contained no organisms other than spirochaetes.

Hadi and Russell³⁰⁵ 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 Leptothrincia 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 (ACPD) 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.³⁰⁶ 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.³⁰⁶

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.²²³ 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.²²³

PERPETUATING FACTORS.

The acute symptoms of NUG may undergo apparently spontaneous remission without treatment^{103, 109, 120}, or resolve very rapidly when treated in a variety of ways.^{137, 267} 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 ¹¹⁷ 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. ¹¹⁷ 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. ¹⁶⁴

Giddon et al. ¹⁸⁴ 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. ¹²⁰ Lehner ²²¹ 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 ^{120, 137} 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 deformity⁹⁹, reverse architecture and chronic periodontitis.

Manson¹²⁰ describes the permanent gingival deformities of RNUG 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).

Stammers¹³¹ 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.

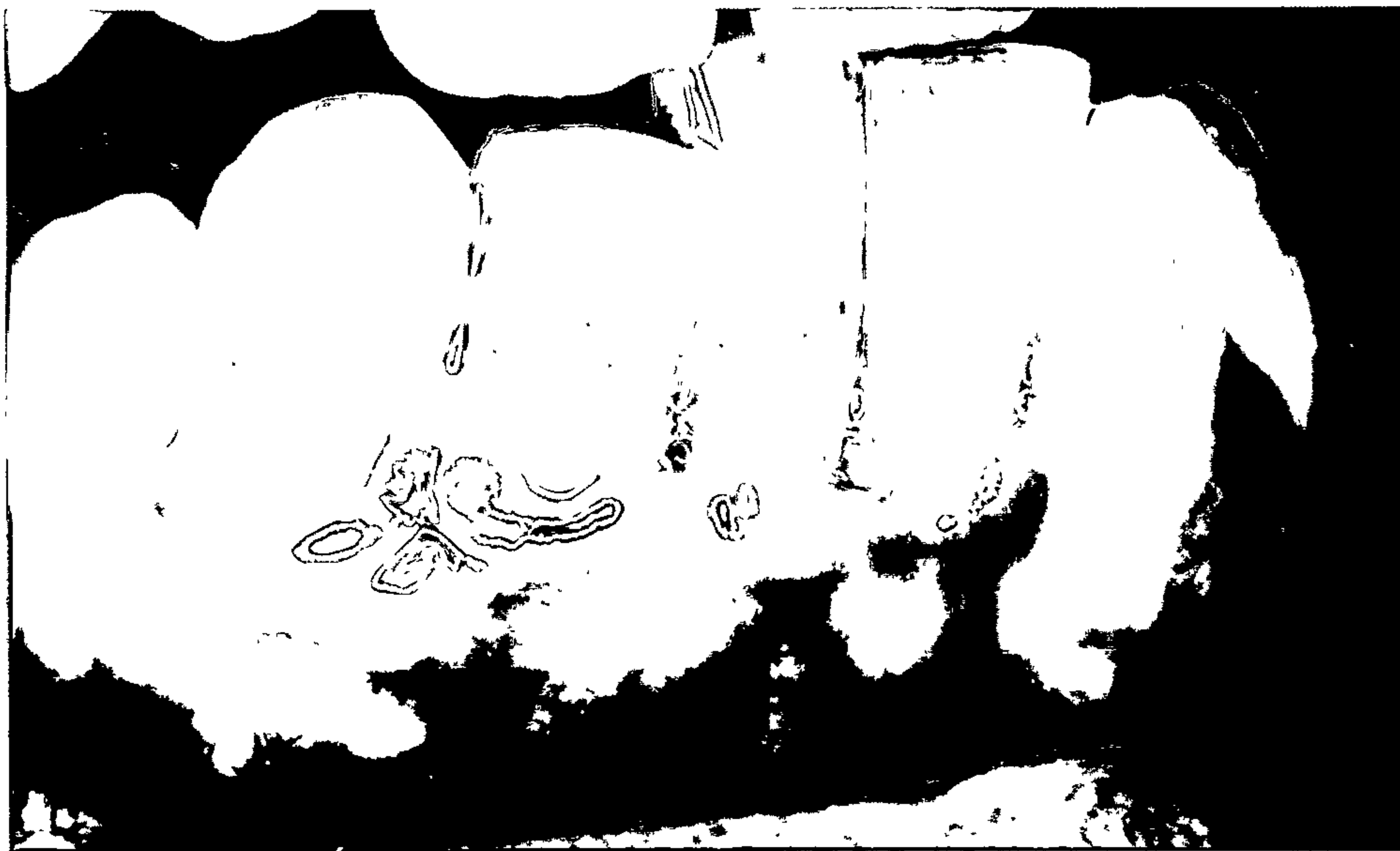


PLATE 7. Recurrent necrotizing ulcerative gingivitis.
Reverse gingival architecture and interdental
cratering.

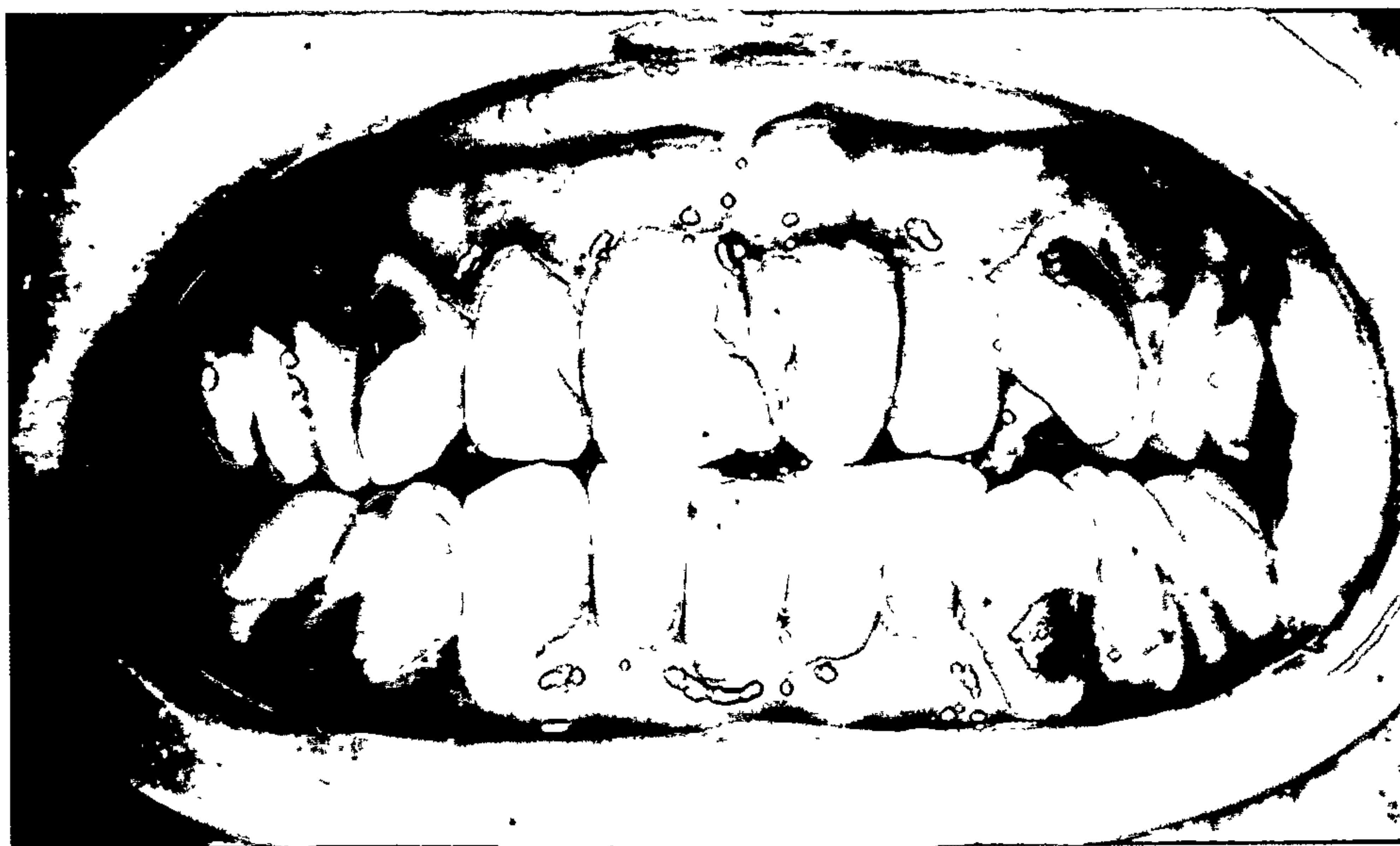


PLATE 8. Recurrent necrotizing ulcerative gingivitis.

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.^{131, 162} The effect of this psychological factor on the achievement of definitive treatment is typified by the observation attributed to Waltzer¹⁶², "patients with NUG never complete their treatment and never pay their bills".

Spouge¹⁰³ 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.^{102, 120}

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 1 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 11 both military ¹⁶⁷ and some civilian populations ¹³¹ 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. ¹⁹³

Pindborg ¹⁷⁹ 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 ¹⁷⁹ classified NUG as incipient (pre-Vincent's), acute, subacute and chronic. The incidence of actual acute NUG was 1.2%. ¹⁷⁹

Grupe and Wilder ¹²⁸ examined over 2000 recently inducted military trainees, and noted that 2.2% had NUG.

