LIMITING FACTORS

It is clear that any research into the problem of pain mechanisms is limited by the subjective nature of the experience as well as by the complex nature of neuro-anatomical connections in the CNS. Thus, attempts so far to evaluate the neurophysiological basis of pain have largely resulted in failure (see Table No. II p. 112). Descriptions of definitive mechanisms are based on well informed assumption rather than absolute fact. Since the earlier concepts of pain are largely refuted in the literature, the controversial specific and pattern theories are reviewed and related to the gate control theory which forms a basis for present-day investigations of pain mechanisms.

THE CLASSICAL THEORY

The conventional approach proposes that pain, like hearing and vision, is a specific sensory experience with its own end organs, specific peripheral nerve pathways, its own nerve tracts within the spinal cord and central nervous system, and its own thalamic pain centre. External stimuli initiate impulses which are mediated by specific peripheral sensory receptors, presumably free nerve endings, to the posterior roots of the spinal cord.

TABLE NO. II

PAIN THEORIES

THEORY	MAIN PROPONENT	CONCEPT
1. INTENSIVE	ERASMUS DARWIN	Pain results from intense stimulation of any receptor by Heat, Cold or pressure. Stimulus - Response
2. TRADITIONAL	PHILOSOPHERS PSYCHOLOGISTS	Pain is an emotional experience - "Passion of the Soul".
3. COMPONENT	BEECHER H.K. and other PHYSIOLOGISTS	A corollary of the specific theory. Pain is two elements - the original sensation and the reaction to that sensation. Line-labelled transmission.
4. SPECIFIC (CLASSICAL)	VON FREY	Pain is a specific sensation with its own sensory apparatus - four modalities. Line-labelled transmission.
5. PATTERN (SUMMATION)	GOLDSCHEIDER LIVINGSTON NOORDENBOS	Several theories under one heading. Coding of sensory information in spatial and temporal patterns. Included transitional theory of NOORDENBOS.
6. GATE CONTROL	MELZACK AND WALL	Alternative to pattern theory - facilitation and inhibition at first presynapse in Spinal Cord - central control modulates sensory input. Pain is triggered after critical excitability is breached.

Either here or at a higher level these impulses are transferred across the cord to connect with specific fibres anatomically arranged in the anterolateral aspect of the opposite side of the spinal cord. These ascending fibres run not only in the lateral spinothalamic tracts but also in a more diffuse pathway, the spino-reticulo-thalamic system.(See Fig. No.17 p. 114). The central termination of these pathways is disputed, but there is sufficient evidence to show that spinothalamic fibres terminate in the posterolateral ventral nucleus of the thalamus. Pain pathways which mediate noxious stimuli via the anterolateral columns may also make connection in the reticular formation and terminate in other intralaminar nuclei in the thalamus, namely, the posterior nuclear group, centre median, nucleus centralis lateralis, and nucleus parafascicularis, BOWSHER (1957). Thus, ascending pathways mediate impulses to the thalamus and, subsequently, to the higher cortical areas of the brain for interpretation.

Recently, the question has been posed by WILSON (1974) that there are two separate ascending systems which appear to function differently:-

(1) A δ transmission of tactile information from low threshold mechanoreceptors ascending via the dorsal column -

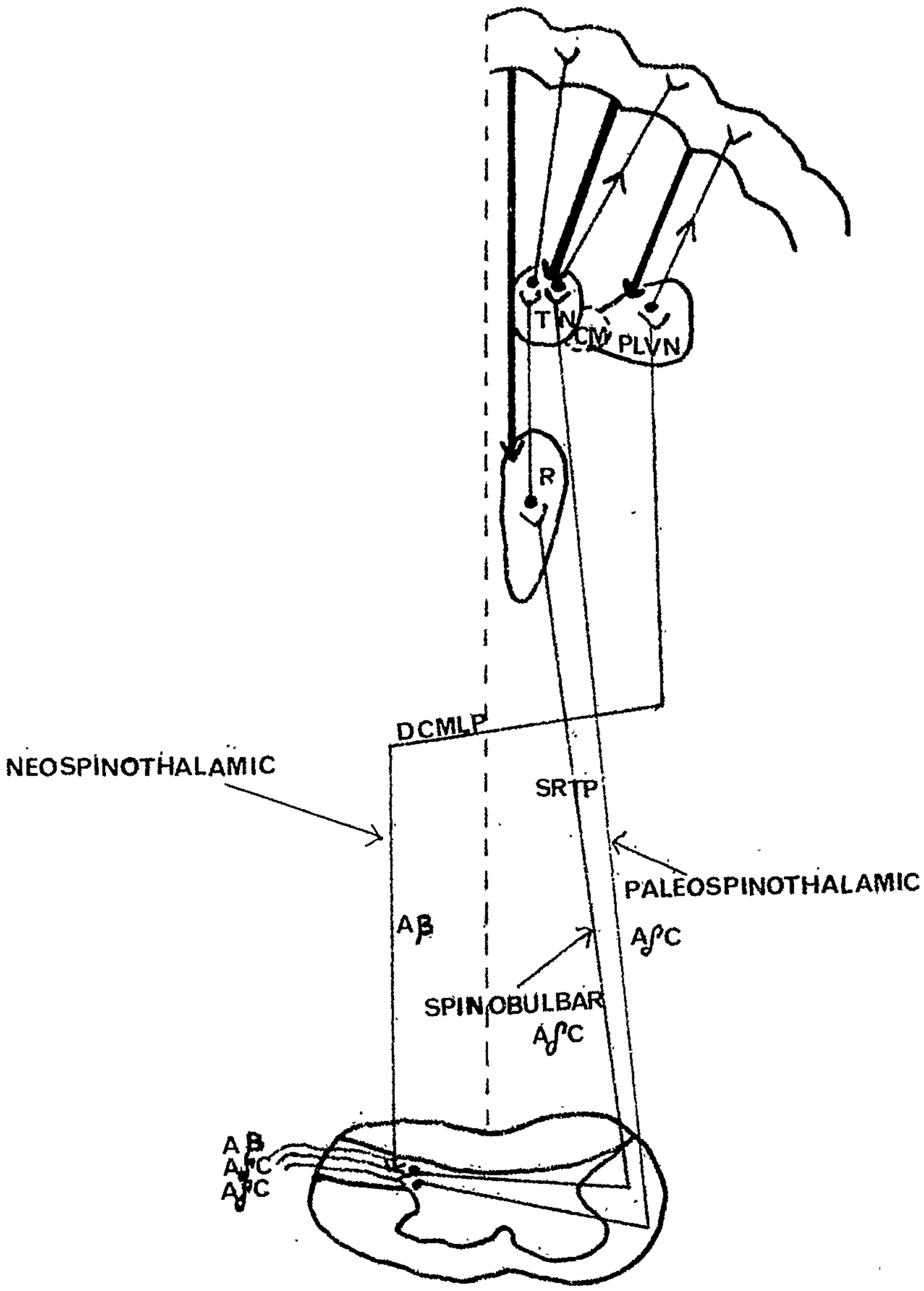


FIG NO 17 SCHEMATIC REPRESENTATION OF PAIN PATHWAYS.

R: RETICULAR FORMATION, ⟶ DESCENDING CONTROLS

TN: THALAMIC NUCLEUS (INTRALAMINAR).

PLVN: POSTERIA VENTRAL NUCLEUS.

DCMLP: DORSAL COLUMN MEDIAL LEMNISCAL PATHWAY

SRTP: SPINO RETICULO THALAMIC PATHWAY

median lemniscus - thalamic pathway to project to the cortex;

(2) slowly conducting afferent fibres presumed to carry pain and temperature sensations ascending, after crossing the cord in the ventro lateral columns to make more diffuse connections in the brain stem, mid-brain, and thalamus. But there is little definitive evidence that this actually occurs since the ventrolateral tracts also carry non noxious information and, as WILSON himself points out, pain may continue to be transmitted after transection of the ventrolateral tracts "perhaps in short neurone links of the grey matter of the cord." This factor seems to support the synaptic chain theory proposed by NOORDENBOS (1959).

QUESTIONS OF VALIDITY

The validity of the classical theory is questioned by psychologists in that it fails to explain several categories of pain including psychogenic pain, psychosomatic pain, and the known influence of suggestion,

attention and distraction on pain, i.e. the theory lacks psychological extension to any great degree.

It also fails to explain pathological pain states such as causalgia, phantom limb pain and pain that persists after neurological section of specific pathways, LIVINGSTON (1943). A contributory weakness to the hypothesis may be the known period of latency that exists between repeated pin prick or low grade tactile and thermal stimuli applied to the skin and the perception of pain, NOORDENBOS (1959), presumably due to temporal and spatial summation of sensory inputs. Also, previous evidence tends to implicate the build up of pain producing substances as a possible major cause of pain in hyperalgesic skin (sunburn) and PPS as a possible delaying factor between some low grade stimuli and a response. In addition, the specific theory embodies the "psychological assumption" already documented, MELZACK & WALL (1970).

STRENGTH

On the other hand, the hypothetical system is physiologically specific - a factor which gives it strength.

Specific monomodal fibres have been identified, POMERANTZ (1973), PERL (1968), (1971), and found to be

line labelled for transmission of noxious input from the periphery to the CNS. Using unilateral and bilateral cordotomy techniques, ROSOMOFF, CARROLL, BROWN & SHEPTAK (1965) achieved 68.5% good relief in their patients, 82.86% of whom suffered intractable pain from malignancy sources. Their evidence suggests that the ventrolateral tract is specifically involved with the transmission of pain, a notion supported by WHITE & SWEET (1955) and largely substantiated by POMERANTZ (1973).

Also, evidence from ISHIJIMA and his co-workers (1975) indicates that there are specific nociceptive neurones (A & B) in the central median - parafascicular complex (CMPf). These neurones respond in a way which is almost identical to the response evoked by stimulation of A δ and C fibres.

ISHIJIMA and his colleagues suggest that the discrepancy between anatomical findings and physiologically recorded responses may be due to the interposition of the diffuse reticular-thalamic connections presumed to project information from the spinothalamic tract to the CMPf complex, and not necessarily due to dissemination of information by the dendritic connections of the A & B type neurones. This adds weight to VON FREY's original theory, and may help to sway the balance of opinion away

from the currently popular "pattern theory".

RATIONALIZATION

BEECHER (1962) attempted to rationalize the whole pain experience by the suggestion that pain is composed of two elements:-

(1) The physiologic sensation (sensory element).

(2) The reaction to that sensation (emotional element).

He attributed the difference between experimental and pathological pain to the existent amount of each component. This dichotomy of pain is generally supported by physiologists but not by psychologists such as MERSKEY & SPEAR (1967) who regard the two components as contributory causes and not as separate or individual parts that tend to conceptually divide the pain experience. It would seem that perception and reaction are coexistent and indivisible one from the other in what constitutes pain. Further comment on the bitter debate between physiologists and psychologists is irrelevant except to point out the consistency of investigator bias which occurs in reports on the nature of pain.

THE PATTERN THEORY

A series of pain mechanisms constitutes what is known

as the "pattern theory". In 1894 GOLDSCHIEDER proposed that large fibre mechanoreceptors were line labelled for touch while information about pain was transmitted in impulse patterns derived from the summation of small fibre activity at dorsal horn cells. This notion was largely supported by LIVINGSTON (1943) who described afferent summation in terms of neurological circuits which banked input of noxious sensory information in sensory pools liable to discharge on further stimulation. He suggested that these reverberating circuits could help to explain the influence of central factors in the mechanism of causalgic pain as an alternative to improved peripheral vasomotor tonus and section of pain carrying fibres. (See Fig. No.18 p. 120). Through this system, pain could presumably be clinically evoked by normally innocuous stimuli. The same concept was presumed to account for inhibition as well as facilitation. In line with the theory that a fast fibre system inhibited the central effect of a slower conducting fibre system, ZOTTERMAN (1939) p. 24, NOORDENBOS (1959) p. 147 suggested that while impulses from both systems summate at dorsal horn cells, sensory patterns transmitted to the brain were modified by a slowly conducting multisynaptic chain. (See Fig. No.19 p. 121). This concept marked the step from the specific theory to the

