CHAPTER 1.

1.1. Introduction.

Temporomandibular disorders (TMD) are chronic disturbances of the musculoskeletal system of the jaws involving muscle and joint disorders. Accepted TMD diagnostic criteria are termed the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) as described by Le Resche et al (1992). These RDC/TMD criteria divide the investigation of patients into two axes. Axis I is a set of operational research diagnostic criteria for use in investigation of masticatory muscle pain, disc displacement, and degenerative changes of the temporomandibular joint (TMJ); Axis II is a set of operational research diagnostic criteria to assess chronic pain dysfunction, depression, non-specific physical symptoms, and orofacial disability. Table 1.1 summarises the RDC/TMD Axis I divisions for diagnosis of orofacial pain patients.

Table 1.1. TMD Research Diagnostic Criteria (Le Resche et al, 1992).

<table>
<thead>
<tr>
<th>AXIS I</th>
<th>Diagnostic Categories</th>
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<tr>
<td>I</td>
<td><strong>Muscle Diagnoses</strong></td>
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<td></td>
<td>a. Myofascial pain.</td>
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<td>b. Myofascial pain with limited opening.</td>
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<td>II</td>
<td><strong>Disc Displacements</strong></td>
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<td>a. Disc displacement with reduction.</td>
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<td>b. Disc displacement without reduction, with limited opening.</td>
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<td>c. Disc displacement without reduction, without limited opening.</td>
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<td>III</td>
<td><strong>Arthralgia, Arthritis, Arthosis</strong></td>
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<tr>
<td></td>
<td>a. Arthralgia.</td>
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<td></td>
<td>b. Osteoarthritis of the Temporomandibular joint (TMJ).</td>
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<td></td>
<td>c. Osteoarthrosis of the TMJ.</td>
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<td>AXIS II</td>
<td><strong>Disability measures.</strong></td>
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<td></td>
<td>a. Pain intensity and disability.</td>
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<td></td>
<td>b. Depression (depression and vegetative symptom scales)</td>
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<td>c. Limitations related to mandibular functioning.</td>
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These diagnostic criteria provide a description of some of the physical and behavioural changes associated with TMD disorders but have limitations as they do not assess other body symptoms associated with TMD and the information does not address the aetiology.

1.2. Proposed Hypothetical Models of the Aetiology of TMD.
The first proposed aetiology of orofacial pain was that loss of posterior teeth resulted in collapse of the vertical dimensions of occlusion causing pressure on the eustachian tube, ear structures, the auriculotemporal nerve and the temporomandibular joint, with evocation of pain (Prentiss, 1918). Costen (1934; 1936) popularised these concepts in his description of partially edentulous patients (posterior tooth loss), with marked mandibular overclosure, with associated impaired hearing, tinnitus, vertigo, pain in the area of the ear, trismus, occipital headache, burning sensations in the tongue, nose and sinuses. However, based on morbid anatomical assessment anatomists, Sicher (1948) and Zimmerman (1951) reported that the nerve impingement and eustachian tube blockage proposed by Prentiss (1918) and Costen (1934, 1936), was not anatomically possible. The nerve impingement hypothesis was developed by clinicians attempting to describe, explain and treat conditions where limited basic knowledge existed.

In his landmark paper, Schwartz (1955) introduced the term "temporomandibular joint-pain dysfunction syndrome". He described a syndrome with three phases: 1) an incoordination phase (minor muscle problems, TMJ clicks and/or recurrent TMJ subluxation); 2) a pain-limitation phase (painful spasm in any of the "antigravity type" muscles and limitations in mandibular movement); and 3) a limitation phase (muscle contractures which were not continually painful). He reported a female/male ratio of 4:1 and proposed that several factors influenced the outcome of the condition. These factors were termed: 1) predisposing factors (constitutional or physiological and temperamental or psychological); 2) contributing factors (occlusal anomalies and malocclusion); 3) precipitating factors (yawning, wide opening, long dental procedures and iatrogenic problems); and 4) aggravating factors (trauma, physiological and psychological influences). Possible aetiological factors were dental pathology, ear nose and throat diseases, adenopathy, neurological disease, rheumatoid arthritis, osteoarthritis, scleroderma, traumatic disorders and neoplasm. This paper was the first attempt to comprehensively describe and understand TMD.