Smitt ¹¹⁷ 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. ¹⁸³ 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 30.¹⁶⁴ This assumption remains unsubstantiated. In the most recent study, Barnes et al.¹²³ 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 1967.¹⁴³

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 11, 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.

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

Studies during World War 11 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.¹²³ Other variables such as differences in oral hygiene performance and in smoking habits have rarely, if ever, been considered.

Stammers¹³¹ 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.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.¹²³

PART 8.TREATMENT.

NUG 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.^{104, 122} Uncertainty over the exact aetiology 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.^{310, 311} At best, they appear to offer no greater accuracy than careful objective clinical assessments.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.^{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.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.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 fulfil 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

Stammers¹³¹ 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 Fletcher³¹² 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 toxæmia. 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.³¹² 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).³¹²

Manson and Rand²⁶⁷ support the view that immediate debridement results in rapid relief of pain and enhanced healing, as do Schluger et al.¹¹⁶

Fitch et al.¹⁶⁶ 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.¹⁶⁶

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. 166

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. 166

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.¹²² 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 Emslie³⁰⁷ 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 phenoxymethylpenicillin (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 preceeding 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 gingivostomatitis¹⁶⁸, 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 daily³¹⁵ 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 mucosa¹⁶³, 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

Holroyd²⁷⁶ 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, bacteriodes 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^{142, 157, 301}, there is disagreement regarding which of these genera is the first to be eliminated in the treatment of mixed infections.^{142, 157}

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.¹⁵⁷ This level appears to have a rapid effect in suppressing spirochaetal activity.¹⁵⁷

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 dose¹⁵⁷, and much higher levels are achieved with subsequent doses.³¹⁰ The salivary levels achieved with even a single dose exceed those required for the in vitro inhibition of spirochaetes.³⁰¹

Serum concentrations following a single dose exceed the minimum inhibitory concentration (MIC) and the minimum bactericidal concentration (MBC) required against some bacteroides species.³²⁹ 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.^{326, 329}

It is not known whether the pharmacological action of metronidazole is due to its presence in the serum, in the saliva or in both.^{310, 319} It is most likely that the combined effect is that which occurs in vivo.³¹⁹

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).³³³ Patients who are using the drug should be cautioned to avoid the concurrent use of alcohol as toxic psychosis³³⁴, nausea¹⁷⁷ or headache³³⁵ may be induced.

Like disulfiram, it has been shown to elevate the circulating blood levels of sodium warfarin, and to potentiate warfarin induced hypoprothrombinaemia.³³³ These effects occur at doses similar to those proposed for the treatment of NUG³³³, 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.³³⁶ 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.¹⁴²

Production of transient hypotension has been reported, and the manufacturer suggests that it may be advisable to lower the dosage of any concurrently administered antihypertensive drug.³³¹ Substitution of another drug for metronidazole appears more logical.

Its use is contraindicated in patients with active established lesions of the central nervous system.^{177, 324} Neurotoxicity has been observed following prolonged administration. Although this peripheral neuropathy is stated to be completely reversible³³⁴, at least two cases of persistent sensory neuropathy have been reported after treatment with large doses, 30.6 gms and 114 gms respectively.³³⁷

Other reported side effects include gastrointestinal discomfort, nausea, unpleasant metallic taste sensations³³², anorexia, vomiting, urticaria¹⁴⁵, headaches and occasionally vertigo.³²⁴

Urine colour changes may occur, due to the formation of water soluble pigments, azoxy hydrochlorides.³²⁴ This dark reddish-brown discolouration may be misdiagnosed as haematuria, but is an infrequent and apparently inconsequential side effect.³⁰³ 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.³³⁸, mutagenic in bacteria³³⁹, and therefore potentially dangerous in humans. Many agents which are mutagenic in bacteria are carcinogenic in animals and may also be teratogenic.³⁴⁰

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.³⁴⁰

To date, no carcinogenic effects have been observed in man as a result of the use of metronidazole.³³⁴

The claim that the patient will only be subjected to a once in a lifetime exposure to the drug³⁴¹ cannot be substantiated. Its effectiveness against anaerobic organisms has led to its use in high concentrations as a therapeutic or a prophylactic measure in abdominal³⁰³ and gynaecological surgery.³²⁶ Large doses are

used for antimicrobial prophylaxis of endogenously derived infection by non-sporing anaerobes. 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. ³³⁵ Long term therapy is employed in the treatment of Crohn's disease. ³³⁷

In addition, there is a possibility of repeated administration of divided doses for the treatment of actual or misdiagnosed NUG and RNUG. Loesche 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. ^{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. ³³⁴

All these uses are additional to its original application in the treatment of urogenital trichomoniasis, amoebiasis and giardiasis. 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. ³³²

Metronidazole diffuses across the placenta, passes freely into the foetal circulation 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 ^{100, 120, 332, 341}, while some suggest

avoiding its use at any time during pregnancy³⁴⁰ 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.^{177, 342} 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.

Emslie¹⁴⁴ 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 taste¹⁴⁴, and might well discontinue treatment for these or for aesthetic reasons, or because of pain due to mastication.

In a later study, Emslie and Ashley³⁰⁷ 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.

Nimorazole. (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 metronidazole¹⁷⁷, 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 effect¹⁷⁷, 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 ³⁰², and is equally or more effective than either metronidazole or nimorazole 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 ³⁴³, although no dysmorphogenetic effects have yet been observed in rodent trials. ³⁴³

Attention has recently been drawn to the fact that both nimorazole 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 fusospirochaetal 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.³⁰⁸ 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 NUG.³¹¹

The use of oxygenating agents may produce mucositis, glossitis³⁰⁹, or with prolonged use the decalcification of tooth structure¹⁰⁴ and damage to epithelial cells.³⁴⁶

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.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.³⁴⁸

Since chlorhexidine apparently has no effect on subgingival plaque³⁴⁹, 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 surface³⁴⁷, and significantly reduce gingival inflammation, provided the depth of the existing periodontal pockets does not exceed 3 mms.³⁴⁹

The benefits of the procedure appear to be:

- (a) ... the mechanical effect of lavage.
- (b) ... removal of residual accessible uncalcified dental plaque.³⁵⁰
- (c) ... chemical inhibition of the development of dental plaque during the time that the patient is unable to perform effective oral hygiene.^{349, 350}

In vivo studies suggest that chlorhexidine may facilitate the healing of gingival wounds, presumably by its plaque inhibitory effect.^{350, 351} 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.³⁵² 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.³⁵²

These findings may not apply in the clinical situation where chlorhexidine becomes bound to salivary proteins, tooth pellicles, and existing dental plaque.^{347, 349, 352} 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, mucositis³⁴⁹, and interference with taste sensation.³⁴⁷ The bitter taste of the compound may be a deterrent to patient compliance.³⁴⁷

Longer use may result in discolouration of the tongue, teeth, or tooth coloured dental restorations.³⁴⁷ There are occasional reports of the development of parotitis during treatment with chlorhexidine³⁴⁹; these may be coincidental.³⁴⁷

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, curettage 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

Smitt 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 symptoms³⁰⁹, others have noted accelerated healing following excision biopsy of severe lesions.¹²⁵

MacPhee and Beagrie¹³⁷ 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.

REFERENCES

1. Squier CA, Johnson NW and Hackemann M. Structure and function of normal human oral mucosa. In: Dolby AE. Oral Mucosa in Health and Disease. Oxford, Blackwell, 1975. p 1-92.
2. Listgarten MA. Normal development, structure, physiology and repair of gingival epithelium. In: Melcher AH and Zarb GA. Gingival Epithelium. Oral Sciences Reviews.1. Copenhagen, Munksgaard, 1972. p 3-67.
3. Schroeder HE. Gingival tissue. In: Cohen B and Kramer IRH. Scientific Foundations of Dentistry. London, Heinemann, 1976. p 426-439.
4. Glickman I and Smulow JB. Periodontal Disease. Philadelphia, Saunders, 1974. p 1-21.
5. Kopczyk RA and Lenox JA. Periodontal health and disease in children: Examination and diagnosis. Dent Clin North Am. 17:1, 25-33, 1973.
6. Listgarten MA and Loe H. Periodontium. In: Goldman HM and Cohen DW. Periodontal Therapy. St Louis, Mosby, 5th ed, 1973. p 1-56.
7. Attström R, Graf-de-Beer M and Schroeder HE. Clinical and histologic characteristics of normal gingiva in dogs. J Periodont Res. 10: 115-127, 1975.
8. Ainamo J and Loe H. Anatomical characteristics of gingiva. A clinical and microscopic study of the free and attached gingiva. J Periodontol. 37: 5-13, 1966.
9. Owings JR. A clinical investigation of the relationship between stippling and surface keratinization of the attached gingiva. J Periodontol. 40: 588-592, 1969.
10. Grant DA, Stern IB and Everett FG. Orban's Periodontics. St Louis, Mosby, 4th ed, 1972. p 3-50.
11. Ainamo J and Talari A. The increase with age of the width of the attached gingiva. J Periodont Res. 11: 182-188, 1976.
12. Lang NP and Loe H. The relationship between the width of keratinized gingiva and gingival health. J Periodontol. 43: 623-627, 1972.
13. McHugh WD. The interdental gingivae. J Periodont Res. 6: 227-236, 1971.
14. Schroeder HE and Page RC. The normal periodontium. In: Schluger S, Yuodelis RA and Page RC. Periodontal Disease. Philadelphia, Lea and Febiger, 1977. p 8-55.
15. Dummett CO and Barens G. Pigmentation of the oral tissues: A review of the literature. J Periodontol. 38:369-377, 1967.
16. Dummett CO and Barens G. Oromucosal pigmentation: an updated literary review. J Periodontol. 42: 726-736, 1971.