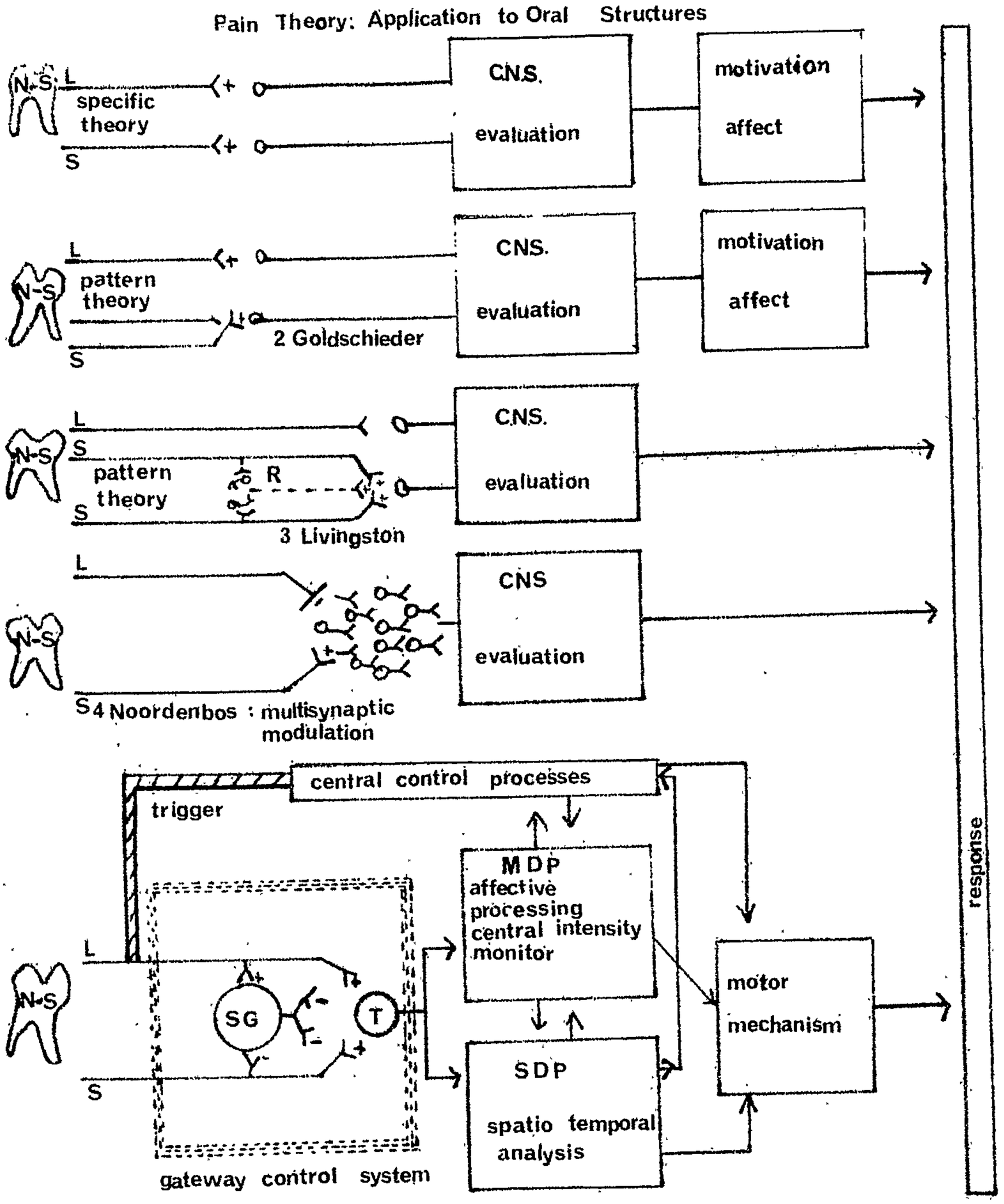


FIG NO 18 modified from Melzack and Wall (1970)

N S : noxious stimulus oral stuctures
L : large diameter afferent fibres
S : small diameter afferent fibres
R : reverberating circuit
S.G : interneurones substantia gelatinosa
T : 1st order "T" cell
MDP: motivational affective processing
SDP: sensory discriminative processing

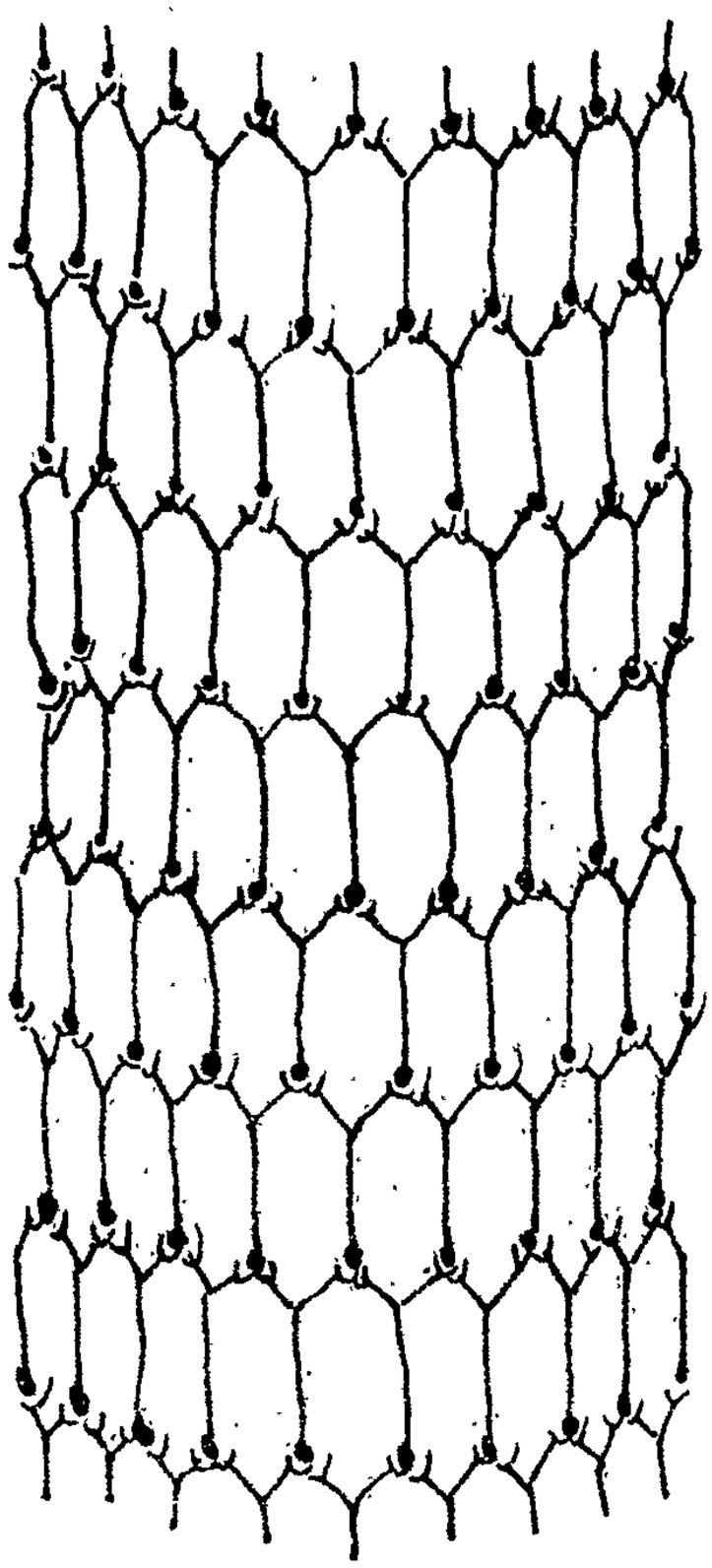


FIG NO(19) AFTER NOORDENBOS (1959).
DIAGRAMMATIC REPRESENTATION OF
MULTISYNAPTIC AFFERENT SYSTEM.

pattern theory since the system no longer implied "the psychological assumption" but held valid the principles of central summation and control of sensory input patterns.

NOORDENBOS (1959) p. 110, also proposed the concept that the removal of the inhibitory influence of the faster conducting fibre system provided the basis for the occurrence of pathological pain. For example, post herpetic neuralgia, NOORDENBOS (1968), (1959) p. 79. A further refinement by WEDDELL (1955), SINCLAIR (1955) confirms the popular notion that sensory information about pain is organised for transmission in spatio-temporal patterns, but assumes that these volleys of impulses are derived from noxious stimulation of non specific receptors - a factor which contravenes known physiological principles of receptor specialization, IGGO (1974).

As a reaction to the lack of unity shown by protagonists of the "pattern theory" and the psychological weakness of the classical theory, MELZACK & WALL (1965) devised an hypothesis based on convergence interaction and control of afferent sensory input at the first synapse in the spinal cord: "the gate control" theory, a mechanism consistent with the three (3) concepts outlined

previously, namely:-

1. Physiological specialization,
2. Central summation, and
3. Input control.

GATE CONTROL THEORY

MELZACK & WALL (1965) propose that pain from the periphery is the response phenomenon derived from noxious stimulation of afferent sensory nerve fibres subserved and controlled by complex integrated central and spinous systems. The activation of these systems is dependent to a large extent on the level of activity of the first order cells ("T-Cells") located in the upper lamina of the dorsal horns of the spinal cord. T-Cell activity is regulated by the interneurones of the substantia gelatinosa (SG). These SG cells, by mechanisms of positive and negative feedback, MENDELL & WALL (1965) respectively facilitate or inhibit the passage of impulses carried by afferent fibres that terminate on the T-Cells, thereby controlling T-Cell activity. As far as pain is concerned, afferent input is a function of:-

1. Tonic activity in smaller myelinated and unmyelinated fibres.

2. The balance of activity in large vs. small fibres.

3. The sensory activity provoked by noxious stimulation, MELZACK & WALL (1965).

4. The number of terminal branches and, hence, the number of synaptic contacts of large vs. small fibres.

5. The frequency of impulse transmission and, hence, the frequency of stimulation.

It is apparent that the gating system is further influenced by dorsal column activity and the general level of other neural activity which varies from time to time according to the central affective control system of each individual. Four main factors seem involved in sensory transmission of cutaneous pain, according to MELZACK & WALL:-

1. Active (intense) stimulation.

2. Background activity.

3. Balance of activity in large and small fibres.

4. Central affective control influences, e.g. environmental, cultural, socio-economic, emotional, past experience, and other perceptual inputs.

CENTRAL CONTROL

Central affective control influences are thought to modulate the response to noxious information in the CNS, MELZACK & CASEY (1968). According to CASEY & MELZACK (1967), both the classical and paramedial systems are subject in some way to neocortical or higher central nervous system control in terms of input of past experience, past behavioural information, emotional states and other perceptual data ("central control determinants"). This central influence is rapidly mediated via cortico-fugal neural mechanisms and may act to modulate sensory information before it is transmitted to both the discriminative and motivational systems. The interaction of all three systems (tri-system) provides knowledge of:-

1. The nature of the stimulation.
2. The spatio-temporal properties of the stimulus.
3. Motivational information (flight - fight).
4. Managerial information (past experience).

In neurological terms, according to CASEY & MELZACK (1967), MELZACK & CASEY (1968):-

1. The sensory discriminative dimension of pain (SDP) is determined by alteration and selection of sensory data through the neospinal - thalamic projection system.

2. The motivational dimension of pain (MDP) related to unpleasant affect and aversive behaviour is mediated by activation of the reticular and limbic systems via the paramedial ascending pathway.

3. Both the SDP and the MDP are subject to neocortical or higher central nervous processes fed by perceptual inputs such as past experience and emotional information.

CASEY & MELZACK suggest that future research may be better directed towards motivational affective and cognitive factors rather than towards traditional sensory evaluation of pain -- a notion which reflects upon the present question of whether pain can be lessened by knowledge,awareness, and a greater sense of control over the situation, i.e. by intracerebral inhibition.

CENTRAL CONTROL TRIGGER

The key factor in central control of pain is the trigger mechanism proposed by MELZACK & WALL (1965) as the activator of corticofugal inhibition at the first cord synapse. Since it was known that centrally activated descending afferents terminate in the substantia gelatinosa, HAGBATH & KERR (1954) and modulate afferent input at the first synapse, KUYPERS, FLEMING & FARINHOLT (1960), LUNDBERG (1964), it was suggested by MELZACK & WALL (1965) that control over sensory input may also be held at the gating level by "selective brain processes" (SBP) which subserve perceptual modalities such as " ..... attention, emotion and memories of past experience". They proposed that a "central control trigger" functions via either the dorsal column - medial lemniscus system or the dorsolateral pathway, or by both routes, to activate the SBP which in turn, by descending fibres, modify gating activity, in particular, those impulses carried via slowly conducting pathways (fast fibre vs. slow fibre system). This notion is supported by SPA experiments by MAYER & LIEBESKIND (1974) who found that somato-sensory input may influence central control of nociceptive information transmitted via the spinal cord (pain suppressive system).

SUMMARY OF GATEWAY THEORY

In sum, pain perception and response follow the modulation of sensory input by descending central control processes as well as by the opposing action of fast and slow peripheral nerves in the dorsal horns of the spinal cord. The dorsal column - medial lemniscal pathway (A β) exerts an inhibitory effect over the two pathways (A δ C) of the anterolateral system.

MODULATION OF SENSORY INPUT

Impulse propogation is not modality specific, MELZACK & WALL (1968). Thus, a wide variety of sensory data travels in waves or patterns of excitation to the dorsal horn cells. The amount of information carried by each fibre is limited by its channel capacity, DARIAN-SMITH et al. (1968).

Sensory input is filtered at presynaptic terminations in the cells of the substantia gelatinosa by processes of facilitation, inhibition and synchronization. Recent evidence also suggests that there are strong post synaptic interactions between cells of the spinal cord, WALL (1974). Neurones in REXED lamina 5 are favoured as the intermediate transmitters of information about

cutaneous pain, BESSON, CONSEILLER, HAMANN & MAILLARD (1972) and mediators of referred pain from visceral afferents which synapse directly and indirectly in this lamina, MELZACK & WALL (1970), WILSON (1974). This theoretical assumption is supported by experiments in the cat using stimulation produced analgesia (SPA), evidence from which indicates that centrally produced analgesia may be linked with selective inhibition of the interneurones of REXED lamina 5, since these interneurones exhibit a constant lack of responsiveness to painful stimuli during SPA - LIEBESKIND, GUILBAUD, BESSON & OLIVERAS (1973). Hence, abstraction of information takes place before central interpretation, the first synaptic filter being only the beginning of a continuing process of selection and filtration of sensory input. For example, ANDY (1975) suggests that a supra spinal gate may operate in the centre median nucleus of the thalamus.