Travell (1960) described in detail the pain referral patterns of the jaw and cervical muscles and the association between head and neck muscle pain. These associations have been summarised in "myofascial pain and dysfunction" (Travell & Simons, 1983) where chronic myalgic syndromes are described as the result of reflex feedback mechanisms between localised muscle "trigger points" and the central nervous system (CNS). The authors describe the many and various "trigger points" within individual muscles and their referred pain sites.
They state "irritability of trigger points are influenced by the number and severity of perpetuating factors", such as mechanical stresses, nutritional inadequacies, metabolic and endocrine inadequacies, psychological factors, chronic infection, allergy, impaired sleep, radiculopathy and chronic visceral disease. Travell’s studies have had a significant influence in understanding TMD and its management and introduced a medical assessment for the condition. Whilst Travell addresses medical conditions associated with TMD, the data presented is predominately from a clinical perspective and does not address associations between the medical problems and TMD symptom expression.

A significant change in diagnosis and management of TMD and orofacial pain followed the work of Ramjford (1961). In an uncontrolled study, Ramjford reported that occlusal adjustment in patients with "temporomandibular joint" symptoms resulted in reduced jaw muscle electromyographic activity and pain. He proposed that TMD arose as a functional disturbance, with differences between centric relation and centric occlusion and that mediotrusive contacts were the cause of increased muscle tone and parafunction. This had a profound effect upon clinicians and focused treatment methods based upon occlusal adjustment. Ramjford and Ash (1966) later qualified the conclusions, from the study, with a statement: "The role of occlusion and occlusal interferences in the cause of functional temporomandibular joint and muscle is controversial. According to recent investigations, patients (as a group) with functional disturbances of joints and muscles do not have any more occlusal interferences than individuals without the disturbances. On the other hand, such disturbances can unquestionably be eliminated in the overwhelming majority of cases by removal of occlusal interferences". Whilst Ramjford reported an association between the removal of occlusal problems and a reduction in symptoms, he recognised the resulting scientific dilemma where many clinicians interpreted the data as occlusal anomalies cause TMD (Geering, 1974; Vanderas, 1996). Subsequent studies by other authors (McCarroll et al, 1984; De Laat et al, 1985; Wanman & Agerberg, 1986; Egermark Eriksson et al, 1987; Meng et al, 1987; Dahl et al, 1988; Nielsen et al, 1989; Pullinger et al, 1992) have addressed this issue. These studies have reported that occlusal problems do not have a causal relationship with TMD when whole populations are studied. Other authors have associated occlusal problems with alterations in jaw muscle activity, which may influence pain (Sheikholeslam & Riise, 1983; Riise & Sheikholeslam, 1984). These data suggest that local functional changes associated with malocclusion are not aetiologically related to TMD, but may be associated with changes in symptom expression within patients with TMD. In support of the contention that local factors are not of aetiological significance, is
that muscle pain is not restricted to the face but is associated with other symptoms including migraines and low back pain (Dixon, 1948; Berry, 1969; Carraro et al, 1969; Heloe, 1976; Weinberg and Lager, 1980; Eriksson et al, 1988; Turp et al, 1998).

Laskin (1969) introduced the term "myofascial pain-dysfunction syndrome" to describe a specific subgroup of TMD disorders and hypothesised that “masticatory muscle spasm” was the result of emotionally derived tension or stress. He suggested that "muscle spasm" was the primary cause of the pain rather than joint pathology and based this on the observation that radiographic evidence of joint pathology occurred in less then 5% of TMD patients. Laskin (1969) further suggested that emotionally derived tension or stress caused muscle fatigue as a result of prolonged "tension relieving" jaw activities. His hypothesis resulted in a shift toward the assessment of stress and TMD symptoms. Other authors suggested an association between stress and TMD (Schwartz, 1955; Yemm 1969a, 1969b; 1971a; 1971b; Fricton et al, 1985), however, recent studies (Schiffman et al, 1992; de Leeuw et al, 1994a; 1994b) have failed to identify a significant relationship between stressful events and TMD. In fact de Leeuw et al (1994b) found that stress was lower in patients with more severe symptoms and negative treatment outcomes. These data do not provide strong evidence linking stress with TMD.