17. Jones J and McFall WT. A photometric study of the color of healthy gingiva. *J Periodontol.* 48: 21-26, 1977.
18. Silverman S. Nonkeratinization and keratinization: The extremes of the human range. In: Squier CA and Meyer J. *Current Concepts of the Histology of Oral Mucosa.* Springfield, Thomas, 1971. p 80-96.
19. Attstrom R. The roles of gingival epithelium and phagocytosing leucocytes in gingival defence, *J Clin Periodontol.* 2: 25-32, 1975.
20. Squier CA. Ultrastructural features of oral epithelium. In: Squier CA and Meyer J. *Current Concepts of the Histology of Oral Mucosa.* Springfield, Thomas, 1971. p 5-33.
21. Fawcett DW. *An Atlas of Fine Structure. The Cell.* Philadelphia, Saunders, 1966. p 353-373.
22. McMinn RMH. Cell structure. In: Cohen B and Kramer IRH. *Scientific Foundations of Dentistry.* London, Heinemann, 1976. p 65-82.
23. Schroeder HE and Theilade J. Electron microscopy of normal human gingival epithelium. *J Periodont Res.* 1: 95-119, 1966.
24. Sagebiel RW, Clarke MA and Hutchens LH. Dendritic cells in oral epithelium. In: Squier CA and Meyer J. *Current Concepts of the Histology of Oral Mucosa.* Springfield, Thomas, 1971. p 143-166.
25. Leeson TS and Leeson CR. *Histology.* Philadelphia, Saunders, 2nd ed, 1970. p 17-58.
26. Fawcett DW. *An Atlas of Fine Structure. The Cell.* Philadelphia, Saunders, 1966. p 63-132.
27. Fawcett DW. op.cit. p 133-212.
28. Susi FR. The basal lamina and its fibrils. In: Squier CA and Meyer J. *Current Concepts of the Histology of Oral Mucosa.* Springfield, Thomas, 1971. p 173-180.
29. Frithiof L and Wersäll J. A highly ordered structure in keratinizing human oral epithelium. *J Ultrastruct Res.* 12: 371-379, 1965.
30. Meyer J, Alvares OF and Gerson SJ. The structure and function of the oral mucosa. In: Cohen B and Kramer IRH. *Scientific Foundations of Dentistry.* London, Heinemann, 1976. p 449-458.
31. Fitzpatrick TB, Quevendo WC, Szabo G and Makato S. Biology of the melanin pigmentary system. In: Fitzpatrick TB, Arndt KA, Clark WH et al. *Dermatology in General Medicine.* New York, Mc-Graw Hill, 1971. p 117-146.
32. Farbman AI and Allgood JP. Innervation, sensory receptors and sensitivity of the oral mucosa. In: Squier CA and Meyer J. *Current Concepts of the Histology of Oral Mucosa.* Springfield, Thomas, 1971. p 250-273.
33. Listgarten MA. Structure of surface coatings on teeth. A review. *J Periodontol.* 47: 139-147, 1976.

34. Ten Cate AR. The dento-gingival junction. An interpretation of the literature. *J Periodontol.* 46: 475-477, 1975.
35. Listgarten MA. Ultrastructure of the dento-gingival junction after gingivectomy. *J Periodont Res.* 7: 151-160, 1972.
36. Odland GF and Short JM. Structure of the skin. In: Fitzpatrick TB, Arndt KA, Clark WH et al. *Dermatology in General Medicine.* New York, Mc-Graw Hill; 1971. p 39-49.
37. Page RC and Schroeder HE. Biochemical aspects of the connective tissue alterations in inflammatory gingival and periodontal disease. *Int Dent J.* 23: 455-469, 1973.
38. Scapino RP. Biomechanics of masticatory and lining mucosa. In: Squier CA and Meyer J. *Current Concepts of the Histology of Oral Mucosa.* Springfield, Thomas, 1971. p181-202.
39. Lozdan J and Squier CA. The histology of the muco-gingival junction. *J Periodont Res.* 4: 83-93, 1969.
40. Fullmer HM, Sheetz JH and Narkates AJ. Oxytalan connective tissue fibers: A review. *J Oral Pathol.* 3: 291-316, 1974.
41. Sheetz JH, Fullmer HM and Narkates AJ. Oxytalan fibers: Identification of the same fiber by light and electron microscopy. *J Oral Pathol.* 2: 254-263, 1973.
42. Folke LEA and Stallard RE. Periodontal microcirculation as revealed by plastic microspheres. *J Periodont Res.* 2: 53-63, 1967.
43. Egelberg J. The blood vessels of the dento-gingival junction. *J Periodont Res.* 1: 163-179, 1966.
44. Nuki K and Hock J. The organization of the gingival vasculature. *J Periodont Res.* 9: 305-313, 1974.
45. Hock J. Gingival vasculature around erupting deciduous teeth of dogs and cats. *J Clin Periodontol.* 2: 44-50, 1975.
46. Ruben MP, Prieto-Hernandez JR, Gott FK et al. Visualization of lymphatic microcirculation of oral tissues. 2. Vital retrograde lymphography. *J Periodontol.* 42: 774-784, 1971.
47. Waterhouse JP. Cells of the lamina propria. In: Squier CA and Meyer J. *Current Concepts of the Histology of Oral Mucosa.* Springfield, Thomas, 1971. p 213-223.
48. Barbanell RL, Lian JB and Keith DA. A review of collagen degradation with particular emphasis upon that which occurs during inflammatory periodontal disease. *Periodont Abstr.* 24: 43-55, 1976.
- 48a Grant PR. Collagen resorption by fibroblasts. A theory of fibroblastic maintenance of the periodontal ligament. *J Periodontol.* 47: 380-390, 1976.
49. Albrecht RM and Hong R. Basic and clinical considerations of the monocyte-macrophage system in man. *J Pediatr.* 88: 751-765, 1976.

50. Dannenberg AM. Macrophages in inflammation and infection. *New Engl J Med.* 293: 489-493, 1975.
51. Robinson LP and De Marco TJ. Alteration of mast cell densities in experimentally inflamed human gingivae. *J Periodontol.* 43: 614-622, 1972.
52. Turk JL and Cole MF. The mechanisms of the immune response. In: Cohen B and Kramer IRH. *Scientific Foundations of Dentistry.* London, Heinemann, 1976. p 123-134.
53. Catchpole HR. The ground substance of the oral mucosa. In: Squier CA and Meyer J. *Current Concepts of the Histology of Oral Mucosa.* Springfield, Thomas, 1971. p 224-230.
54. Brandtzaeg P. Immunoglobulin systems of oral mucosa and saliva. In: Dolby AE. *Oral Mucosa in Health and Disease.* Oxford, Blackwell, 1975. p 137-213.
55. Turk JL and Edwards MB. Immunological aspects of infection. In: Cohen B and Kramer IRH. *Scientific Foundations of Dentistry.* London, Heinemann, 1976. p 135-149.
56. Roitt IM. *Essential Immunology.* Oxford, Blackwell, 1971. p 1-16.
57. Miller JFAP. Induction of the immune (allergic) response. In: Gell PGH, Coombs RRA and Lachmann PJ. *Clinical Aspects of Immunology.* Oxford, Blackwell, 3rd ed, 1975. p 447-469.
58. Knox KW and Wicken AJ. Immunological properties of teichoic acids. *Bacteriol Rev.* 37: 215-257, 1973.
59. Knox KW. The potential role of bacteria and their antigens in periodontal disease. *Aust Dent J.* 21: 397-404, 1976.
60. Schwab JH. Suppression of the immune response by microorganisms. *Bacteriol Rev.* 39: 121-143, 1975.
61. Lehner T. Immunological aspects of oral diseases. In: Gell PGH, Coombs RRA and Lachmann PJ. *Clinical Aspects of Immunology.* Oxford, Blackwell, 3rd ed, 1975. p 1387-1427.
62. Duquesnoy RJ and Abramoff P. Immunodeficiency diseases and tumor immunobiology. In: Sodeman WA and Sodeman WA. *Pathologic Physiology Mechanisms of Disease.* Philadelphia, Saunders, 5th ed, 1974. p 124-145.
63. Weir DM. *Immunology for Undergraduates.* Edinburgh, Churchill, 3rd ed, 1973. p 6-17.
64. Ferguson Anderson W. Involution and senescence. In: Bodley Scott R Price's *Textbook of the Practice of Medicine.* Oxford University Press, 11th ed, 1973. p 387-396.
65. Coombs RRA and Smith H. The allergic response and immunity. In: Gell PGH, Coombs RRA and Lachmann PJ. *Clinical Aspects of Immunology.* Oxford, Blackwell, 3rd ed, 1975. p 473-505.