THE GATING MECHANISM

The exact nature of the first synapse gating mechanism for pain is still not clear. POMERANZ (1973) has shown that 30% of small nociceptive afferents which synapse with somato-sensory projection cells of the ventro lateral tract (VLT) transmit information on a straight

through basis without any noticeable gating influence.

However, this evidence does not preclude gating in the other two afferent lines, i.e. the remaining 70% of the VLT and the dorsolateral tract (DLT). Presynaptic control in the DLT was previously confirmed, POMERANZ, WALL & WEBER (1968), inhibition being ascribed to activity in large mechanoreceptor afferents and facilitation to impulses carried by small non specific afferent fibres. BURGESS (in the problem of pain) supports the gating notion but describes a system in which high intensity (noxious) stimuli impede rather than facilitate transmission of impulses, i.e. the gate is shut even tighter by increased inhibition presumably derived from the stimulation. Contrary to the gating concept, electrical stimulation of C fibres in cat superficial peroneal nerve by FRANZ & IGGO (1968) evoked only negative dorsal root potentials. Similarly, ZIMMERMAN (1968) found dorsal root potentials of the same polarity as the myelinated afferent terminations at the first synapse and VYKLICKY, RUDOMIN, ZAJAC & BURKE (1969) found neither positive dorsal root potentials nor PAH and, therefore, no evidence of a gating system at all. YOUNG & KING (1972) support the gating concept for the trigeminal system, but found that the

neural response to noxious tooth pulp stimuli (primary afferent hyperpolarization (PAH)) was greater in nucleus oralis than in nucleus caudalis, the opposite of what could be expected if the gate control theory is held valid. They suggest that this discrepancy is explained by the interposition of a series of interneurones linked with nucleus caudalis as an integral part of the mechanism responsible for the modulation of sensory information via the rostral segments of the trigeminal system. Without the interposition of an interneurone, the gate control system implies that the same C fibre terminations on T-Cells are inhibitory as well as excitatory in function, a factor which contravenes Dale's Principle.

Also, PERL ascribes to the view that there are different afferent nociceptive pathways but that these pathways are not gated in the manner described by MELZACK & WALL.

SICUTERI, FRANCHI, ANSELMI & DEL BIANCO (1974) cite evidence which suggests that serotonin (5 HT) may be the chemical transmitter substance at the gateway on the substantia gelatinosa. The actual transmitter mechanism is unknown.

APPLICATION OF THE GATE CONTROL THEORY

The gate control theory provides a better model than

other theories presented for the explanation of:-

(a) The influence of the psyche and other emotive forces on the pain experience, e.g. anxiety and states of excitement.

(b) The modification of pain by past experience, attention and distraction.

(c) Why pain results from the interaction of many neural pathways, not just those presumed to subserve pain.

In addition, the gate control theory is capable of extension to explain:-

1. The mechanism of acupuncture analgesia, CASS (1973) - increased afferent input closes the gate.

2. Pain from oral structures via the 5th cranial nerve (trigeminal) LIEBMAN (1972). (See Fig. No.20 p. 133)

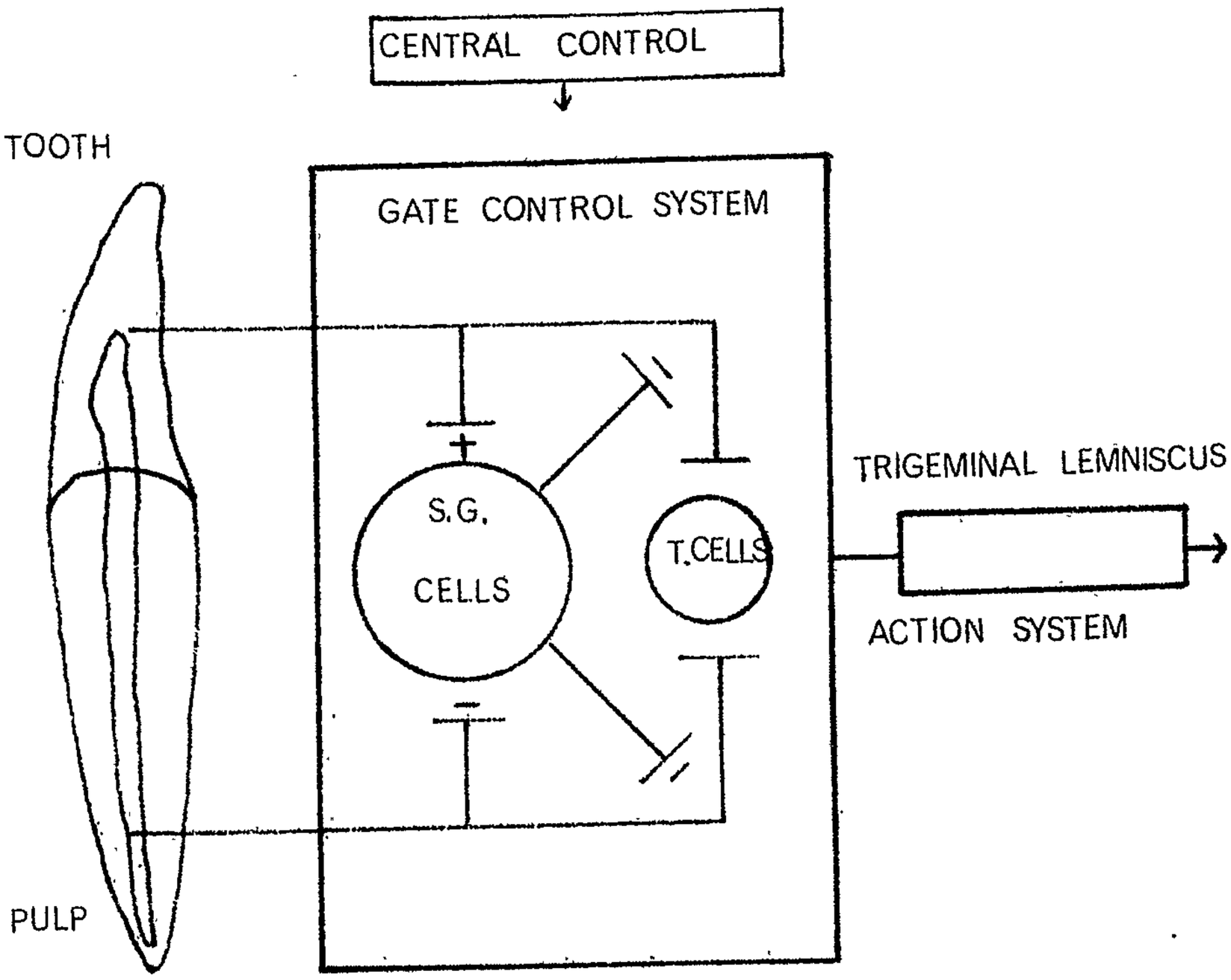


FIG NO(20) AFTER LIEBMAN(1972).

APPLICATION OF GATE CONTROL.

THEORY TO TRIGEMINAL SYSTEM

3. The presence of intense pathological pain in diabetic or alcohol neuropathy.

4. Delay in onset often observed in pathological pain states, MELZACK & WALL (1968).

But these factors do not mean that the gate control theory is valid. They merely suggest that the best features of the specific and pattern theories have been applied to better rationalise the psychological extension of pain mechanisms in order to provide a basis for further discussion. As DARIAN-SMITH (1974) puts it: the gate control theory "continues to be presented in too general a form to be carefully tested: testable aspects of the model for the most part have not proven to be correct."

CHAPTER IV

SUMMARY

PAIN & TISSUE DAMAGE

1. There is no direct quantitative relationship between pain and tissue damage, although pain may be qualified according to the extent and locus of damage. The significance of pain from tissue damage is altered by underlying emotional phenomena. The disparity in the severity of pain arising from damage to different areas of the body may be due to the intervention of some form of neuronal amplification system, the definitive nature of which remains unknown.

2. Minor injury to tissue results in immediate pain followed later by secondary pain of a dull, throbbing character presumed to be due to the accumulation of pain producing substances in the tissues.

3. Much of the spread of tenderness in tissues adjacent to the site of injury is a result of the "brush fire" effects of cellular damage.

4. Observable "bulls eye" colour changes in the skin after stimulation demonstrate two distinct zones of inflammatory spread - an inner erythralgic zone and an outer area of diffuse hyperalgesia.

5. Temperature and pressure changes evoked by inflammatory conditions are possible contributory causes of pain.

6. Spread of hyperalgesia may be mediated by a specialized nocifensor system. Pain may also be referred by direct anatomical involvement to other areas served by the involved nerve. The diagnosis of maxillary sinusitis should at first discount common pains of dental origin.

7. The theory that pain is mediated by specialized chemoreceptors stimulated by pain producing substances is subject to a controversy that remains unsolved. Bradykinin is the most likely candidate amongst a wide variety of substances that will cause pain when applied to naked nerve endings.

8. The concentration of each endogenous substance at the receptor site is subject to the prevailing tissue conditions. The onset and duration of action of each substance differs. The latency of action observed with bradykinin and 5 HT is thought to be due to some intermediary action not yet discovered.

9. Under certain conditions vasoneuroactive substances such as serotonin and bradykinin may block the microcirculation and cause ischaemic pain - a double action considered to be a possible mechanism involved in vascular headache and cardiac pain.

10. Factors which result in 5 HT deficiency are thought to trigger migraine headache. Recent evidence indicates that 5 HT may trigger the release of prostaglandins presumed to cause pain by their action on the blood flow in the external carotid artery.

PATHOLOGICAL MECHANISMS

The evidence presented so far indicates that the occurrence of pain generally requires some form of tissue damage or physiological source of stimulation. The relationship between the degree of tissue damage and initiation of noxious impulses forms an interesting facet of pain mechanisms.

PAIN AND TISSUE DAMAGE

Present evidence suggests that there is no direct quantitive relationship between pain and tissue damage. BEECHER (1946) showed that soldiers with war wounds suffered very little pain despite the extent of their injuries. Later, BEECHER (1956) compared soldiers with war wounds to civilians with less extensive injuries. He found that only 32% of the soldiers required a narcotic or sedative to ease their suffering, in contrast to the civilian group, 83% of whom needed a narcotic for adequate relief of pain. He concluded that the difference lay in the significance of the wound and in the underlying emotional factors which influenced the intensity of pain felt at that time.

LIM (1967) also acknowledged the implication of psychological factors in the relationship between pain

and tissue damage. He showed that both synthetic and natural bradykinin,when injected via the peritoneum, produced pain at levels of concentration below that necessary for tissue damage. WOLF & WOOLF (1958) suggested that traumatised tissues may lack sensitivity to pain due to damage to nerve endings and their protection by serum oedema and devitalized tissue. This phenomenon may help to explain why, after a period of latency, suturing or manipulation of damaged tissue can sometimes be achieved with little evidence of pain. Transection and damage to nerve fibres obviously plays a major part in the lack of responsiveness of injured tissue.

DAMAGE OR TRANSECTION

It is well known that crushing or transection of a nerve changes its excitability. Degenerative changes take place in the injured segments dependent on the extent of damage. The cell body shows signs of chromatolysis (Disintegration of nissl substance, golgi fragmentation), swelling from increased fluid content, and other histological changes, SAMPSON WRIGHT (1965).

WALL (1974) suggests that chromatolytic neurones reset their excitability upward, evoking impulse conduction in dorsal root ganglia and other central terminals which

may be a persistent source of pain after transection of the nerve supply to a part. HARDY, WOLFF & GOODELL (1951) showed that pain impulses commenced at a critical level of temperature (approx. 45^{o}C) consistent with that necessary to produce breakdown of tissue protein. Partial denaturation of cell protein by thermal, electrical, mechanical, or chemical energy may well be the initiating factor in pain impulse propogation, HARDY (1962).

CHAIN REACTION

It is clear that whatever the rationale provided for pain that persists after injury, the first input from tissue damage is the inevitable barrage set up by stimulation of receptors or axons lying in the path of injury. Injury also causes destruction of other cells with concomitant liberation of lysosomal enzymes which may produce a chain reaction of damage with release of inflammatory peptides and other pain producing substances (PPS). Histamine is released from mast cell storage, whereas the prostaglandins are synthesised locally at a subcellular level in response to stimulation, GREAVES (1974). Platelet synthesised prostaglandins are released within seconds of vascular damage. The platelet seems to be the "predominant link"

in the series of events between haemostasis and inflammation, SILVER, SMITH & INGERMAN (1974). The interesting mechanism by which histamine and E type prostaglandins influence the inflammatory reaction is illustrated by MELMON & BOURNE (1974). (See Fig. No.21 p. 142)

It is notable that E series prostaglandins stimulate the elaboration of cyclic AMP, a known antagonist of morphine analgesia, and a "messenger-regulator" of the allergic and inflammatory response, FERRI, SANTAGOSTINO, BRAGA & GALATULAS (1974). The biological reaction to damage proceeds until body defences provoked by the inflammatory response either return the tissue to normal or conditions worsen. (See Fig. No.22 p. 143)

An interesting connection with the cyclic reaction to damage is that cationic protein from lysosomes has been found to produce pain when applied to nerve endings in a blister base preparation, ARMSTRONG, DRY, KEELE & MARKHAM (1953), KEELE & ARMSTRONG (1968) p. 16.