Lund et al, (1991) proposed a model of pain adaptation, where patients have differences in normal masticatory activities which are attributed to the pain response. Molin et al (1972) showed that bite force was negatively correlated with levels of muscle pain and tenderness, whilst Bessette et al (1971) showed that alterations in chin tap electromyography (EMG) occurred in pain patients. Although these alterations in activity appear to be a response to pain, the results are heterogeneous and not found in all patients (Sharav et al, 1982; Zulqarnain et al, 1989). Increased spontaneous facial muscle EMG activity was first noted by Jarabak (1956) and again by Ramjford (1961). Munro (1975) found that unlike control subjects, 50% of TMD patients had spontaneous EMG activity whilst their mouth was open. This was the basis of the hyperactivity model for muscle pain (Travell & Simons, 1993). Sharav & Benoliel (1993) discussed the proposal that muscle hyperactivity may cause muscle pain especially the day following increased activity (Travell & Simons, 1993). However, Lund et al, (1991) concluded that muscle hyperactivity is not associated with chronic pain. Whilst muscle EMG hyperactivity does occur in muscle pain patients, it is likely that it results from the disease process and is not of aetiological significance.
Sessle (1992; 1995) described the central connections and neurobiology of pain responses in the trigeminal system. He proposed that alterations in the chemicals that modulate nociceptive transmission (substance P, enkephalin, serotonin and gamma-aminobutyrate) might play a role in excitation of pain responses. Neuroplasticity of the central and peripheral nervous system induced by inflammatory products or alterations in N-Methyl-D-Aspartate (NMDA) receptors in the brain has also been proposed as a mechanism for initiation of TMD pain (Dubner 1992; Mense 1993; Schaible & Grubb 1993). TMD dysfunction syndrome has been associated with phenothiazine medication (Evans, 1965; Hiatt & Schwartz, 1966) and Pertoutka et al (1988) reported parafunction and/or trismus in the majority of users of the narcotic drug 3,4 methylenedioxymeth-amphetamine ("Ecstasy"). These data are highly suggestive of an association between a central nervous system dopaminergic anomaly and TMD. This is supported by the observation that tricyclic antidepressants, which increase noradrenaline activity, are associated with a reduction in TMD symptoms (Tura & Tura, 1990). Thus, the onset of TMD muscle pain may be associated with alterations in CNS dopamine associated changes. Examination of amino acid metabolism in TMD subjects is warranted as it may allow detection of alterations in the precursors of neurotransmitters and illuminate further avenues for research.

Diverse hypotheses have been proposed for the aetiology of TMD disorders. The dental literature is predominately of a mechanical-functional approach, which concentrates largely on the facial area, but has failed to identify the aetiology. The data reviewed in this chapter suggests that TMD is part of a systemic condition and may be associated with alterations in CNS nociceptive and neuronal plasticity changes that may be associated with dysregulated neurotransmission and inflammation. As a result a series of pilot studies were undertaken to investigate TMD from a systemic infection associated model.

1.3. Pilot study data.

Three pilot studies were conducted and reported as abstracts (McGregor et al, 1992a; 1992b; 1993a; 1993b; 1994a; 1994b; Zerbes 1993). These studies were firstly designed to assess pain distribution, factors related to onset or exacerbation, the prevalence of the associated signs and symptoms, the incidence of any muscle pain-associated condition and alterations in serum and urinary biochemistry compared with laboratory normal values. The second pilot study assessed the carriage of urinary tract staphylococcus whilst the third study assessed the
toxicity of the staphylococcus obtained from the pain patients in a series of simple in vitro experiments.