66. Roitt IM. Essential Immunology. Oxford, Blackwell, 1971. p 95-152.
67. Valdimarsson H. Immunity and immunity deficiency. In: Hobart MJ and McConnell I. The Immune System. Oxford, Blackwell, 1975. p 317-332.
68. Johnston RB and Stroud RM. Complement and host defence against infection. J Pediatr. 90: 169-179, 1977.
69. Lachmann PJ. Complement. In: Gell PGH, Coombs RRA and Lachmann PJ. Clinical Aspects of Immunology. Oxford, Blackwell, 3rd ed, 1975. p 323-364.
70. Holland PDJ. Inflammation, regeneration and repair. In: Cohen B and Kramer IRH. Scientific Foundations of Dentistry. London, Heinemann 1976. p 106-121.
71. Champion RH and Parish WE. Allergic diseases in the skin. In: Gell PGH, Coombs RRA and Lachmann PJ. Clinical Aspects of Immunology. Oxford, Blackwell, 3rd ed, 1975. p 1183-1215.
72. Walter JB and Israel MS. General Pathology. Edinburgh, Churchill, 3rd ed, 1970. p 152-153.
73. Swartz MN and Weinberg AN. Bacterial diseases with cutaneous involvement - general considerations. In: Fitzpatrick TB, Arndt KA, Clark WH et al. Dermatology in General Medicine. New York, McGraw Hill, 1971. p 1684-1685.
74. Weinstein L and Swartz MN. Pathogenic properties of invading microorganisms. In: Sodeman WA and Sodeman WA. Pathologic Physiology. Mechanisms of Disease. Philadelphia, Saunders, 5th ed, 1974. p 457-472.
75. Holborow EJ. Immune mechanisms in disease. In: Bodley Scott R. Price's Textbook of the Practice of Medicine. Oxford University Press. 11th ed, 1973. p 414-421.
76. White RG. Immunological functions of lymphoreticular tissues. In: Gell PGH, Coombs RRA and Lachmann PJ. Clinical Aspects of Immunology. Oxford, Blackwell, 3rd ed, 1975. p 411-445.
77. Weir DM. Immunology for Undergraduates. Edinburgh, Churchill, 3rd ed, 1973. p 57-97.
78. Brandtzaeg P. Immunology of inflammatory periodontal lesions. Int Dent J. 23: 438-453, 1973.
79. Miller F. Applications of immunology to understanding mechanisms of human disease. Fed Proc. 34: 1635-1640, 1975.
80. Cohen S and Winkler S. Cellular immunity and the inflammatory response. J Periodontol. 45: 348-350, 1974.
81. Schluger S, Yuodelis RA and Page RC. Periodontal Disease. Philadelphia, Lea and Febiger, 1977. p 199-238.
82. Williams RC and Gibbons RJ. Inhibition of bacterial adherence by secretory immunoglobulin A: A mechanism of antigen disposal. Science. 177: 697-699, 1972.

83. Rowe DS. Immunoglobulins. In: Gell PGH, Coombs RRA and Lachmann PJ. Clinical Aspects of Immunology. Oxford, Blackwell, 3rd ed, 1975. p 285-306.
84. Holborow EJ. An ABC of Modern Immunology. London, Lancet, 2nd ed, 1973. p 24-92.
85. Schwartz J and Dibblee M. The role of IgE in the release of histamine from human gingival mast cells. J Periodontol. 46: 171-177, 1975.
86. Coombs RRA and Gell PGH. Classification of allergic reactions responsible for clinical hypersensitivity and disease. In: Gell PGH, Coombs RRA and Lachmann PJ. Clinical Aspects of Immunology. Oxford, Blackwell, 3rd ed, 1975. p 761-781.
87. Weir DM. Immunology for Undergraduates. Edinburgh, Churchill, 3rd ed, 1973. p 84-143.
88. Brocklehurst WE. Pharmacological mediators of hypersensitivity reactions. In: Gell PGH, Coombs RRA and Lachmann PJ. Clinical Aspects of Immunology. Oxford, Blackwell, 3rd ed, 1975. p 821-846.
89. Nisengard R. Immediate hypersensitivity and periodontal disease. J Periodontol. 45: 344-347, 1974.
90. Dolby AE. Oral ulceration: Immunological aspects. In: Dolby AE. Oral Mucosa in Health and Disease. Oxford, Blackwell, 1975. p 415-437.
91. Genco RJ, Mashimo PA, Krygier G and Ellison SA. Antibody-mediated effects on the periodontium. J Periodontol. 45: 330-337, 1974.
92. Powell RN. Progress in understanding periodontal disease. Proc R Soc Med. 68: 121-125, 1975.
93. Horton JE, Oppenheim JJ and Mergenhagen SE. A role for cell-mediated immunity in the pathogenesis of periodontal disease. J Periodontol. 45: 351-360, 1974.
94. Turk JL. The concept of auto-immunity. In: Cohen B and Kramer IRH. Scientific Foundations of Dentistry. London, Heinemann, 1976. p 160-162.
95. Roitt IM. Essential Immunology. Oxford, Blackwell, 1971. p 179-209.
96. Burnet FM. The Clonal Selection Theory of Acquired Immunity. Cambridge University Press. 1959. p 54-56.
97. Lachmann PJ. Auto-allergy. In: Gell PGH, Coombs RRA and Lachmann PJ. Clinical Aspects of Immunology. Oxford, Blackwell, 3rd ed, 1975. p 859-875.
98. Levy BM. Prevention of periodontal disease- a pathologist's view. Int Dent J. 23: 446-480, 1973.
99. Cawson RA. Infections of the oral mucous membrane. In: Cohen B and Kramer IRH. Scientific Foundations of Dentistry. London, Heinemann, 1976. p 484-497.
100. Macphee T and Cowley G. Essentials of Periodontology and Periodontics. Oxford, Blackwell, 2nd ed, 1975. p 139-159.

101. Shields WD. Acute necrotizing ulcerative gingivitis. A study of some of the contributing factors and their validity in an army population. J Periodontol. 48: 346-349, 1977.
102. Tyldesley WR. Oral medicine for the dental practitioner. 2. Infections of the oral mucosa. Br Dent J. 135: 449-455, 1973.
103. Spouge JD. Oral Pathology. St Louis, Mosby, 1973. p 210-216.
104. Grant DA, Stern IB and Everett FG. Orban's Periodontics. St Louis, Mosby, 4th ed, 1972. p 335-351.
105. Wilhelm DL. Inflammation and healing. In: Anderson WAD. Pathology. St Louis, Mosby, 6th ed, 1971. p 44-51.
106. Walter JB and Israel MS. General Pathology. Edinburgh, Livingstone, 3rd ed, 1970. p 109.
107. Walter JB and Israel MS. op.cit. p 777.
108. Thompson AD and Cotton RE. Lecture Notes on Pathology. Oxford, Blackwell, 2nd ed, 1968. p 33.
109. Glickman I. Clinical Periodontology. Philadelphia, Saunders, 4th ed, 1972. p 126-145.
110. Glickman I and Smulow JB. Periodontal Disease. Philadelphia, Saunders, 1974. p 54-56.
111. Pindborg JJ. Atlas of Diseases of the Oral Mucosa. Copenhagen, Munksgaard, 2nd ed, 1973. p 50-51.
112. Shafer WG, Hine MK and Levy BM. A Textbook of Oral Pathology. Philadelphia, Saunders, 3rd ed, 1974. p 724-729.
113. Jiménez ML and Baer PN. Necrotizing ulcerative gingivitis in children: A 9 year clinical study. J Periodontol. 46: 715-720, 1975.
114. Pindborg JJ. The epidemiology of ulceromembranous gingivitis showing the influence of service in the armed forces. Parodontologie. 10: 114-117, 1956.
115. Robbins SL. Pathologic Basis of Disease. Philadelphia, Saunders, 1974. p 55-105.
116. Schluger S, Yuodelis RA and Page RC. Periodontal Disease. Philadelphia, Lea and Febiger, 1977. p 243-250.
117. Smitt PAES. Some clinical and epidemiological aspects of Vincent's gingivitis. Dent Pract. 15: 281-286, 1965.
118. Zulqar-nain BJ. Recognition and treatment of periodontal emergencies. J Can Dent Assoc. 41: 651-655, 1975.
119. Burket LW. Oral Medicine. Diagnosis and Treatment. Philadelphia, Lippincott, 6th ed, 1971. p 33-44.