NUMBER OF INVOLVED FIBRES

The number of nerve endings damaged by trauma is often unrelated to the amount of pain experienced, e.g. a fist to the mouth hurts through stimulation of many receptors, but it does not produce the same agonizing effect as

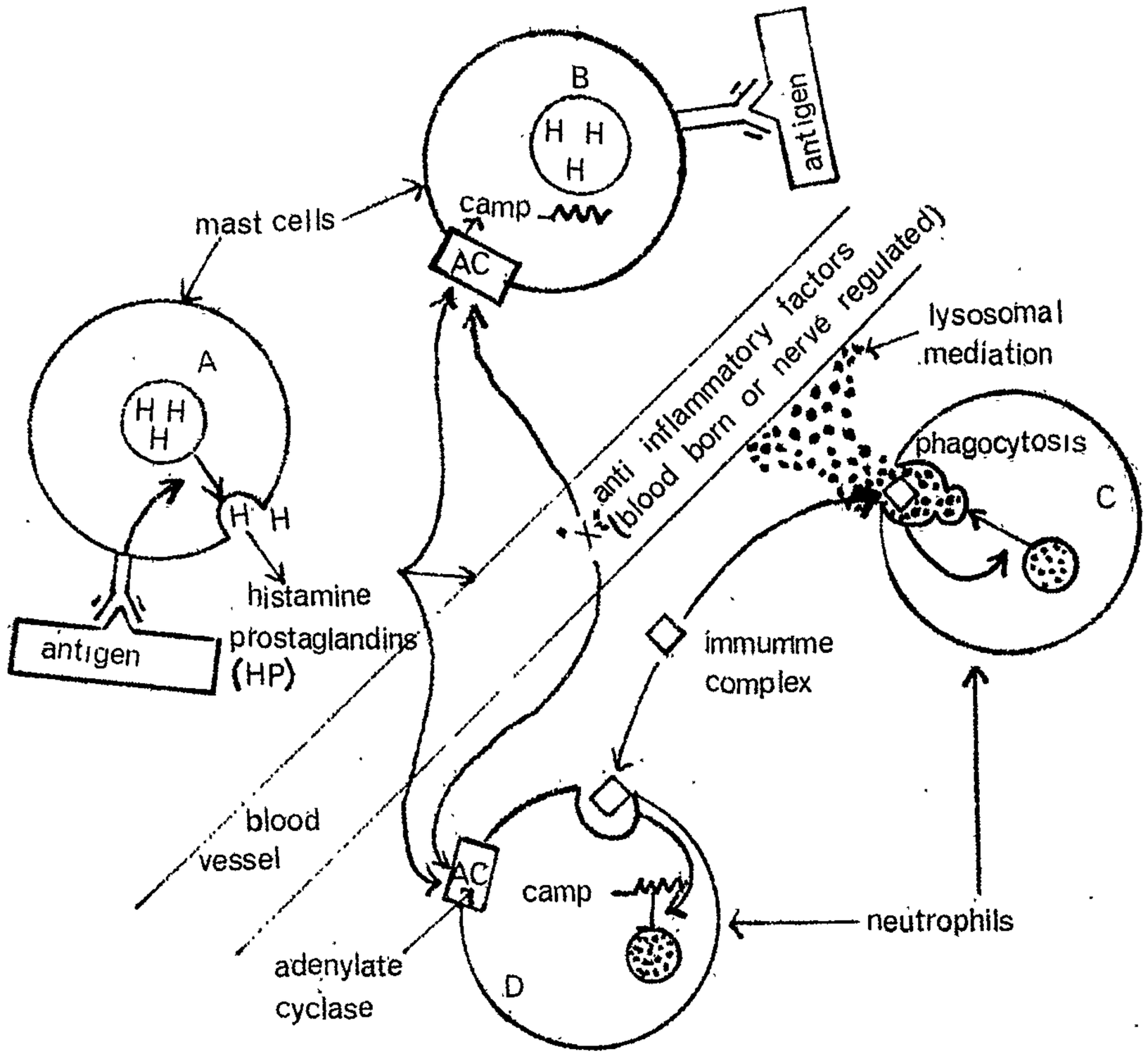


FIG NO (21) After Melmon and Bourne (1974).

Diagramatic representation of proposal that histamine and prostaglandins mediate as well as regulate extent and severity of an inflammatory reaction, "X" factors act through cyclic amp, H.P. stimulates A.C. which inhibits further release of intracellular inflamatory mediators.

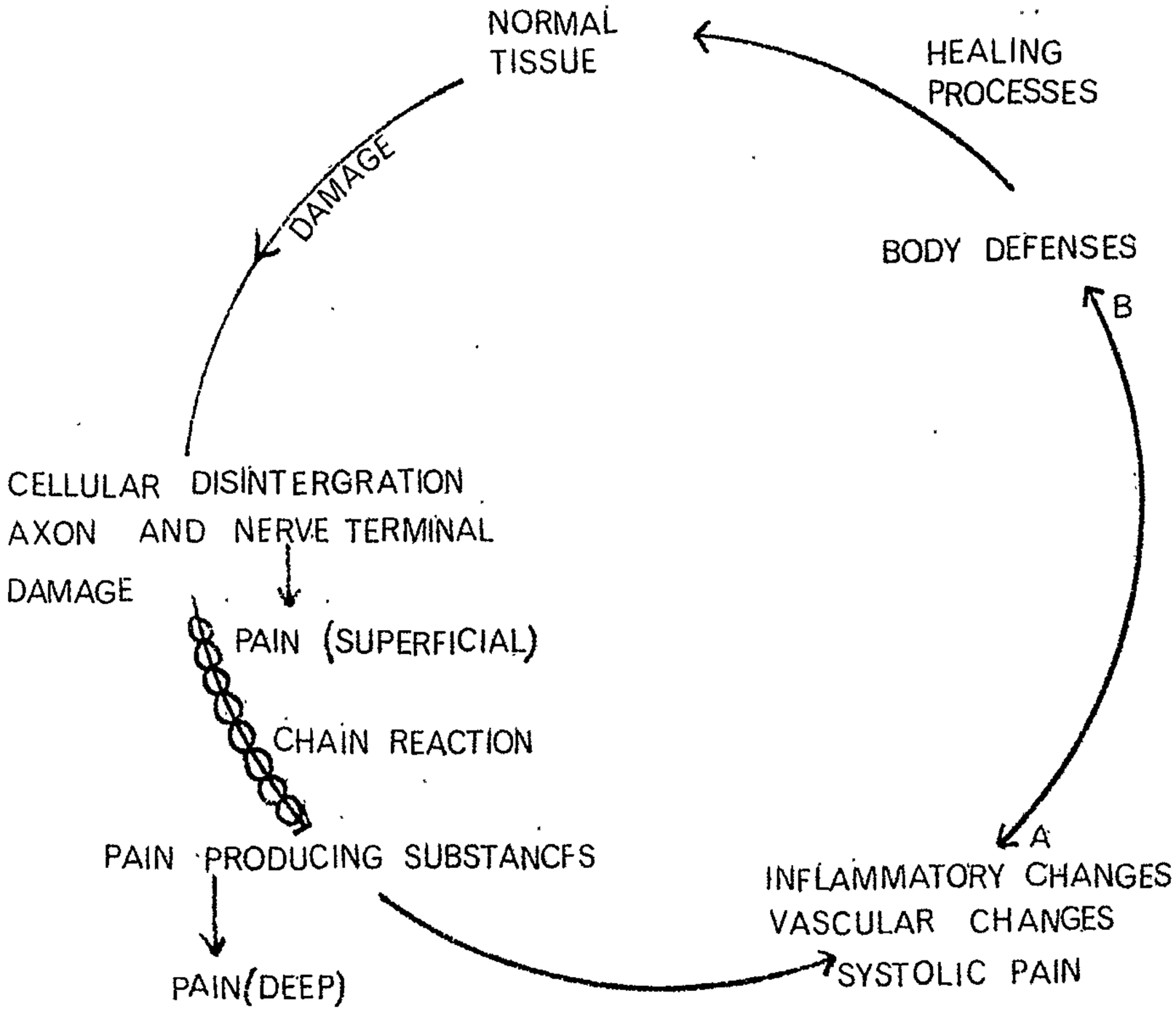


FIG NO(22) PAIN AND TISSUE DAMAGE. SCHEMATIC REPRESENTATION OF HEALING CYCLE (SIMPLIFIED)

A: EXACERBATION

B: RECOVERY

acute pulpitis where fewer receptors are involved. A similar kind of relationship between pain derived from poorly vs. richly inervated structures is explained by WALL (1974) who suggests that the difference in the quantitative pain experience may be due to several factors including:-

(a) Some nerves may have preferential connections in the CNS.

(b) There may be some form of central amplification system.

(c) The effect of inhibiting nerves normally present may be absent.

According to WALL (1974), normal ongoing activity in the CNS is altered by afferent sensory input derived from noxious peripheral stimulation; impulses from smaller fibre afferents are amplified and reverberate for some time, while impulses derived from larger diameter fibres produce inhibition following initial excitation. As WALL (1974) puts it, "the picture is rather one of convergence, interaction and control". There is no definitive evidence as yet concerning the exact nature of either an amplification system or an inhibitory system associated with afferent sensory

barrage from either kind of fibre. Regardless of the number of involved fibres, it follows that various biological substances are liberated in the tissue as a result of cellular damage as well as through mobilization of body defences in response to injury.

PAIN PRODUCING SUBSTANCES - "ALGOGENIC SUBSTANCES"

Does pain result from direct sensory interference by noxious stimuli alone, or is pain a secondary response evoked by the release of amines and polypeptide substances at damaged nerve endings? It is known that endogenous chemical substances, namely, substances P, potassium ions (K^+), lactic acid, serotonin (5 HT) (5 hydroxy-tryptamine), oxytocin, histamine, kallidin, acetylcholine (ACh), angiotensin, adenosine triphosphate (ATP), prostaglandins E & F_{2a}, polypeptides, and bradykinin, are often present at the site of injury; they occur in inflammatory exudates, and they produce pain of varying degree when applied to naked nerve endings, GANONG (1967, 1971), LEWIS (1942), LIM (1967), KEELE (1966), KEELE & ARMSTRONG (1968).

Glass activated (in vitro) blister fluid and plasma have also been implicated, KEELE (1966), as have the prostaglandin precursor arachidonic acid, COLLIER,

DINEEN, JOHNSON & SCHNEIDER (1968), blood and tissue extracts, and cationic protein from lysosome disintegration. These endogenous chemical substances have been labelled as pain producing substances (PPS) on the basis that pain is the outcome of their application to afferent sensory nerve endings:-

(a) by direct application to nerve terminals exposed by a cantheradin skin blister base technique - the response being proportional to the size of the blister area, ARMSTRONG et al. (1953);

(b) by intra-arterial injection, LIM (1967);

(c) by intraperitoneal injection, LIM et al. (1967);

(d) by intradermal or jet-injection skin techniques.

Pain producing substances may be released as part of the reaction of the tissues to damage (histamine and the prostaglandins) through cellular rupture (K^+), or via the action of proteolytic enzymes on protein (bradykinin and polypeptides).

Algogenic substances most capable of reproducing "recurrent pain" symptoms include:-

1. Lipid soluble substances found in tissue extracts.

2. Plasma, blood or blister fluid - activated in vitro.

3. Bradykinin, ARCANGELI & GALLETTI (1974).

The active agents in plasma are more likely to be bradykinin, kallidin and other plasma kinins, KEELE & ARMSTRONG (1968), since other PPS such as ATP, 5 HT, histamine, acetylcholine, and K^+ produce comparatively little effect, when applied to nerve endings, ARMSTRONG et al. (1953). However, pain is more likely the outcome produced by activity of many PPS combinations than by any single substance, ARCANGELI & GALLETTI (1974). For example, a mixture of histamine and ACh is more potent than either chemical used alone, FJÄLLBRANT & IGGO (1961), and histamine is more likely to mediate itch than pain, KEELE & ARMSTRONG (1968).

PPS Action at receptor site

The concentration of pain producing substances (PPS) or vasoneuroactive substances (VNS) at any given receptor site is subject to such tissue conditions that prevail at the time, e.g. the amount of interstitial fluid, osmosis, extent of diffusion into surrounding tissue,

the vascular supply and the molecular size of each substance.

It follows that the onset and duration of action of individual substances vary. The slower acting substances 5 HT, K^+ and polypeptides exhibit a latency of effect and greater duration of action than quicker acting substances, histamine or ACh where the onset is rapid and the effect quickly dissipated, FJÄLLBRANT & IGGO (1961).

The latency of effect observed with blister fluid, ARMSTRONG et al. (1953), 5 HT and bradykinin, IGGO (1974) may be due to some chemical intermediary action as yet unknown. Recent evidence suggests that peptides and ACh act on different receptors and that prostaglandin E_1 (PG E_1) enhances receptor sensitivity to PPS including 5 HT, bradykinin, substance P, histamine and ACh, JUAN & LEMBECK (1974).