### 1.3.1. First pilot study.

The first pilot study involved a questionnaire survey of 35 sequentially presenting RDC/TMD type 1a patients. Thirty-two females (age = 40.6±16 years; age range = 17-65 years; age of onset = 32.1±14; duration = 5-53 years) and 3 males (age = 49.7±13 years; age range = 38-73 years; age of onset = 45.3±15; duration = 32-67 years) completed the questionnaires and provided pathology tests from their medical practitioners. Twenty-three (66%) reported a gradual onset to their condition. Only 8% of subjects reported facial pain alone, whilst most patients had a pain pattern with a facio-scalpo-humeral distribution. Onset was reported to be associated with muscle fatigue (25 – 71%), stress (20 – 57%), trauma (8 – 23%), a genitourinary tract infection (6 – 17%), bells palsy (1 – 3%) and nasal surgery (1 – 3%). The predominant symptoms reported were parafunction (23 - 66%), sleep disturbances (22 - 63%), tinnitus (18 - 51%), gastroesophageal reflux (15 - 43%), chronic upper respiratory tract infections (13 - 37%), cardiac dysrhythmias (11 - 31%), skin dysesthesia (9 - 26%), aphthous ulceration (7 - 20%) and dermatitis or skin rashes (7 - 20%). Thus a strong suggestion of a wide-spread pain condition with multiple organ system involvement emerged, suggesting a systemic aetiology.

Known acquired or genetic diseases were found in 6 patients (17%). These diseases were diabetes mellitus (2 - 6%), sucrase-isomaltase deficiency (1 - 3%), myophosphorylase deficiency (1 - 3%), polycystic kidney (1 - 3%) and spina bifida (1 - 3%). These conditions were infrequently reported and their significance unknown but needed to be further investigated. Medical histories, obtained from medical records and patient histories, revealed a diagnosis and/or treatment for urinary tract infection (32 - 91%), measles (19 - 54%), mumps (15 - 43%), glandular fever (5 - 14%), giardiasis (2 - 6%) and dengue fever (1 - 3%). Eight of the 35 (23%) TMD patients reported investigation by urologists for repeated genitourinary tract symptoms - all with negative results under the accepted urology criteria (presence of haematuria, increased white cell count and bacterial counts >10^6 colony forming units per litre – Balows et al, 1991). Only urinary tract infections and glandular fever were reported to coincide with TMD onset.

A history of genitourinary infections was reported by 32 (91%) patients who had medical diagnosis of cystitis (19 - 54%) and/or renal infection (7 -20.0%); 4 patients who reported a history of genitourinary infections without medical diagnosis; low back pain was
reported by 20 (60%) and irritable bowel by 9 (26%). Recurrent low-grade fever was reported by 10 (29%) TMD patients whilst 19 of the 32 females (59%) reported menstrual problems. These preliminary data suggested an association between infectious events, particularly genitourinary infectious events, and TMD symptoms.

If an infectious agent was involved, evidence of similar pain in the sexual partners of the TMD patients may give evidence of a potential transmissible agent. Seven of the 35 patients (20%) reported that onset of their condition occurred following establishment of a new sexual relationship, whilst 16 of the 19 (84%) TMD patients in long-term relationships, reported that their partners had chronic muscle pain. Thus, there was some evidence to suspect a transmissible pathogen may be involved in TMD conditions.

A biochemical assessment of 20 of the 32 patients was undertaken with each patient being assessed for alterations in standard serum chemistry (electrolytes, muscle enzymes) and 24-hour urinary electrolytes. All the serum measures were within the normal range however there was a reduction in 24-hour urinary sodium (79.9±19.9 – normal range 90-170 mmoles/L) and chloride (76.9±25.6 – normal range 170-250 mmoles/L) levels compared with the laboratory reference data. This suggests that an alteration in kidney function may be present.

1.3.2. Second pilot study.

As there was a history of urinary tract infection, with 23% of TMD subjects having multiple urological investigations, and evidence of a transmissible pathogen, a subgroup of 9 of the 35 TMD patients were assessed to determine if there was any alteration in their urinary tract microbial flora. These 9 TMD patients (age = 40.0±8 years; age of onset = 29.0±9 years; duration = 8.5±10 years; Female: Male ratio 8:1) were compared with 6 control subjects (age = 35.0±2 years; Female: Male ratio 4:2) who had no current muscle pain or fatigue. Three first of the morning urine samples were collected (urethral, midstream and last voided). Microscopic examinations for leukocytes and squamous cells were undertaken to assess pyuria and haematuria as evidence of infection. Microbial samples were cultured on blood layer and CLED agar plates in a humidified, CO₂ supplemented, incubator at 37°C. No subject had evidence of a current infectious event (haematuria or pyuria). Three of the 6 control subjects had no microbial growth whilst the remaining 3 had growth of diptheroids and/or *Lactobaccilus*. All TMD patients had heavy growths of *Staphylococcus* spp.. Bowel contaminant organisms *E.coli* and *Enterococcus* spp. were detected in 4 of the 9 TMD patients. *Staphylococcus epidermidis, Staphylococcus saprophyticus, Staphylococcus hominus* and *Staphylococcus haemolyticus* were
isolated from the samples and are members of the Micrococcus subgroup 3, known enterouropathogens. Thus the urethral microbial flora of the TMD patients was quite different from the pain-free control subjects. These data suggested that the increased staphylococcal carriage was linked to TMD.