120. Manson JD. Periodontics. London, Henry Kimpton, 3rd ed, 1975. p 225-235.
121. Prichard JF, Kramer G, Stahl SS et al. Glossary of Terms. J Periodontol. 48: 1-34 (supplement) 1977.
122. Goldhaber P and Giddon DB. Present concepts concerning the aetiology and treatment of acute necrotizing ulcerative gingivitis. Int Dent J. 14: 468-496, 1964.
123. Barnes GP, Bowles WF and Carter HG. Acute necrotizing ulcerative gingivitis: A survey of 218 cases. J Periodontol. 44: 35-42, 1973.
124. Klotz H. Differentiation between necrotic ulcerative gingivitis and primary herpetic gingivostomatitis. N Y State Dent J. 39: 283-293, 1973.
125. Carter WJ and Ball DM. Results of a three year study of Vincent's infection at the Great Lakes naval dental department. J Periodontol. 24: 187-194, 1953.
126. Goldberg HJV. Acute necrotizing ulcerative gingivitis. J Oral Ther. 2: 451-459, 1966.
127. Southam JC. Bacterial and viral diseases and the oral mucosa. In: Dolby AE. Oral Mucosa in Health and Disease. Oxford, Blackwell, 1975. p 374-377.
128. Grupe HE and Wilder LS. Observations of necrotizing gingivitis in 870 military trainees. J Periodontol. 27: 255-261, 1956.
129. Proctor DB and Baker CG. Treatment of acute necrotizing ulcerative gingivitis with metronidazole. J Can Dent Assoc. 37:376-380, 1971.
130. Seidberg BH. A vexatious erratic oral lesion: necrotizing ulcerative gingivitis. Dental Progress. 4: 37-42, 1963.
131. Stammers AF. Vincent's infection. Observations and conclusions regarding the aetiology and treatment of 1,017 civilian cases. Br Dent J. 76: 147-155, 171-205, 1944.
132. Hirschfeld I, Beube F and Siegel EH. The history of Vincent's infection. J Periodontol. 11: 89-98, 1940.
133. Blake GC. The microbiology of acute ulcerative gingivitis with reference to the culture of oral trichomonads and spirochaetes. Proc R Soc Med. 61: 131-136, 1968.
134. Rateitschak KH and Pluss E. The initial lesion in ulcerative gingivitis. Deutsche Zahn Zeitung. 27: 283, 1972. Abstract. Advances in Periodontics. 6: No 288, 1975.
135. Powell RN and Alexander AG. The treatment of periodontal disease.4. Initial preparation of the mouth. Br Dent J. 119: 522-524, 1965.
136. Barletta BO, Plot CR and Caffesse RG. Necrotizing ulcerative gingivitis: statistical analysis of several factors. Rev Assoc Odont Argent. 60: 505-508, 1972. Abstract. Advances in Periodontics. 6: No 291, 1975.

137. MacPhee IT and Beagrie GS. Treatment of ulcero-membranous gingivitis. Br Dent J. 113: 107-111, 1962.
138. Stephens AP. Acute fusospirochaetal stomatitis associated with a partial upper denture. Dent Pract. 22: 305-306, 1972.
139. Segal T. Acute necrotising ulcerative gingivitis. Diastema. 3: 15-19, 1972.
140. Uohara GI and Knapp MJ. Oral fusospirochetosis and associated lesions. Oral Surg. 24: 113-123, 1967.
141. Kardachi BJR and Clarke NG. Aetiology of acute necrotising ulcerative gingivitis: a hypothetical explanation. J Periodontol. 45: 830-832, 1974.
142. Fletcher JP and Plant CG. An assessment of metronidazole in the treatment of acute ulcerative pseudomembranous gingivitis. (Vincent's disease). Oral Surg. 22: 729-736, 1966.
143. Skach M, Zabrodsky S and Mrklas L. A study of the effect of age and season on the incidence of ulcerative gingivitis. J Periodont Res. 5: 187-190, 1970.
144. Emslie RD. Treatment of acute ulcerative gingivitis. A clinical trial using chewing gums containing metronidazole or penicillin. Br Dent J. 122: 307-308, 1967.
145. Glenwright HD and Sidaway DA. The use of metronidazole in the treatment of acute ulcerative gingivitis. Br Dent J. 121: 174-177, 1966.
146. Wade AB and Mirza KB. The relative effectiveness of sodium peroxyborate and hydrogen peroxide in treating acute ulcerative gingivitis. Dent Pract. 14: 185-187, 1964.
147. Wade AB, Blake GC, Manson JD et al. A comparative assessment of three medicaments for the treatment of acute ulcerative gingivitis of the Vincent's type. Br Dent J. 111: 280-285, 1961.
148. Polson AM. Gingival and periodontal problems in children. Pediatrics. 54: 190-195, 1974.
149. Kramer IRH. Ulceration of the mouth in children. Aust Dent J. 12: 83-91, 1967.
150. Enwonwu CO. Epidemiological and biochemical studies of necrotizing ulcerative gingivitis and noma (cancrum oris) in Nigerian children. Arch Oral Biol. 17: 1357-1371, 1972.
151. Sheiham A. An epidemiological survey of acute ulcerative gingivitis in Nigerians. Arch Oral Biol. 11: 937-942, 1966.
152. Malberger E. Acute infectious oral necrosis among young children in the Gambia, West-Africa. J Periodont Res. 2: 154-162, 1967.
153. Pindborg JJ, Bhat M and Roed-Petersen B. Oral changes in South Indian children with severe protein deficiency. J Periodontol. 38: 218-221, 1967.

154. Pindborg JJ, Bhat M, Devanath KR et al. Occurrence of acute necrotizing gingivitis in South Indian children. *J Periodontol.* 37: 14-19, 1966.
155. Aquino BA and Gomez Sierra C. Ulcerative necrotizing gingivitis in a five-year-old child. *Rev Assoc Odont Argent.* 61: 123-4, 1973. Abstract. *Advances in Periodontics.* 6: No 290, 1975.
156. Jiménez LM, Ramos J, Garrington G and Baer PN. The familial occurrence of acute necrotizing gingivitis in children in Colombia, South America. *J Periodontol.* 40: 414-416, 1969.
157. Davies AH, McFadzean JA and Squires S. Treatment of Vincent's stomatitis with metronidazole. *Br Med J.* 1: 1149-1150, 1964.
158. Emslie RD. Cancrum oris. *Dent Pract.* 13: 481-495, 1963.
159. Brown RH. Necrotizing ulcerative gingivitis in mongoloid and non-mongoloid retarded individuals. *J Periodont Res.* 8: 290-295, 1973.
160. Pindborg JJ. Disorders of the oral cavity and lips. In: Rook A, Wilkinson DS and Ebling FJG. *Textbook of Dermatology.* Oxford, Blackwell, 2nd ed, vol 2. p 1682-1683.
161. Tonzetich J. Production and origin of oral malodor: A review of mechanisms and methods of analysis. *J Periodontol.* 48: 13-20, 1977.
162. Prichard JF. *Advanced Periodontal Disease.* Philadelphia, Saunders, 2nd ed, 1972. p 721-734.
163. Collins JF. Antibiotic therapy in the treatment of acute necrotizing ulcerative gingivitis. *J Oral Med.* 25: 3-6, 1970.
164. Goldhaber P. Acute necrotizing ulcerative gingivitis. In: Goldman HM and Cohen DW. *Periodontal Therapy.* St Louis, Mosby, 5th ed, 1973. p 167-177.
165. Pickard HM. Historical aspects of Vincent's disease. *Proc R Soc Med.* 66: 695-698, 1973.
166. Fitch HB, Bethart H, Alling CC and Munns CR. Acute necrotizing ulcerative gingivitis. *J Periodontol.* 34 : 422-426, 1963.
167. Schluger S. Necrotizing ulcerative gingivitis in the army: incidence, communicability and treatment. *J Am Dent Assoc.* 38: 174-183, 1949.
168. Zegarelli E. Diseases of the oral cavity. In: Avery GS. *Drug Treatment.* Sydney, Adis, 1976. p 309-310.
169. Cassingham RJ, O'Leary TJ, Hansen NM et al. A possible relationship between acute necrotizing ulcerative gingivitis and infectious mononucleosis. *J Oral Med.* 26: 134-137, 1971.
170. Bhaskar SN. *Synopsis of Oral Pathology.* St Louis, Mosby, 4th ed, 1973. p 191-193.
171. Macalister AD. The management of oral ulceration. *Current Therapeutics.* 14: 29-36, 1973.

172. Schluger S. The aetiology and treatment of Vincent's infection. J Am Dent Assoc. 30: 524-532, 1943.
173. MacPhee T and Cowley G. Essentials of Periodontology and Periodontics. Oxford, Blackwell, 2nd ed, 1975. p 58-59.
174. Carpenter PL. Immunology and Serology. Philadelphia, Saunders, 3rd ed, 1975. p 252-253.
175. Shapiro L, Lodato FM, Courant PR and Stallard RE. Endotoxin determinations in gingival inflammation. J Periodontol. 43: 591-596.1972.
176. Nicol AD, Muir KF, Harkness RA and MacPhee IT. Erythrocyte catalase activity in human ulceromembranous gingivitis. Arch Oral Biol. 16: 21-28, 1971.
177. Lozdan J, Sheiham A, Pearlman BA et al. The use of nitrimidazine in the treatment of acute ulcerative gingivitis. A double-blind controlled trial. Br Dent J. 130: 294-296, 1971.
178. Miller SC and Greene HI. A world-wide survey of acute necrotizing ulcerative gingivitis: A preliminary report. J Dent Med. 13: 66-81, 1958.
179. Pindborg JJ. Influence of service in armed forces on incidence of gingivitis. J Am Dent Assoc. 42: 517-522, 1951.
180. Pedler JA and Radden BG. Seasonal incidence of acute ulcerative gingivitis. Dent Pract. 8: 23, 1957.
181. Miller SC and Greenhut WM. Acute necrotic gingivitis (Vincent's infection); seasonal and age relations. J Am Dent Assoc. 31:910-913, 1944.
182. Giddon DB, Goldhaber P and Dunning JM. Prevalence of reported cases of acute necrotizing ulcerative gingivitis in a university population. (Abstract) No 28: IADR Program and Abstracts. 1962.
183. Giddon DB, Zackin SJ and Goldhaber P. Acute necrotizing ulcerative gingivitis in college students. J Am Dent Assoc. 68: 381-386, 1964.
184. Giddon DB, Goldhaber P and Dunning JM. Prevalence of reported cases of acute necrotizing ulcerative gingivitis in a university population. J Periodontol. 34: 366-371, 1963.
185. Ruben MP, Goldman HM and Schulman SM. Diseases of the periodontium. In: Gorlin RJ and Goldman HM. Thoma's Oral Pathology. St Louis, Mosby, 6th ed, 1970. vol 1. p 424-427.
186. Kay LW. Investigations into the nature of pericoronitis. Br J Oral Surg. 3: 188-205, 1966.
187. Haskell R. Oral vesiculo-bullous lesions. J Laryngol Otol. 90: 101-104, 1976.
188. Silverman S and Beumer J. Acute herpetic gingivostomatitis of adult onset. Oral Surg. 36: 496-503, 1973.
189. Knox JDE. Trench mouth in children. J R Coll Gen Pract. 16: 23-30, 1968.