Pain may be evoked by some PPS in small quantity or in low concentrations. For example, 5 HT released by platelet disintegration can produce pain at concentrations as low as 10^{-3} - 10^{-8} g/ml., histamine at concentration 10^{-3} g/ml., and ACh at concentration 10^{-5} - 5×10^{-5} g/ml., ARMSTRONG et al. (1953). Heating of the

skin produces approximately ten times the stimulatory effect on single unit afferent fibres than the chemical action of injected ACh, 5 HT, and histamine, indicating that these substances exert a weak,excitatory effect on nociceptor afferents, FJÄLLBRANT & IGGO (1961). This effect is more apparent than real, being modified by the quantum input of all nociceptors in any given area, IGGO (1974). It is notable that sensitivity of nerve fibres to natural stimuli is markedly depressed after following the application of PPS, FJÄLLBRANT & IGGO (1961).

CHEMORECEPTION

LIM (1967) showed that very small doses, 2 - 4 µg of synthetic and natural bradykinin peptide, given intra-arterially in man and dogs, produced behavioural responses characteristic of pain, namely:-

(1) Somatic withdrawal reflex.

(2) Autonomic responses (elevated blood pressure, tachycardia).

(3) Psychic reactions (anxiety, agression, struggling and vocalization).

On the basis that sensory afferent nerve fibres were demonstrated in perivascular tissue, and that these receptors seemed to respond to chemical energy, LIM (1967) suggested that specialized receptors lying close to blood vessels were responsible for mediation of pain, i.e. chemoreception rather than nociception. This evidence was supported by the premise that bradykinin was destroyed too rapidly by kininases in the blood to diffuse through the arterial wall and therefore to be able to excite any receptors other than those situated in a perivascular location. LIM and his co-workers (1966) were able to show that small doses of mild analgesics blocked the action of injected bradykinin by a direct influence on peripheral nociceptors. It has since been shown that in addition to a direct effect, mild aspirin-like analgesics may act indirectly to suppress elaboration of prostaglandins and other PPS produced by inflammatory conditions in the tissues, COLLIER & SCHNEIDER (1972).

The notion that substances may act as analgesics by chemical antagonism at chemoreceptive nerve endings suffers in as much as it is known that many such antagonists are poor analgesics, WISE (1966a). LIM also fails to mention whether antagonists to bradykinin and other PPS are also successful analgesic agents. In

addition, intra-ventricular bradykinin has an antinociceptive effect which is dose dependent, probably amine mediated in a similar way to morphine analgesia, RIBERIRO, CORRADO & GRAEFF (1971) and unrelated to any increase in vascular permeability or lowering of blood pressure in neighbouring vessels, RIBERIRO & ROCHA E. SILVA (1973). IGGO (1974) does not place much faith in the theory of chemical mediation of pain, but qualifies his argument with the statement that " . . . . . in the skin there is not much scope for a new kind of nociceptor in addition to the thermal and the mechanical (pin prick) nociceptors unless, as suggested by LIM, these additional nociceptors end on the blood vessels and, more important, do not send their axons into the peripheral cutaneous nerves".

It is unlikely that a mechanism of chemical transmission operates at many sensory nerve endings since nerve fibres continue to respond to mechanical stimuli after chemical sensitivity has been blocked by a specific antagonist, KRNJEVIĆ (1974). The fact that these substances are ineffective when applied to freshly cut dentine, DELLOW & ROBERTS (1966), indicates that for pain to be evoked, at least in these circumstances, there must be direct contact between the chemical and the nerve fibre at the receptor site.

VASOACTIVE SUBSTANCES

Biological mechanisms responsible for headache and other pain of vascular origin may be triggered by monoamines and other vasoactive endogenous chemicals released in the blood stream.

Substances such as bradykinin, 5 HT, K^+, and ATP are known to affect blood vessel motility as well as to produce pain, their pain producing ability being directly related to their respective concentrations in the blood stream. Because of this "double action", SICUTERI et al. (1974) have labelled them vasoneuroactive substances (VNS), and produce evidence to indicate that pain in angina and ischaemic conditions may result from impedance of normal blood supply due to accumulation of VNS in the microcirculation, i.e. the vessels dilate but do not fill - "microvasodilation failure". An increase in concentration of VNS past a critical level is then presumed to be responsible for stimulation of nociceptors and, hence, pain. This mechanism is thought to occur in myocardial ischaemia where endogenous substances stimulate both A δ and C fibres, UCHIDA & SATORU (1974).

VNS AND MIGRAINE

It is possible that the concept of chemical mediation

may apply to bradykinin specifically and not to any of the other pain producing substances, although the plasma kinins have been implicated, KEELE & ARMSTRONG (1968), and SICUTERI et al. (1974) implicate 5 HT deficiency derived from either genetic enzyme deficiency or from central factors (see Fig. No.23 p. 154) as a probable cause of migraine, since they report favourable pain relief by administration of 5 HT precursors to migraine sufferers. It is now well established that changes in cranial blood flow occur during migraine attacks. The headache phase is possibly triggered by excessive vaso-dilation of the external carotid vasculature, O'BRIEN (1971) under the humoral control of one or more vaso-active substances, possibly serotonin, released from blood plasma, ANTHONY, HINTERBERGER & LANCE (1967). SANDLER (1972) also suggests that platelet stored 5 HT triggers the release of pulmonary prostaglandins which then circulate to the brain to presumably cause symptoms of migraine. Tyramine has also been similarly implicated but failure to produce a migraine attack by capsular administration of this MAOI drug suggests a need for further evaluation of the tyramine concept, SICUTERI et al. (1974).

An interesting connection with tyramine intake is that drug interaction can cause a pressor activated cere-brovascular accident in patients under medication with

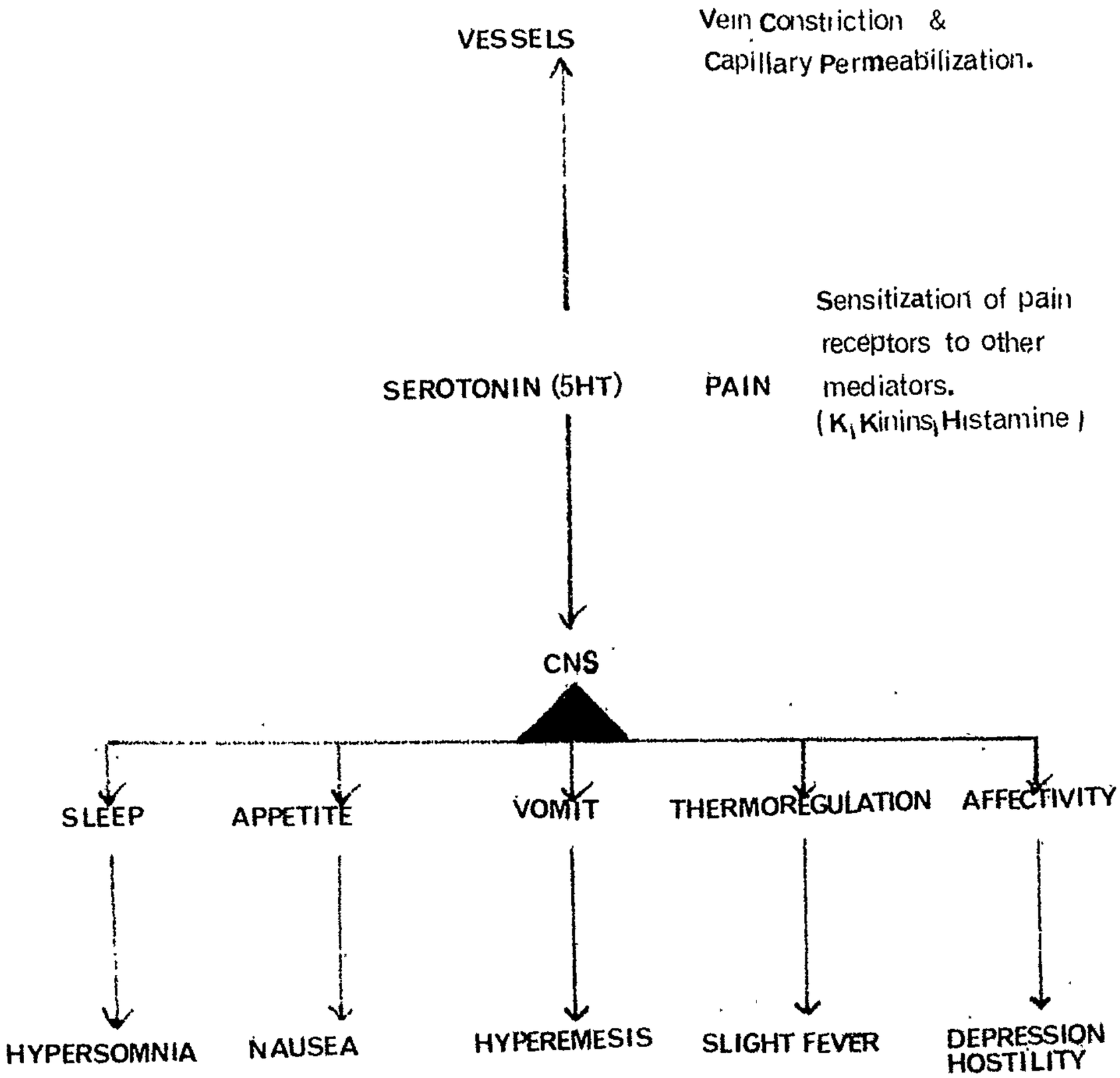


FIG. NO.23. Schematic Representation Of Central Factors Involved In The Action Of Serotonin(5HT).
After Sicuteri et Al (1974).

monoamine oxidase inhibitor (MAOI) drugs, McIVER (1965), (1967), GLOVER (1967). In contrast, narcotics such as pethidine may evoke an hypotensive crisis in these patients.

The hypothesis that serotonin (5 HT) release is the critical determinant in intracerebral ischaemia is not yet proven, but recent evidence, WELCH, SPIRA, KNOWLES & LANCE (1974a) lends support to the concept that platelet released 5 HT may initiate ischaemic pain and other early vascular symptoms of migraine such as intracerebral vasoconstriction and reduced blood flow to the scalp. Other evidence, SPIRA, WELCH & LANCE (1973), WELCH, SPIRA, KNOWLES & LANCE (1974b) also suggests that whatever the cause of migraine there is a compensatory change in intracerebral circulation or a "steal from the internal carotid" which may be due to an increase in external carotid blood flow brought about by the release of a vasoactive substance. Of the VNS tested by WELCH and his colleagues, prostaglandin E_1 (PGE_1), possibly released by the action of serotonin, appears to be the likely mediator of a "steal" from the internal carotid and, hence, symptoms of migraine. If it is assumed that aspirin and other mild analgesics depress the synthesis and release of prostaglandins, SMITH & WILLIS (1971), VANE (1971), then it is readily

seen that these analgesics may relieve symptoms of vascular headache through the above mechanism. A connection of dental interest is the possibility that the use of local anaesthetic agents containing a vasoconstrictor may trigger an attack of migraine in susceptible patients, particularly if there occurs an inadvertent intravascular injection.

It would seem, therefore, that the weight of evidence leans against the theory of chemical mediation, but there is enough experimental data to indicate that pain producing substances play an important contributory role, particularly in inflammatory conditions. The mechanism of action of these substances, like the definitive nature of central transmission, remains unknown.

PPS AND INFLAMMATION

It is clear that the accumulation of pain producing substances (PPS) in the tissues is responsible, at least in part, for tenderness and tissue reactivity commonly associated with inflammatory conditions. Minor tissue damage such as inadvertent probing of gingival tissue results in sharp pain of short duration ("immediate pain"). After a period of latency, pain of

a dull, throbbing character may develop (secondary "recurrent pain") concomitant with the classical signs of inflammation, namely calor, dolor, rubor, tumor et functio laesa.

Similar responses have been observed in artificially produced skin lesions and by other skin stimuli in experiments by ARCANGELI & GALLETTI (1974) who suggest that, during the interval between the two pain responses, pain producing vasoneuroactive substances (VNS)are released, accumulate in the tissues, and depolarize sensory afferent fibres, thereby triggering action potentials in peripheral nerves.

ALTERATIONS IN THE SKIN

These sensory changes are accompanied by visible alterations in the skin adjacent to the site of injury, namely:-

(a) An "erythralgic zone" at the stimulus site - an inner area of persistent redness darker than the surrounding skin (stable erythema) with lowered pain perception threshold to mechanical and thermal stimuli.

(b) A larger <u>outer</u> area of diffuse hyperalgesia where pain perception threshold is lowered for all stimuli and microvascularity is altered.

Apparently this reaction varies from person to person and is a reflection of the "pain historeactivity" specific for each individual.

SPREAD OF HYPERALGESIA

LEWIS (1942) thought that a nocifensor system was responsible in part for the spread of "flare" and hyperalgesia in inflammatory skin conditions. This system relied on a local axonal reflex with branching sensory connections to the microcirculation - each sensory fibre sending a branch to an arteriole. (See Fig. No.24 p. 159)

LIVINGSTON (1943) cited LEWIS (1942) and indicated that the development of hyperalgesia was nerve mediated as well as being due to elaboration of a chemical substance in the tissues. MUMFORD (1973) p. 14 also cites LEWIS (1942) suggesting that pulpal pain may be mediated by autonomic nerves which control vascular tone and which may enter the sympathetic system in company with sensory nerve fibres.