1.3.3. Third pilot study.

Observation of the agar plates showed that many of the staphylococcal species isolated from the urinary tracts of the TMD patients were haemolytic, as they degraded the blood cells in the blood agar. Haemolysins are a group of membrane-damaging toxins produced by staphylococcal organisms. To assess the toxic characteristics of these organisms, supernatants from 12 different staphylococci obtained from the 9 TMD patients were acquired after overnight growth of the organisms in brain heart infusion broth (BHI). The supernatants were filtered to remove all bacteria and the filtrate was applied to chicken renal fibroblast cultures along with fresh BHI as a control. The cultures were observed microscopically for disruption of fibroblast morphology. Filtrate supernatants from staphylococci that were haemolytic were observed to significantly disrupt the fibroblast morphology and in the cases of very haemolytic organisms, complete destruction of the fibroblasts was observed. The control BHI broth did not disrupt fibroblast morphology. These data suggested that the toxicity of the staphylococci may be associated with symptom expression in the TMD patients.

1.4. Pilot study conclusions.

RDC/TMD type 1a patients (Le Resche et al, 1992) appear to be:
1. A clinically discrete sub-component of more generalised muscle pain conditions such as fibromyalgia or myofascial pain syndrome.
2. Further, TMD symptoms occur in association with systemic multi-organ changes and do not appear to be a localised functional disorder.
3. There is a high-level reporting of a history, and signs and symptoms consistent with a gastro-genito-urinary condition, and evidence of a transmissible pathogen.
4. There was also evidence of a change in renal handling of electrolytes (sodium and chloride).
5. Heavy colonisation of urinary staphylococcal species was noted in the TMD patients.
6. There was no evidence of current urinary tract infections, but the staphylococcal species were observed to produce large quantities of membrane damaging toxins.
1.5. Hypothesis

The carriage of toxic organisms that produce lipid soluble toxins, such as staphylococci producing haemolysins, can induce muscle-associated TMD symptoms.

1.6. Aims.

The study aims to examine the hypothesis that toxic staphylococcus species can induce TMD associated muscle pain.

1. A group of TMD patients defined to have RDC/TMD type 1a facial muscle pain and an age- and sex-matched control group will be assessed. These study subjects will be acquired through clinical referral. This study will involve urinary amino and organic acid assessment as well as an assessment of staphylococcal toxicity.

2. A group of chronic fatigue syndrome patients will be studied collaboratively. Patients will be independently selected and assessed by medical specialists at Royal North Shore Hospital. The prevalence of TMD symptoms within this group will be assessed to see if the changes found in the first study are reproducible and unique to TMD. This study will include assessment of serum amino acids, antinuclear antibody (ANA) responses and standard blood chemistry, which will extend the assessments of the first study. This study will only assess the changes in CFS patients in association with TMD expression in an attempt to assess the homogeneity of TMD symptoms determined in the assessment of the defined RDC/TMD type 1a study (Study 1).

3. A third group of pain/fatigue subjects selected independently of the writer to assess the reproducibility of staphylococcal toxicity in relationship to body pain distribution and potential cytokine associations.

These data will allow the assessment of the association between symptoms, biochemical changes and bacterial toxicity. The independently selected study groups will provide objective assessment of the findings of the separate studies and will allow an assessment of the homogeneity of the changes associated with TMD symptoms in patients with other defined pain conditions.

1.7. References.


Costen JB. Neuralgias and ear symptoms associated with disturbed function of the TMJ. *JAMA* 1936; 43:1-9.