190. Segelman AE and Doku HC. Treatment of the oral complications of leukaemia. *J Oral Surg.* 35: 469-477, 1977.
191. Fiumara NJ. Venereal diseases of the oral cavity. *J Oral Med.* 31: 36-55, 1976.
192. Pindborg JJ. Atlas of Diseases of the Oral Mucosa. Copenhagen, Munksgaard, 2nd ed, 1973. p 46.
193. Davies RK and Baer PN. Necrotizing ulcerative gingivitis in drug addict patients being withdrawn from drugs. *Oral Surg.* 31: 200-204, 1971.
194. Colon PG. Dental disease in the narcotic adult. *Oral Surg.* 33: 905-910, 1972.
195. Zamet JS. Report of a case of mercurial periodontitis. *J Periodontol.* 38: 255-258, 1967.
196. Marsland EA and Browne RM. Colour Atlas of Oral Histopathology. Aylesbury, HM and M Publishers, 1975. p 34.
197. Listgarten MA. Electron microscopic observations on the bacterial flora of acute necrotizing ulcerative gingivitis. *J Periodontol.* 36: 328-339, 1965.
198. Heylings RT. Electron microscopy of acute ulcerative gingivitis (Vincent's type). *Br Dent J.* 122: 51-56, 1967.
199. Theilade E and Theilade J. Role of plaque in the etiology of periodontal disease and caries. *Oral Sciences Reviews.* 9. Copenhagen, Munksgaard, 1976. p 23-64.
200. Gilmour MN and Nisengard RJ. Interactions between serum titres to filamentous bacteria and their relationship to human periodontal disease. *Arch Oral Biol.* 19: 959-968, 1974.
201. Thomas W, Holt PG and Keast D. Effect of cigarette smoking on primary and secondary humoral responses of mice. *Nature.* 243: 240-241, 1973.
202. Thomas WR, Holt PG and Keast D. Recovery of immune system after cigarette smoking. *Nature.* 248: 358-359, 1974.
203. Bastiaan RJ and Reade PC. The effects of tobacco smoking on oral and dental tissues. *Aust Dent J.* 21: 308-315, 1976.
204. Kenney EB, Kraal JH, Saxe SR and Jones J. The effect of cigarette smoke on human oral polymorphonuclear leucocytes. *J Periodont Res.* 12: 227-234, 1977.
205. Roszman TL and Rogers AS. The immunosuppressive potential of products derived from cigarette smoke. *Am Rev Resp Dis.* 108: 1158-1163, 1973.
206. Finklea JF, Hasselblad V, Riggan WB et al. Cigarette smoking and hemagglutination inhibition response to influenza after natural disease and immunization. *Am Rev Resp Dis.* 104: 368-376, 1971.

207. Schwartz SL. Interaction of nicotine and other amines with the endocytic and exocytic functions of macrophages. *Fed Proc.* 35: 85-88, 1976.
208. Chellemi SJ, Olson DL and Shapiro S. The association between smoking and aphthous ulcers. *Oral Surg.* 29: 832-836, 1970.
209. Shapiro S, Olson DL and Chellemi SJ. The association between smoking and aphthous ulcers. *Oral Surg.* 30: 624-630, 1970.
210. Lehner T. Immunologic aspects of recurrent oral ulcers. *Oral Surg.* 33: 80-85, 1972.
211. Honma T. Electron microscopic study on the pathogenesis of recurrent aphthous ulceration as compared to Behcets syndrome. *Oral Surg.* 41: 366-377, 1976.
212. Lund WS. Treatment of superficial lesions of the mouth and pharynx. *J Laryngol Otol.* 90: 105-112, 1976.
213. Scully C. Down's syndrome: aspects of dental care. *J Dent.* 4: 167-174, 1976.
214. Khan AJ, Evans HE, Glass L et al. Defective neutrophil chemotaxis in patients with Down syndrome. *J Pediatr.* 87: 87-89, 1975.
215. Gregory L, Williams R and Thompson E. Leucocyte function in Down's syndrome and acute leukaemia. *Lancet.* 1: 1359-1361, 1972.
216. Rozner F and Kozinn PJ. Leucocyte function in Down's syndrome. *Lancet.* 2: 283-284, 1972.
217. Goodman RM. The Respiratory System. In: Sorsby A. *Clinical Genetics.* London, Butterworth, 2nd ed, 1973. p 405-406.
218. Ugazio AG, Maccario R, Duse M and Burgio GR. T-lymphocyte deficiency in Down syndrome. *Lancet.* 1: 1062, 1977.
219. Thomas HC, Ferguson A, McLennan JG and Mason DK. Food antibodies in oral disease: A study of serum antibodies to food proteins in aphthous ulceration and other oral diseases. *J Clin Pathol.* 26: 371-374, 1973.
220. Lehner T and Clarry ED. Acute ulcerative gingivitis: An immunofluorescent investigation. *Br Dent J.* 121: 366-370, 1966.
221. Lehner T. Immunoglobulin abnormalities in ulcerative gingivitis. *Br Dent J.* 127: 165-169, 1969.
222. Provisor AJ, Iacuone JJ, Chilcote RR et al. Acquired agammaglobulinemia after a life-threatening illness with clinical and laboratory features of infectious mononucleosis in three related male children. *New Engl J Med.* 293: 62-65, 1975.
223. Wilton JMA, Ivanyi L and Lehner T. Cell-mediated immunity and humoral antibodies in acute ulcerative gingivitis. *J Periodont Res.* 6: 9-16, 1971.

224. Shapiro L, Cuevas P, Stallard RE and Ruben MP. Absence of the localized Schwartzman reaction following 6-OH dopamine sympathectomy. *J Periodont Res.* 9: 207-210, 1974.
225. Rizzo AA and Mergenhagen SE. Local shwartzman reaction in rabbit oral mucosa with endotoxin from oral bacteria. *Proc Soc Exp Biol Med.* 104: 579-582, 1960.
226. Rizzo AA and Mergenhagen SE. Histopathologic effects of endotoxin injected into rabbit oral mucosa. *Arch Oral Biol.* 9: 659-670, 1964.
227. Movat HZ. Pathways to allergic inflammation: the sequelae of antigen-antibody complex formation. *Fed Proc.* 35: 2435-2441, 1976.
228. Andrews BS and Penny R. The role of immune complexes in the pathogenesis of disease. *Aust N Z J Med.* 6: 591-602, 1976.
229. MacPhee T and Cowley G. *Essentials of Periodontology and Periodontics.* Oxford, Blackwell, 2nd ed, 1975. p 70-72.
230. Dolby AE. Acute ulcerative gingivitis: Immune complex. *J Dent Res.* 51: 1639-1641, 1972.
231. Carpenter PL. *Immunology and Serology.* Philadelphia, Saunders, 3rd ed, 1975. p 280-282.
232. Tempest MN. Cancrum oris. *Br J Surg.* 53: 949-969, 1966.
233. Ruben MP and Miller M. Noma: its association with nutritional deprivation and physical debilitation. *Oral Surg.* 18: 167-175, 1964.
234. Reddy V, Raghuramulu N and Bhaskaram C. Secretory IgA in protein-calorie malnutrition. *Arch Dis Child.* 51: 871-874, 1976.
235. Gibbons RJ and van Houte J. Bacterial adherence in oral microbial ecology. *Annu Rev Microbiol.* 29: 19-44, 1975.
236. Davies RM. Bacteriological problems in general practice. *Proc R Soc Med.* 67: 1263-1264, 1974.
237. Robertson PB and Cooper MD. Oral manifestations of IgA deficiency *Adv Exp Med Biol.* 45: 447-503, 1974.
238. Feigin RD and Shearer WT. Opportunistic infection in children. 2. In the compromised host. *J Pediatr.* 87: 677-694, 1975.
239. Grant DA, Stern IB and Everett FG. *Orban's Periodontics.* St Louis, Mosby, 4th ed, 1972. p 170-187.
240. Freeman BM. Physiological basis of stress. *Proc R Soc Med.* 68: 427-429, 1975.
241. Bartrop RW, Lazarus L, Luckhurst E et al. Depressed lymphocyte function after bereavement. *Lancet.* 1. 834-836, 1977.
242. Pindborg JJ. Tobacco and gingivitis. 2. Correlation between consumption of tobacco, ulceromembranous gingivitis and calculus. *J Dent Res.* 28: 460-463, 1949.