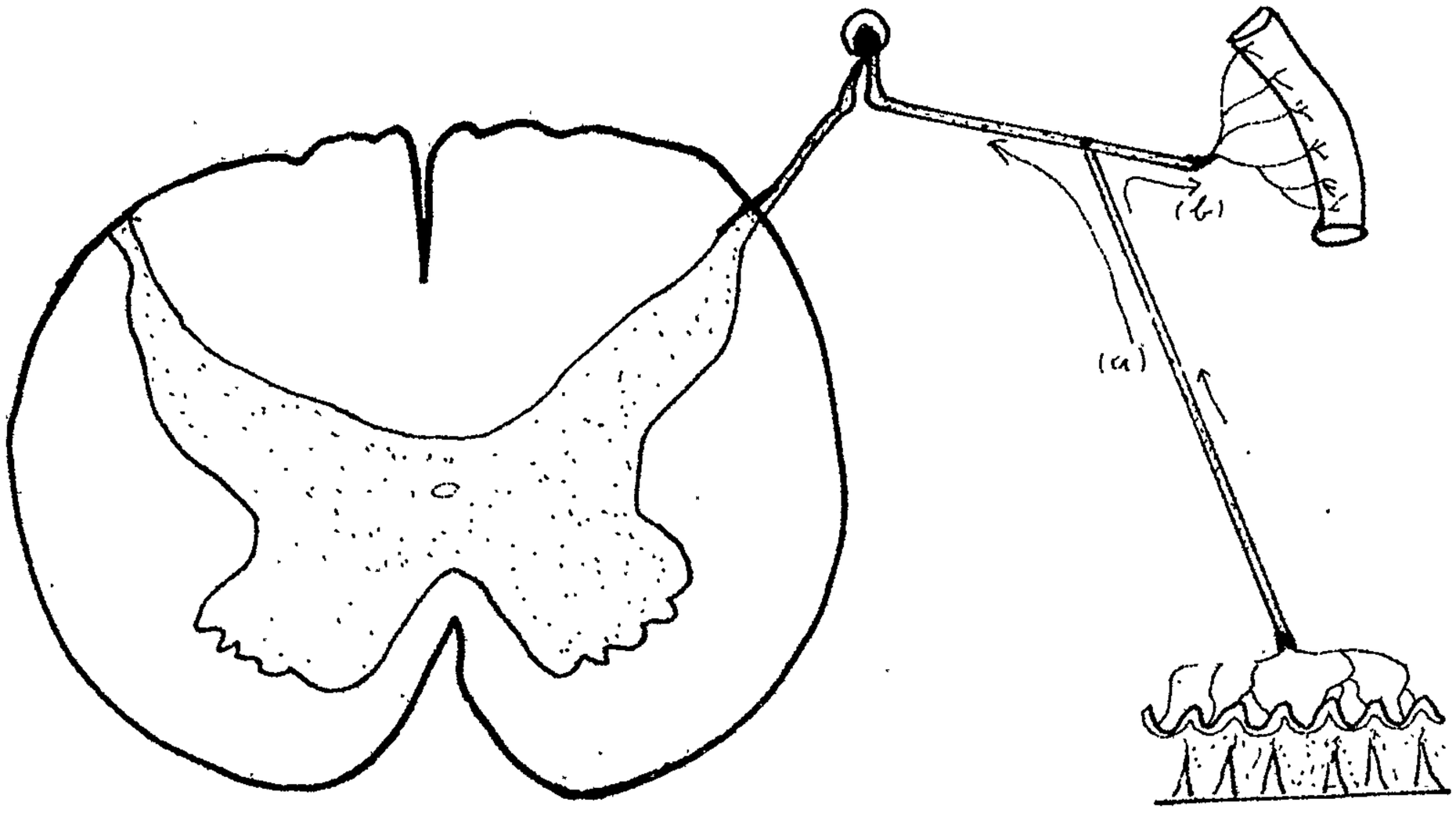


Fig.No.24. Schematic Representation Of AXON REFLEX. Impulses From Damaged Skin Pass (a) Direct To CNS & (b) By Local Axon Branch Back To The Regional Skin Arterioles To Alter Vascular Tonus.

After Payling Wright (1956).

ARCANGELI et al. (1974) again cite the work of LEWIS but suggest a nervous system response of a more "reticular structural distribution" for the spread of hyperalgesia.

BRUSH FIRE EFFECT

In minor injury such as a shallow cut with a scalpel, only a few cells or nerve fibres may be damaged as they lie in the path of injury. Release of lysosomic enzymes may produce further damage to adjacent cells in the microenvironment with elaboration of polypeptide substances. This creates a "brush fire" effect, WALL (1974) which may account, in part, for the apparent hyperalgesia and spread of tenderness in tissues adjacent to the site of injury. As the chain reaction of cellular damage gains momentum, sufficient quantities of pain producing chemicals may be elaborated in the immediate vicinity of an afferent receptor to fire the nerve involved, i.e. the "all or none law" is enacted, the nerve fires at maximum quantum and "pain" is experienced.

OTHER CAUSES OF PAIN

The other possible contributory causes of pain in inflammatory conditions include pressure, intercellular oedema, vasodilation and temperature changes in the

microenvironment. It is possible to account for pain referred to other areas either by:-

1. Direct anatomical involvement, for example maxillary sinusitis involves the superior dental nerves, BRODAL (1972). Therefore, the diagnosis of maxillary sinusitis should take into account the common pains of dental origin, BARCLAY (1975) (see Table No.III p. 162), or by

2. Common convergence of visceral and cutaneous afferents on spinal cells, e.g. REXED lamina 5, WALL (1974).

Another example of anatomical referral is the fact that viral inflammation of the geniculate ganglion, which contains the pseudounipolar cell bodies of intermediate nerve afferents, may refer early pain to the external ear and to the external auditory meatus, BRODAL (1972).

The conclusions of ARCANGELI & GALLETTI indicate that the accumulation of pain producing substances in the tissues may cause both "recurrent pain" and pain associated with inflammatory conditions. But there is little definitive evidence that this actually occurs,

TABLE NO. III

COMMON PAINS OF DENTAL ORIGIN (TOOTHACHE)

Pulpitis Pain poorly Localised		Pain intermittent then continuous	No soft tissue changes
Periapical Abscess	Tooth percussion sensitive	Pain continuous	Intra-oral or facial swelling
Pericoronitis	Diffuse pain, usually associated with wisdom tooth	Pain continuous may be trismus	Inflammation around tooth
Periodontitis	Pain well localised. Tooth percussion sensitive	Persistent gnawing pain	Localised gum margin
Dry Socket (Localised osteitis)	Pain well localised	Pain continuous	Inflammation. Recent extraction socket devoid of organising blood clot

Modified from BARCLAY (1975)

as WALL (1974) states: "While this effect may be relevant to an understanding of membrane structure, it has no relevance to naturally occurring pain in pathological situations outside a chemical factory".

Whatever the mechanism may be, it is clear that inflammatory processes tend to lower the threshold of receptors so that normally innocuous stimuli may cause pain. The classical dental example is the temperature sensitive receptor mechanism observable in cases of pulpal hyperaemia. It is notable that hypersensitivity after excessive polishing of a restoration can be attributed to the development of hyperaemia, MUMFORD (1973) p. 143. Another case in point is the reactivity of a recently restored tooth to cold water. A final example is the tenderness of the gingival tissue that persists after removal of the subgingival calculus.

CHAPTER V

SUMMARY

1. The body is functionally organised to inhibit aberrant sensory information. Central inhibition and excitation are equal in magnitude but opposite in sign. The amount of pain and its behavioural responses are inversely related to the existent level of inhibition. The absence of central inhibition forms the basis of painful neuropathy. A pain suppressive system may operate at spinal levels to inhibit transmission of noxious information.

2. The progressive depletion of inhibitory control may account for avoidance of potentially traumatic experiences such as dental treatment.

3. Electrical stimulation affords temporary pain relief for chronic pain sufferers either by A δ fibre activated central inhibition or by peripheral blockade of A δ fibres. Painful neuropathies such as phantom limb pain and amputation neuroma are thought to be sensory deprivation syndromes.

4. The practice of dorsal column electro-analgesia is complicated by the formation of haematomas at electrode implant sites as well as by damage as a result of the repeated passage of electrical current. Results of electrical stimulation of other areas tend to reinforce the theory that central inhibitory processes operate at spinal levels.

5. Acupuncture methods meet with greater success in Eastern countries than in the West as a result of ethnic preconditioning and greater operator experience. In the dental situation acupuncture requires skill and training not easily obtained. Acupuncture is also a time consuming method of analgesia.

6. Pain derived from local injections depends on prevailing tissue conditions, the substances injected, and the proximity of the needle to a nerve fibre. Pressure may be a major contributory cause of pain, especially in the anterior part of the mouth.

7. Chemical substances may interfere with or block transmission of noxious information at various sites from reception to interpretation. The definitive nature of both central

and peripheral mechanisms of analgesia remains unknown.

8. The use of chemical methods is more desirable than more traumatic procedures such as surgical intervention and osmotic neurolysis.

INHIBITION

It is clear that the degree of inhibition exerted by the individual over incoming impulses is one of the critical determinants in any consideration of biological responses to injurious afferent input.

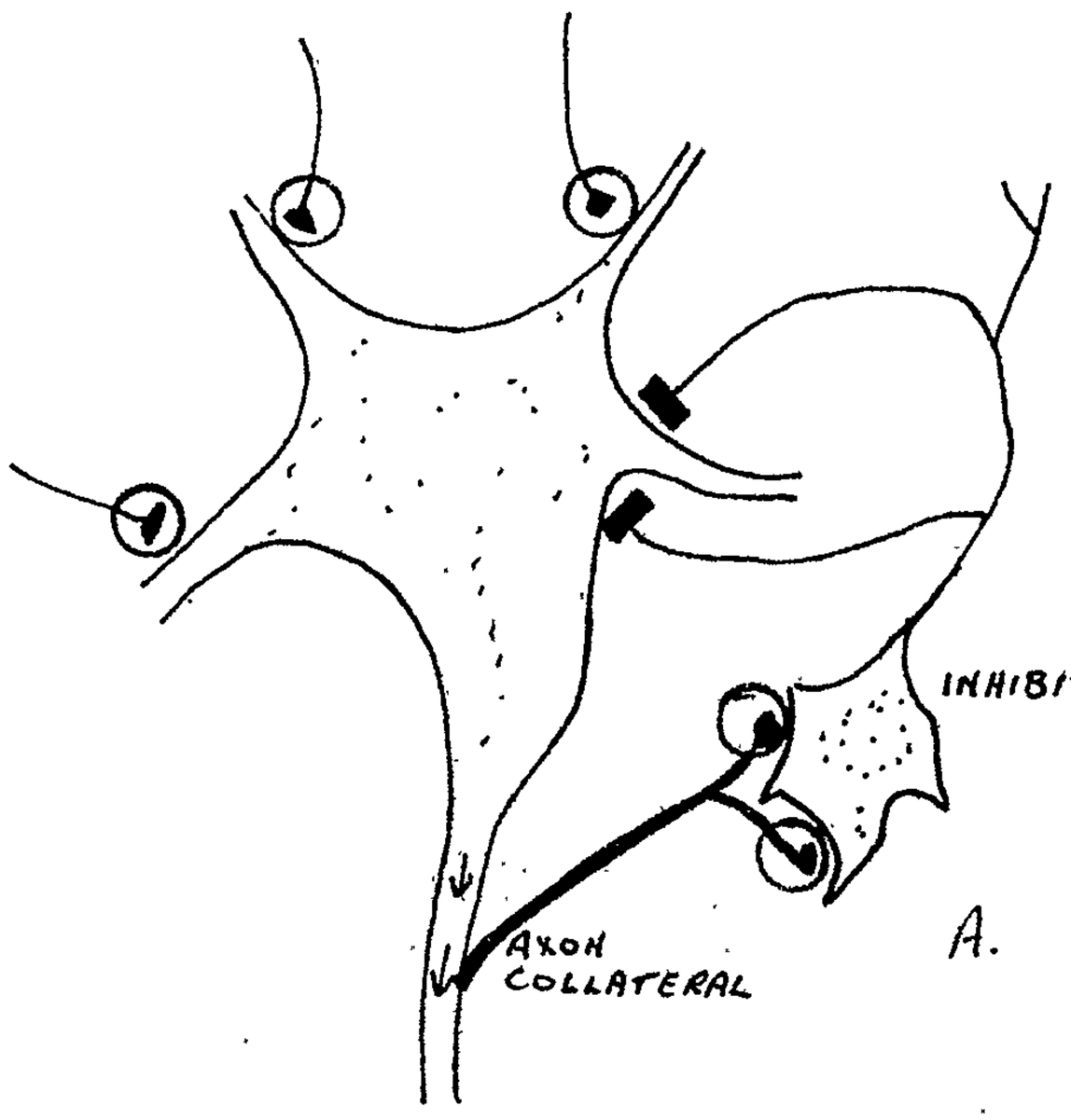
A nerve cell is either inhibitory or excitatory in action at all points along its terminal axonal distribution (Dale's Principle), DALE (1934), (1935). There is always present in the nervous system an inhibitory effect which counteracts the tendency for impulse propogation along nerve fibres. Central inhibition and excitation are equal but opposites; a similar annulment occurs in spinal reflex actions, e.g. flexor versus extensor muscle movement, SAMPSON WRIGHT (1965). Inhibitory interneurones counteract excitation by either "feedback" or "feed forward" mechanisms or by combinations thereof, ECCLES (1969) (pp. 43-45). (See Fig. No.25 p. 168). For example, golgi bottle neurones convert afferent excitation into inhibition and somato-sensory neurones tend to inhibit their own presynaptic afferent terminals by negative feedback, GANONG (1971) (pp. 51, 54).

In fact, the spinal cord functions to reduce the level of sensory input, especially if excitation is weak.

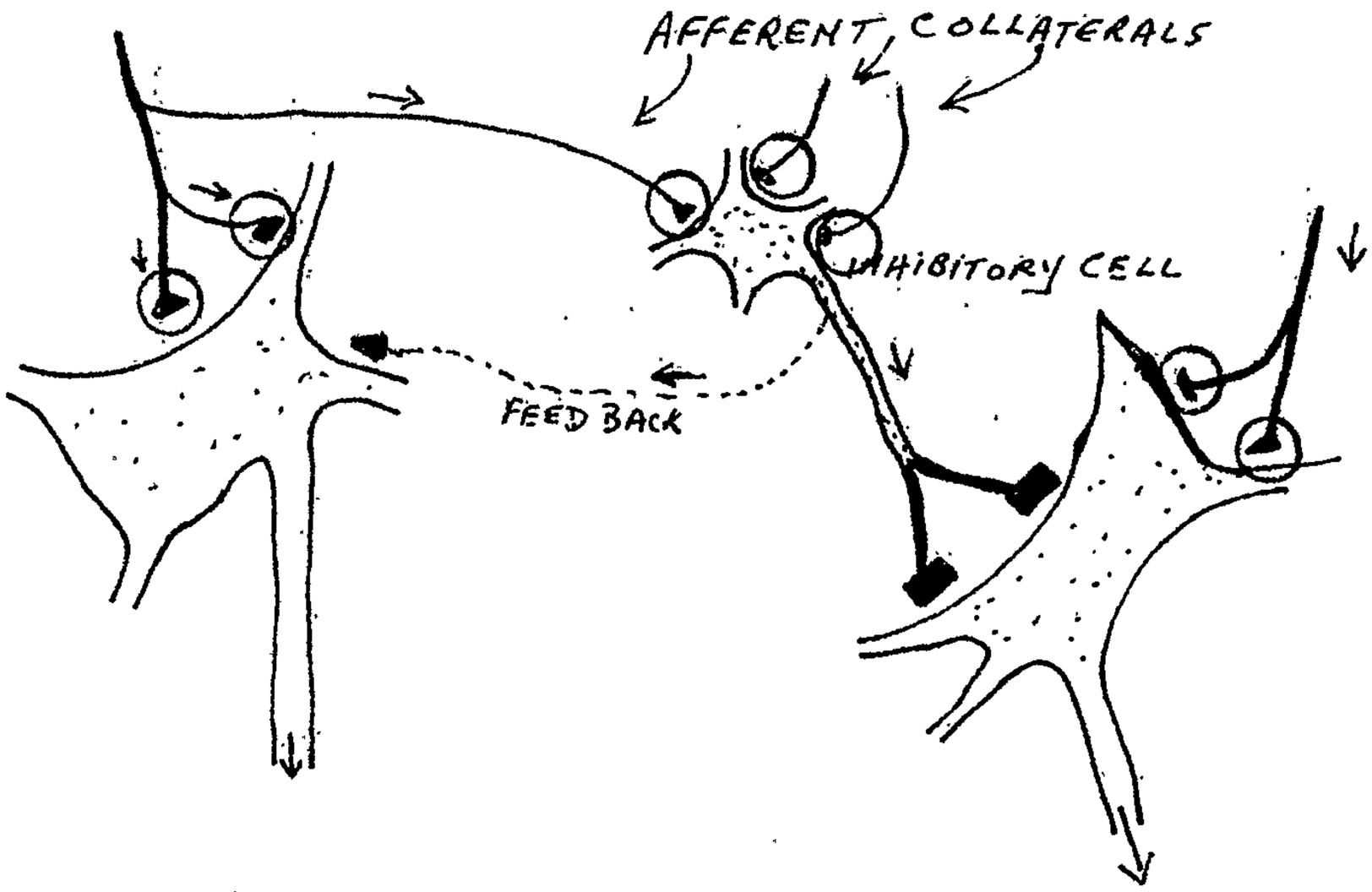
FIG. No.25. DIAGRAMATIC REPRESENTATION OF FEED FORWARD AND FEED BACK MECHANISMS OF INHIBITION. (AFTER ECCLES J.C. (1969) P.44).

INHIBITORY

EXCITATORY



A. RECURRENT INHIBITION



B. AFFERENT COLLATERAL INHIBITION

This "functional organisation" is influenced by descending pathways, particularly by the pyramidal tract and also by the reticulo-spinal, vestibulo-spinal, and rubro-spinal tracts, ECCLES (1967).

THE ROLE OF INHIBITION

The body at all times attempts to maintain homeostasis by breaking down the message content embodied in sensory impulse patterns (functional organization). When excitement derived from sensory disturbance to peripheral afferents exceeds a critical pre-set level in the CNS, MELZACK & WALL (1965), it is possible that when the response occurs it may be graded according to the degree of existent inhibition, i.e. the greater the inhibition, the less pronounced the response.

This notion that pain is not as much an event caused by nervous excitement as a response derived from a progressive lack of central inhibition is supported by:-

(a) Evidence that inhibitory impulses induced by electrical methods produce hyper-algesia, WALL & SWEET (1967).

(b) Pain in causalgic states may be due to loss of central inhibitory control, WALL (1974).

(c) Spontaneous pain occurs in cases where cortical lesions cause breakdown of inhibitory circuits in somato-sensory projection cells, FIELDS & ADAMS (1974).

(d) Nerve fibres are normally inhibited with negative resting potential.

(e) Introducing a new impulse barrage in mechanoreceptor afferents by rubbing or massage after injury tends to diminish pain.

(f) In cases of peripheral nerve damage, pain is relieved by electrical stimulation of the nerve fibre proximal to the lesion; pain is the outcome of all stimuli when the inhibitory influence of myelinated afferents over C fibres is removed by disease or damage, NOORDENBOS (1968). This concept favours HEAD's original inhibitory theory of epicritic and protopathic nervous systems exerting reciprocal influence one over the other, HEAD (1920).

(g) Stimulation produced analgesia (SPA) experiments conducted by LIEBESKIND et al. (1973) indicate that there may be a central pain suppressive system which inhibits responsiveness to noxious stimuli. This system appears to operate in 90.5% of tested inter-neurones of REXED lamina 5 in the spinal cord.

(h) This pain suppressive system may function to inhibit transmission of noxious impulses via the spinal cord, MAYER & LIEBESKIND (1974).

(i) Many of the neuronal effects of anaesthetic drugs in low dose ranges are likely to be due to cyclic changes in cortical inhibitory processes, ROBSON (1967).

(j) There appears to be a progressive dilution of sensory information as it passes from the periphery towards the CNS for final interpretation.

(k) Increased inhibition by other methods such as audioanalgesia, attention and distraction, suggestion, hypnosis, radio signals, verbal sedation, atavistic auto-suggestion, and the building of rapport and empathy by mood amelioration techniques, appears to reduce perception of pain. An example of profound inhibition is the extraordinary ability of fakirs and yogi to exclude perceptual stimuli including pain. This provides indirect evidence that intracerebral stimulation inhibits pain. In the absence of direct evidence, other than that already stated, it would be interesting if chemical substances with specific stimulatory effects on inhibitory circuitry could be found.

THE BEHAVIOURAL RESPONSE

If pain is a function of the degree of central inhibitory control, it follows that the behavioural response associated with noxious stimulation is similarly related to inhibitory processes.

Thus, it is conceivable that the prevailing level of inhibition may be one of the deciding factors in the

quality of "pain" experience and therefore in the nature of the behavioural response. Each experience of pain may progressively weaken central interpretation of the next experience. This notion is reflected by the pain-memory association usually ascribed to a painful experience since pain per se has no memory. As inhibition is depleted, tolerance is breached and the central aversive drive of the individual is activated. The reticular and limbic systems have been implicated as the central co-ordinators for aversive drive and behavioural response, MELZACK & CASEY (1968), GOLDSTEIN (1974).

THE DENTAL SITUATION

The above physiological model may account for avoidance of dental treatment by some patients after the first few visits. In the same way, anticipatory phenomenon, such as anxiety and apprehension prior to treatment may reduce the level of inhibition, thereby facilitating the effect of excitatory stimulation.

In the extreme view, decreased inhibitory control may be the governing factor in deciding whether "pain proper" at first level vigilance described by SOULAIRAC (1968) becomes "suffering" or pain at

second level vigilance. The former state is easily reversible, the latter difficult to return to a normal pattern of sensory and emotive behaviour.

Thus, it would seem that there exists a delicate balance between ongoing and incoming sensory activity in the CNS. This balance is largely governed by the level of central inhibition which is related quantitatively and qualitatively to the behavioural response associated with noxious stimulation.

ELECTRICAL STIMULATION

If the level of inhibition dictates the amount of pain experienced, then it would be advantageous to see how and where mechanisms of inhibition can be influenced so as to afford relief of pain.

It is known that electrical stimulation of a nerve fibre produces a "current sink" which facilitates action potential at the electrode site or point of stimulation. The rate of electrical impulse propogation is proportional to the degree of myelination of the nerve fibre and to the size of the internal core of the conducting fibre, WALL (1974). The discontinuation of the myelin sheath of a myelinated axon at the node of RANVIER, at 1 mm. intervals, is essential for conduction and rapid transmission of action potential, BRAZIER (1969a). The

plasma membrane may be polarized or depolarized according to the direction of the current, BRAZIER (1969b). This factor has been utilized clinically to produce a form of analgesia in patients with chronic pain syndromes such as post herpetic pain, phantom limb pain, and central pain, all of which have not responded well to medical or surgical treatment.

WALL & SWEET (1967) obtained temporary relief for chronic pain sufferers by electrical stimulation of peripheral nerves serving areas to which pain was referred. They observed a depreciation in the pain from "pin prick" in areas served by the inferior orbital nerve after 100 Hertz 0.1 m sec. electrical stimulus was applied by subcutaneous needle electrodes.

Their evidence suggests that peripheral stimulation of large A δ fibres produced central inhibition and therefore relief of pain. The explanation of this event was based on the premise that:-

(1) The gate control theory held by MELZACK & WALL (1965) was valid.

(2) The hypalgesia produced was due to the stimulation of large myelinated fibres only.

The evidence of WALL & SWEET (1967) is supported by MEYER & FIELDS (1972) and, in accordance with these authors, WALL (1974) suggests that pain and sensitivity (hyperesthesia) evident in traumatic conditions, such as acute causalgia, may be due to a type of sensory deprivation. This process apparently involves the filtration at the periphery of afferent impulse barrages carried by large diameter fibres so that impulses which normally activate central inhibitory processes are left out. Electrical stimulation presumably supplies the missing impulses. Other pain states such as phantom limb pain and pain due to amputation neuroma are also thought to be due to this sensory deprivation syndrome, MASPES & PAGNI (1974).

MECHANISM

Previous evidence indicates that electrical stimulation of large diameter fibres alone affords relief of pain presumably by reintroducing impulses which activate central inhibitory processes in the spinal cord. The alternate view of CAMPBELL & TAUB (1973) that analgesia results at least in part from peripheral blockade of A δ fibres now appears more likely. CAMPBELL & TAUB (1973) used a special purpose digital computer in eleven subjects, aged 20 - 27 years, to show that peripheral

blockade of smaller myelinated fibres produced sensory block in larger A δ fibres, thereby inhibiting transmission of nociceptive information derived from stimulation of these larger fibres. The question as to whether pain relief afforded by peripheral electrical stimulation is due to central inhibition or a peripheral inhibition of noxious information or through a mechanism involving both of these effects is therefore at present still not clearly decided.

DORSAL COLUMN - ELECTROANALGESIA

Temporary periods of chronic pain relief have been obtained by intermittent electrical stimulation of selected spinal cord areas, SHEALY (1969), NASHOLD & FRIEDMAN (1972), where implanted stimulators produce antidromic impulses presumed to activate large diameter afferents (by firing axons passing on to the brain backwards) thereby resulting in inhibition of pain impulses at the spinal cord level. Recent evidence also indicates that dorsal column stimulation modifies the response of thalamic nuclei to noxious impulses derived from stimulation of afferent peripheral nerves (Median), GILDENBERG & MURTHY (1975). This system of pain relief is not without complications. GRILLO, YU & PATTERSON (1974) reported the case of a 46 year old woman who suffered

the implantation of a dorsal column stimulator in the subarachnoid space at C4-5. Eighteen months later, investigatory surgery to relieve symptoms of neck pain and right hemiplegia revealed the presence of a haematoma compressing the spinal cord at the electrode site. GRILLO et al. (1974) suggested that this complication may relate to the fault of positioning the electrode in an area of spinal cord mobility rather than to the effects of electrical stimulation.