243. Giddon DB. Psychophysiology of the oral cavity. J Dent Res. 45:(supplement), 1627-1636, 1966.
244. Schwartz DM and Baumhammers A. Smoking and periodontal disease. Periodont Abstr. 20: 103-106, 1972.
245. Bastiaan RJ. The effects of tobacco smoking on the periodontal tissues. Aust Soc Periodontol. Newsletter. 6: 2-3, 1977.
246. Sheiham A. Periodontal disease and oral cleanliness in tobacco smokers. J Periodontol. 42: 259-263, 1971.
247. Colman G, Beighton D, Chalk AJ and Wake S. Cigarette smoking and the microbial flora of the mouth. Aust Dent J. 21: 111-118, 1976.
248. Frewin DB, Hume WR, Waterson JG and Whelan RF. The histochemical localisation of sympathetic nerve endings in human gingival blood vessels. Aust J Exp Biol Med Sci. 49: 573-580, 1971.
249. Cryer PE, Haymond MW, Santiago JV and Shah SD. Norepinephrine and epinephrine release and adrenergic mediation of smoking-associated hemodynamic and metabolic events. New Engl J Med. 295: 573-577, 1976.
250. Shuler RL. Effect of cigarette smoking on the circulation of the oral mucosa. J Dent Res. 47:(supplement), 910-915, 1968.
251. Listgarten MA, Mayo HE and Tremblay R. Development of dental plaque on epoxy resin crowns in man. J Periodontol. 46: 10-26, 1975.
252. Kenney EB and Ash MM. Oxidation reduction potential of developing plaque, periodontal pockets and gingival sulci. J Periodontol. 40: 630-633, 1969.
253. Kenney EB, Saxe SR and Bowles RD. The effect of cigarette smoking on anaerobiosis in the oral cavity. J Periodontol. 46: 82-85, 1975.
254. Shannon IL, Kilgore WG and O'Leary TJ. Stress as a predisposing factor in necrotizing ulcerative gingivitis. J Periodontol. 40: 240-242, 1969.
255. Williams W. The current management of anxiety states. Modern Medicine of Australia. 19: 13-18, 1976.
256. Roth H and Stone A. Psychosomatic and nutritional factors related to recurrent necrotizing ulcerative gingivitis. J Am Dent Assoc. 42: 474-475, 1951.
257. Moulton R, Ewen S and Thieman W. Emotional factors in periodontal disease. Oral Surg. 5: 833-860, 1952.
258. Goldberg H, Ambinder WJ, Cooper L and Abrams AL. Emotional status of patients with acute gingivitis. N Y State Dent J. 22: 308-318, 1956.
259. Formicola AJ, Witte ET and Curran PM. A study of personality traits and acute necrotizing ulcerative gingivitis. J Periodontol. 41: 36-38, 1970.

260. Maupin CC and Bell WB. The relationship of 17-Hydroxycorticosteroid to acute necrotizing ulcerative gingivitis. *J Periodontol.* 46: 721-722, 1975.
261. Manhold JH, Doyle JL and Weisinger EH. Effects of social stress on oral and other bodily tissues. 2. Results offering substance to a hypothesis for the mechanism of formation of periodontal pathology. *J Periodontol.* 42: 109-111, 1971.
262. Giddon DB, Clark ER and Varni JG. Apparent digital vasomotor hypotonicity in the remission stage of acute necrotizing ulcerative gingivitis. *J Dent Res.* 48: 431-438, 1969.
263. Clarke RE and Giddon DB. Body geometry of patients who had recurrent attacks of acute necrotizing ulcerative gingivitis. *Arch Oral Biol.* 16: 205-213, 1971.
264. Rook A and Wilkinson DS. Psychocutaneous disorders. In: Rook A, Wilkinson DS and Ebling FJG. *Textbook of Dermatology.* Oxford, Blackwell, 2nd ed. vol 2. 1972. p 1819-1830.
265. Burnett GW, Scherp HW and Schuster GS. Oral Microbiology and Infectious Disease. Baltimore, Williams and Wilkins, 4th ed, 1976. p 153-164.
266. Listgarten MA and Socransky SS. Electron microscopy as an aid in the taxonomic differentiation of oral spirochetes. *Arch Oral Biol.* 10: 127-138, 1965.
267. Manson JD and Rand H. Recurrent Vincent's disease: A survey of 61 cases. *Br Dent J.* 110: 386-390, 1961.
268. Hartenian KM and Stenger TG. Postanesthetic palatal ulceration. *Oral Surg.* 42: 447-450, 1976.
269. King JD. Nutritional and other factors in "Trench Mouth" with special reference to the nicotinic acid component of vitamin B2 complex. *Br Dent J.* 74: 169-176, 1943.
270. Kindlova M. Glomerular vascular structures in the periodontium. In: *The Mechanisms of Tooth Support.* Bristol, Wright, 1967. p 76-79.
271. Kindlova M. The development of the vascular bed of the marginal periodontium. *J Periodont Res.* 5: 135-140, 1970.
272. Listgarten MA. Structure of the microbial flora associated with periodontal health and disease in man. *J Periodont.* 47: 1-18, 1976.
273. Grigsby WR and Sabiston CB. The periodontal disease process. *J Oral Pathol.* 5: 175-188, 1976.
274. McLaren DS. Cutaneous lesions in nutritional deficiencies. In: Fitzpatrick TB, Arndt KA, Clark WH et al. *Dermatology in General Medicine.* New York, Mc-Graw Hill, 1971. p 1073-1088.
275. Parsons JC. Chemotherapy of dental plaque-a review. *J Periodontol.* 45: 177-186, 1974.

276. Holroyd SV. Antibiotics in the practice of periodontics. J Periodontol: 42: 584-589, 1971.
277. Thomas CGA. Medical Microbiology. London, Balliere Tindall, 3rd ed, 1973. p 274-275.
278. White RG and Timbury MC. Essentials of Immunology and Microbiology. London, Pitman, 1973. p 328-329.
279. Berman KS and Gibbons RJ. Bacteriologic census of debris obtained from Vincent's infection. IADR Program and Abstracts.No 267. 1965.
280. Rosebury T, Clark AR, Engel SG and Tergis F. Studies of fusospirochetal infection.1. Pathogenicity for guinea pigs of individual and combined cultures of spirochetes and other anaerobic bacteria derived from the human mouth. J Infect Dis. 87: 217-225, 1950.
281. Hampp EG and Mergenhagen SE. Experimental infections with oral spirochetes. J Infect Dis. 109: 43-61, 1961.
282. Hampp EG and Mergenhagen SE. Experimental intracutaneous fusobacterial and fusospirochetal infections. J Infect Dis. 112: 84-99, 1963.
283. Macdonald JB, Socransky SS and Gibbons RJ. Aspects of the pathogenesis of mixed anaerobic infections of mucous membranes. J Dent Res. 42:(supplement), 529-544, 1963.
284. Macdonald JB, Sutton RM, Knoll ML et al. The pathogenic components of an experimental fusospirochetal infection. J Infect Dis. 98: 15-20, 1956.
285. Socransky SS and Gibbons RJ. Required role of Bacteroides melaninogenicus in mixed anaerobic infections. J Infect Dis. 115; 247-253, 1965.
286. Okuda K and Takazoe I. Haemagglutinating activity of Bacteroides melaninogenicus. Arch Oral Biol. 19: 415-416, 1974.
287. Kaufman EJ, Mashimo PA, Hausmann E et al. Fusobacterial infection: enhancement by cell free extracts of Bacteroides melaninogenicus possessing collagenolytic activity. Arch Oral Biol. 17: 577-580, 1972.
288. Loesche WJ, Paunio KU, Woolfolk MP and Hockett RN. Collagenolytic activity of dental plaque associated with periodontal pathology. Infect Immun. 9: 329-336, 1974.
289. Courant PR, Paunio I and Gibbons RJ. Infectivity and hyaluronidase activity of debris from healthy and diseased gingiva. Arch Oral Biol. 10: 119-125, 1965.
290. Berke JD. Experimental study of acute ulcerative stomatitis. J Am Dent Assoc. 63: 86-90, 1961.
291. Van Campen GJ, Wouters SLJ, Mikx FHM and van der Hoeven JS. The occurrence of acute necrotizing ulcerative gingivitis in a beagle dog colony. J Dent Res. 56. IADR Program and Abstracts. No 12. 1977.

292. Wouters SLJ, Van Campen GJ, Mikx FHM and van der Hoeven JS. Experimental induced ANUG in beagle dogs. J Dent Res. 56. IADR Program and Abstracts. No 13. 1977.
293. Mikx FHM, Van Campen GJ, van der Hoeven JS and Wouters SLJ. Comparison of the microbial flora of gingival plaque from healthy and ANUG sites in beagle dogs. J Dent Res. 56. IADR Program and Abstracts. NO 14. 1977.
294. Listgarten MA and Socransky SS. Ultrastructural characteristics of a spirochete in the lesion of acute necrotizing ulcerative gingivostomatitis (Vincent's infection). Arch Oral Biol. 9: 95-96, 1964.
295. Loesche WJ. Chemotherapy of dental plaque infections. Oral Sciences Reviews.9. Copenhagen, Munksgaard, 1976. p 65-91.
296. Listgarten MA and Lewis DW. The distribution of spirochetes in the lesion of acute necrotizing ulcerative gingivitis: An electron microscopic and statistical survey. J Periodontol. 38: 379-386, 1967.
297. Listgarten MA. Personal communication. 1977.
298. Socransky SS and Manganiello AD. The oral microbiota of man from birth to senility. J Periodontol. 42: 485-494, 1971.
299. Kelstrup J. The incidence of Bacteroides melaninogenicus in human gingival sulci, and its prevalence in the oral cavity at different ages. Periodontics. 4: 14-18, 1966.
300. Reade PC. Infantile acute ulcerative gingivitis. J Periodontol. 34: 387-390, 1963.
301. Davies RM and Stirland RM. The in vitro sensitivity of oral spirochaetes to metronidazole. J Periodont Res. 5: 183-186, 1970.
302. Reynolds AV, Hamilton-Miller JMT and Brumfitt W. A comparison of the in vitro activity of metronidazole, tinidazole and nimorazole against Gram-negative anaerobic bacilli. J Clin Pathol. 28: 775-778, 1975.
303. Willis AT, Ferguson IR, Jones PH et al. Metronidazole in prevention and treatment of bacteroides infections after appendicectomy. Br Med J. 1: 318-321, 1976.
304. Quayle AA. Bacteroides infections in oral surgery. Oral Surg. 32: 91-99, 1974.
305. Hadi AW and Russell C. Quantitative estimations of fusiforms in saliva from normal individuals and cases of acute ulcerative gingivitis. Arch Oral Biol. 13: 1371-1376, 1968.
306. Hadi AW and Russell C. Fusiforms in gingival material. Quantitative estimations from normal individuals and cases of periodontal disease. Br Dent J. 126: 82-84, 1969.

307. Emslie RD and Ashley FP. Topical treatment of acute ulcerative gingivitis: A comparison of vancomycin with penicillin and metronidazole. *Paradontologie*. 25: 3-8, 1971.
308. Wade AB, Blake GC and Mirza KB. Effectiveness of metronidazole in treating the acute phase of ulcerative gingivitis. *Dent Pract*. 16: 440-443, 1966.
309. Glickman I. *Clinical Periodontology*. Philadelphia, Saunders, 4th ed, 1972. p 799-813.
310. Duckworth R, Waterhouse JP, Britton DER et al. Acute ulcerative gingivitis. A double-blind controlled clinical trial of metronidazole. *Br Dent J*. 120: 599-602, 1966.
311. Silver JG, Southcott RJ and Wade AB. Acute necrotizing ulcerative gingivitis-an evaluation of the ulcer improvement index. *J Periodontol*. 45: 308-311, 1974.
312. Oliver WM and Fletcher JP. Oral hygiene in the treatment of acute ulcerative gingivitis. *Br Dent J*. 106: 177-180, 1959.
313. Fletcher PD, Wyman BS and Scopp IW. Acute necrotizing ulcerative gingivitis- sequelae following treatment with silver nitrate. *N Y J Dent*. 46: 122-124, 1976.
314. Ciancio SG. Tetracyclines and periodontal therapy. *J Periodontol*. 47: 155-159, 1976.
315. Mitchell DF and Baker BR. Topical antibiotic control of necrotizing gingivitis. *J Periodontol*. 39: 81-82, 1968.
316. Bhaskar SN, Grower MF and Cutright DE. Gingival healing after hand and ultrasonic scaling- biochemical and histologic analysis. *J Periodontol*. 43: 31-34, 1972.
317. Jacobson L. Ultrasonic scaling. *Aust Dent J*. 19: 379-383, 1974.
318. Suppiat N. Ultrasonics in periodontics. *J Clin Periodontol*. 1: 206-213, 1974.
319. Stephen KW, McLatchie MF, Mason DK et al. Treatment of acute ulcerative gingivitis (Vincent's type). *Br Dent J*. 121: 313-321, 1966.
320. Tolhurst JC, Buckle G and Williams SW. *Chemotherapy with antibiotics and allied drugs*. Canberra. Aust Govt Publishing Service. 3rd ed. 1972. p 236-237.
321. Tolhurst JC, Buckle G and Williams SW. op.cit. p 141-145.
322. Kaslick RS, Tuckman MA and Chasens AI. Effect of topical vancomycin on plaque and chronic gingival inflammation. *J Periodontol*. 44: 366-368, 1973.
323. Hamilton-Miller JMT. Antimicrobial agents acting against anaerobes. *J Antimicrob Chemother*. 1: 273-289, 1975.

324. Barker BM and Prescott F. Antimicrobial Agents in Medicine. Oxford, Blackwell, 1973. p 52.
325. Chow AW, Patten V and Guze LB. Susceptibility of anaerobic bacteria to metronidazole: Relative resistance of non-spore-forming Gram-positive bacilli. J Infect Dis. 131: 182-185, 1975.
326. Study Group. Metronidazole in the prevention and treatment of bacteroides infections in gynaecological patients. Lancet.2. 1540-1543, 1974.
327. Dornbusch K and Nord CE. In vitro effect of metronidazole and tinidazole on anaerobic bacteria. Med Microbiol Immunol. 160: 265-267, 1974.
328. Ingham HR, Rich GE, Selkon JB et al. Treatment with metronidazole of three patients with serious infections due to Bacteroides fragilis. J Antimicrob Chemother. 1: 235-241, 1975.
329. Whelan JPF and Hale JH. Bactericidal activity of metronidazole against Bacteroides fragilis. J Clin Pathol. 26: 393-395, 1973.
330. Willis AT, Ferguson IR, Jones PH et al. Metronidazole in prevention and treatment of bacteroides infections in elective colonic surgery. Br Med J. 1. 607-610, 1977.
331. Flagyl. Metronidazole. Manufacturer's information. May and Baker. 7th ed. 1975.
332. Peterson WF, Stauch JE and Ryder CD. Metronidazole in pregnancy. Am J Obstets Gynec. 94: 343-349, 1966.
333. O'Reilly RA. The stereoselective interaction of warfarin and metronidazole in man. New Engl J Med. 295: 354-357, 1976.
334. Ingham HR, Hood FJC, Bradnum P et al. Metronidazole compared with penicillin in the treatment of acute dental infections. Br J Oral Surg. 14: 265-269, 1977.
335. Pye RJ and Burton JL. Treatment of rosacea by metronidazole. Lancet.1. 1211-1212, 1976.
336. Lipman A and Wade DN. Drug interactions involving antiepileptic agents. Modern Medicine of Australia. 20: 69-70, 1977.
337. Coxon A and Pallis CA. Metronidazole neuropathy. J Neurol Neurosurg Psychiatry. 39: 403-405, 1976.
338. Cowdrey SC. Hazards of metronidazole. New Engl J Med. 293: 454, 1975.
339. Legator MS, Connor TH and Stoeckel M. Detection of mutagenic activity of metronidazole and niridazole in body fluids of humans and mice. Science. 188: 1118-1119, 1975.
340. Is flagyl dangerous? Med Lett Drugs Ther. 17: 53-54, 1975.

341. Dykers JR. Hazards of metronidazole. N Engl J Med. 293: 454, 1975 .
342. McGowan DA, Murphy KJ and Sheiham A. Metronidazole in the treatment of severe acute pericoronitis. A clinical trial.
Br Dent J. 142: 221-223, 1977.
343. Sawyer PR, Brogden RN, Pinder RM et al. Tinidazole. A review of its antiprotozoal activity and therapeutic efficacy.
Drugs. 11: 423-440, 1976.
344. Komaroff AL, Cohen AB and McCue J. Alternatives to metronidazole.
JAMA. 235: 2081-2082, 1976.
345. Graykowski EA and Holroyd SV. Therapeutic management of primary herpes, recurrent labial herpes, aphthous stomatitis and Vincent's infection. Dent Clin North Am. 14:4, 721-731, 1970.
346. Martin JH, Bishop JG, Guentherman RH and Dorman HL. Cellular response of gingiva to prolonged application of dilute hydrogen peroxide. J Periodontol. 39: 208-210, 1968.
347. Gjermo P. Chlorhexidine in dental practice. J Clin Periodontol. 1: 143-152, 1974.
348. Moustafa MH, Sadek SI and Salam NA. Treatment of acute necrotizing ulcerative gingivitis by chlorhexidine and cetrimide.
Egypt Dent J. 21: 19-24, 1975. (Abstract) Oral Research Abstracts 11: 8138, 1976.
349. Fløtra L, Gjermo P, Rolla G and Waerhaug J. A four month study on the effect of chlorhexidine mouthwashes on 50 soldiers.
Scand J Dent Res. 80: 10-17, 1972.
350. Hamp SE, Rosling B and Lindhe J. Effect of chlorhexidine on gingival wound healing in the dog. A histometric study.
J Clin Periodontol. 2: 143-152, 1975.
351. Plüss EM, Engelberger PR and Rateitschak KH. Effect of chlorhexidine on dental plaque formation under periodontal pack.
J Clin Periodontol. 2: 136-142, 1975.
352. Goldschmidt P, Cogen R and Taubman S. Cytopathologic effects of chlorhexidine on human cells. J Periodontol. 48: 212-215, 1977.
353. Klingsberg J. Patient education about necrotizing gingivitis.
N Y State Dent J. 37: 413-416, 1971.