However, TAUB, COLLINS & VENES (1974) transfer the onus of damage to the actual electrical stimuli since their patient suffered extreme disability and no relief of pain from electrical stimulation of the dorsal column. On removal of the electrode, the abberant symptoms disappeared at a rate related to the duration of the electrical stimulation. This evidence leads to the conclusion that further investigation of dorsal column stimulation is necessary.

STIMULATION OF OTHER AREAS

Responsiveness to noxious stimuli is reduced by focal electrical stimulation of other parts of the nervous system in man and animals. MAYER & LIEBESKIND (1974) describe a variety of analgesia tests, namely,pinch, jump, tail flick, self stimulation to show that analgesia

equal to or greater than 10 mg/kg morphine can be induced in rats subjected to stimulation of selected brain areas. They postulate that electrical stimulation initiates a "pain suppressive system" which, when activated, produces a reduced responsiveness to noxious stimuli. This analgesic effect is presumably due, at least in part, to the blockage of nociceptive information via the spinal cord. Similar evidence is produced by MELZACK & MELINKOFF (1974) who used multiple electrode implants in cats to demonstrate the powerful inhibitory influence of the brain stem reticular formation over transmission of pain impulses. MELZACK & MELINKOFF (1974) found that stimulation in the region of the central grey and adjacent tegmetal tracts of the brain produces analgesia in rats and cats and activates descending fibres which inhibit transmission of nerve impulses from sensory nerve fibres to spinal horn cells that project to the brain.

These findings seem to strengthen the position of adherents to the theory that replacement of central inhibitory influences by electrical hyperpolarization of peripheral nerves actually relieves pain.

ACUPUNCTURE

Recently, interest in pain mechanisms has been revived by the Chinese practice of acupuncture analgesia.

Briefly, this manoeuvre requires the manual or electrical vibration of special needles inserted subcutaneously at selected points on the body surface. Reports by McLEOD, SAINSBURY & JOSEPH (1974), McLEOD (1974), MEDICAL JOURNAL OF AUSTRALIA (1974), indicate that this form of pain relief relies heavily on ethnic preconditioning, anxiety relief, distraction and a high degree of suggestability. CHISHOLM (1972) indicates that the level of inhibition achieved by acupuncture "is no more remarkable" than that induced by methods of suggestion.

The experimental observations of MANN (1974), in 35 English subjects, indicate that acupuncture is 90% ineffective in obtaining the level of pain relief required for surgical procedures. MANN (1974) concludes that the technique is inadequate - the pain from insertion of needles alone being "unacceptable to most western patients".

LATENCY IN EFFECT

A latency in response is found in acupuncture techniques for dental extractions where onset of analgesia Te - ch'i or "take" - a feeling of tingling numbness, distension and heaviness often accompanied by reflex muscle activity, is delayed 5 - 10 minutes after initial needle insertions, McLEOD et al. (1974). An interesting connection is that this delayed hyperalgesic response is

also found in conditions of aerodontalgia where central pressure changes excite dental nerves, HUTCHINS & REYNOLDS (1947), WOLF (1963) and, in experimental situations, KAWAMURA (1968), where electrical stimulation of antral nerves results, after a 10 minute delay, in a persistent hyperalgesic response in the overlying facial skin.

In neurological terms, the delay in onset of analgesia may possibly be explained by two factors:-

(1) Time taken for recruitment of a critical number of active neurones.

(2) Time taken for released neurotransmitters to affect adjacent and distant neurones, MELZACK & MELINKOFF (1974).

MECHANISM

The definitive mechanism of acupuncture has not yet been demonstrated, but suggestions by CASS (1973), LANCET I (1973), and SICUTERI et al. (1974) tend to give support to the concept that increased afferent input derived from acupuncture stimulation inhibits transmission of pain in accord with the gate control hypothesis (i.e. the input closes the gate).

The gating hypothesis does not supply all the answers. LOONEY (1974) suggests that pain relief afforded by acupuncture may be involved in some way with the effect of acupuncture on pain mediated via the autonomic nervous system. In addition, ECCLES (1973) p. 95 suggests that acupuncture may suppress pain in a way similar to counterirritation.

CLINICAL USAGE - Dental

The delay observed in obtaining satisfactory states of analgesia, McLEOD et al. (1974), MUMFORD (1973), and the lack of training or experience with acupuncture techniques in dentistry, are obvious barriers to the clinical usage of acupuncture for dental purposes. A connection of interest is that the same factors preclude the use of hypnosis which carries the additional hazard of being extremely dangerous in unskilled hands, MEARES (1967a). On the other hand, acupuncture may be useful for simple extractions of monorooted teeth in patients with known hypersensitivity to local anaesthetic solutions, RIDDLE (1974).

ANODAL CURRENT

NEWMAN (1973) reports a progressive decline in amplitude of action potential to zero after application of anodal

current to nerve fibre. He suggests that the observed period of prolonged hyperpolarization ("after depression") that persists after removal of the current, may be of use in the clinical situation. The latency of effect is not indicated, nor is the degree of pain experienced on initial application of the current, but the evidence presented is sufficient to indicate that further investigation of electrical methods is highly desirable.

An interesting dental connection is the electrical device CITA (constant intensity tooth anaesthetic) claimed by its manufacturers to inhibit pain or fear of pain by the passage of a similar controlled current. Unfortunately, there is insufficient evidence yet published to support or deny the efficacy of this method which shows immense promise when compared with earlier methods, SHANE & KESSLER (1967) involving subanaesthetic measures.

CHEMICAL INHIBITION

A therapeutic way of changing the effect of pain mechanisms lies in the common use of chemical substances to inhibit pain. Drugs may interfere with the transmission of noxious sensory impulses at various levels in the nervous system:-

(i) At the receptor site.

(ii) At synapses.

(iii) In the spinal cord and thalamic connections.

(iv) By interference with cortical interpretation.

(v) Or at other sites either peripherally or centrally located along the various pathways from perception to interpretation.

Pain inhibiting substances are generally known as analgesic drugs. The mode of action of mild and potent analgesic drugs is described elsewhere, GOODMAN & GILMAN (1970), SWERDLOW (1967), HOFFMEISTER (1970). It is sufficient to state that analgesic activity is a function of either:-

(a) Inhibition of sensory transmission of noxious impulses, or

(b) Amelioration of underlying emotional factors associated with pain, or

(c) Both of these phenomena at the same time.

Pain may be relieved by drugs other than true analgesics by modifying peripheral factors or mechanisms responsible

for pain perception, for example, the use of tegretol and dilantin in the treatment of trigeminal neuralgia, HEYCK (1970), the action of atropine on gastrointestinal spasm, and ergotamine in the relief of vascular headache. LIM (1967) suggests that amphetamine and other non narcotic analgesics may inhibit pain centrally by a mechanism similar to that of appetite suppression.

MECHANISMS OF ANALGESIA

CENTRAL

Although the general pharmacological effects of analgesics on pain are known, GOODMAN & GILMAN (1970), definitive mechanisms of analgesia have not yet been demonstrated. Synonomous adrenolytic, adrenergic, postganglionic anticholinergic, and cholinergic effects of morphine have been described, WIKLER (1950), HOFFMEISTER (1970). Morphine induced analgesia is thought to be more likely related to an adrenergic than a cholinergic mechanism. PEPEU & NISTRI (1974) postulate that more than one neurotransmitter is likely to be involved - possibly a delicate balance "between the relative amount of dopamine and serotonin", MAJOR & PLEUVRY (1971) and the inhibition of ACh release in ascending cortical fibres, PEPEU & NISTRI (1974).

It is possible that morphine-like substances act centrally by interference with the metabolism of an unknown transmitter substance necessary for conduction of noxious information along excitatory pathways in the brain.

PERIPHERAL

Despite LIM's evidence that aspirin-like analgesics act by direct intervention at peripheral sites, it seems more likely that some intermediary such as the prostaglandins is involved, COLLIER & SCHNEIDER (1972).

Pain is also relieved by the anti-inflammatory action of aspirin-like drugs. Aspirin specifically prevents blood platelet synthesis of the potent inflammatory agents PGF_2 and prostaglandin E_2, SMITH & WILLIS (1971). Aspirin and salicylates uncouple ATP dependent oxidative phosphorylation reactions in connective tissue necessary for the biosynthesis, composition, and metabolism of mucopolysaccharide ground substances such as chondroitin sulphuric acids and hyaluronic acid, GOODMAN & GILMAN (1966). Hydrated hyaluronic acid forms a viscous barrier to the spread of infection and inflammation.

It is therefore possible that this uncouling mechanism may account for the reduction in fluid movement, tissue

swelling, and other responses associated with inflammation. Since the sodium pump also depends on phosphorylation mechanisms in the mitochondria, it is possible that the peripheral pain relieving mechanism of aspirin-like analgesics may rely at least in part on this energy uncoupling reaction.

ANTIPYRETIC EFFECT

A minor contributory role in symptomatic pain relief may be played by the general decrease in body temperature produced by aspirin-like drugs. The antipyretic effect of these substances is thought to be achieved by their action on a hypothalamic temperature regulator ("thermostat") which resets itself upwards in times of fever, thereby permitting increased dissipation of heat, through increased peripheral blood flow and sweating, without actual interference with heat production and loss, GOODMAN & GILMAN (1966).

INJECTION PAIN MECHANISMS

Unfortunately, local injection techniques are subject to many pain producing hazards, namely: pressure from needle and in-tissue volume of chemical substance, pH changes in the tissue, direct injection into a nerve, needle contact with nerve,diffusion, intravascular

injection, temporary dehydration in the zone of injection possibly due to high osomotic pressure of injected material, membrane degeneration and other miscellaneous chemical effects, some or any of which may contribute to changes in ionic equilibrium in the neuronal micro-environment and, hence, provoke alterations in nerve cell membrane potential.

An interesting connection is that pain from needle damage has been avoided by using an electrical method based on motor response before sensory response to locate deeply situated nerves, CHAPMAN (1972).

In the dental situation, the everyday use of "the needle" multiplies pain producing hazards. Maxillary and mandibular block techniques augment the possibility of axonal interference as well as the danger of intravascular injection with aberrant cardiovascular sequelae, particularly when the agent contains a vasoconstrictor. The average incidence of intravascular injection increases markedly posterior to the bicuspid region, OLIVER (1974). In addition, local anaesthetic agents containing vasoconstrictors may contribute to localized ischaemia with concomitant anoxia which is known to cause depolarization of a nerve fibre membrane, McDOWELL (1952).

Thus, any injected substance may cause sufficient depolarization to fire an action potential, dependent on the electrotonic state of the target nerve fibre at any given time. The abundant distribution of mechano-receptor afferents in the upper lip suggests that pain from labial injections may be mainly due to pressure of in-tissue volume of fluid. It is postulated that this discomfort may be reduced by a double injection technique. The use of topical lignocaine adhesive on dried mucosa and an initial submucosal deposit of 0.5 ml local anaesthetic solution is followed after 30 seconds by a further dose introduced via the same puncture point.

CHEMICAL INHIBITION IN THE DENTAL SITUATION

No pain inhibiting substance better than morphine has yet been discovered for the treatment of severe or intractable pain. The undesirable side effects of morphine, namely drowsiness, lethargy, respiratory depression, nausea, vomiting, addiction and constipation are generally outweighed by its beneficial analgesic and sedative properties, DILLE (1963). However, in the dental situation, the need for morphine seldom arises, DILLE (1963) since dental pain can usually be

effectively controlled by less potent agents such as codeine or aspirin, GOULDING (1960). Codeine is about three times more effective than aspirin in controlling pain arising from dental pulp stimulation, SHERMAN, FIASONARO & GRUNDFEST (1963). Morphine is indicated only when other measures fail, MONHEIM (1965).

DRUG COMBINATIONS

Pethidine, fenantyl, phenoperidine, and other less potent narcotic substances have been utilized in "cocktail" combinations with sedatives or hypnotics (pentobarbital), JORGENSON (1953), JORGENSON & LEFFINGWELL (1953) or neuroleptics, (haloperidol, droperidol), SHEPHARD (1965) in order to dull the perceptual awareness of dentistry as well as to obtain some degree of euphoria and amnesia. Similar time consuming pharmacological approaches including Intravenous Sedation, MAIN (1968), FOREMAN (1966), (1967), (1970), Hydroxyzine usage, SMALL (1966), Twilight Sedation, BERNS (1963), Chemanesia, PEIFFER & MONHEIM (1957), Intravenous Amnesia, SHANE (1966), POSWILLO (1967), Synergistic Basal Narcosedation, CRANIN & CRANIN (1960), and submucosal injection techniques, CHAMBIRAS (1969), COPEN (1947), (1952), have been used with local analgesia to control pain and to lessen the impact of either oral surgical procedures or protracted operative dentistry.

In the main, these "sledgehammer" methods, when used for routine procedures, tend to over subdue the patient, in many ways acting as a "substitute" for personal care and attention. The interposition of pharmacology between the dentist and his patient would seem to solve the initial problem of interrelated stress between dentist and patient described by MARTIN (1970), but in the long term may do little to create a lasting co-operative relationship which requires the realistic attention of the dentist to the patient management problem, i.e. the essential build up of rapport, empathy, and a sympathetic understanding of "his" patients' needs.

Hence, what is needed in dentistry is the strengthening of natural inhibitory processes aided by the elimination of the physiological syndrome known as pain, before, during, and after dental treatment. The use of chemical substances to inhibit pain mechanisms is not a universal panacea for the problem of pain, but merely one of the methods available in the wide range of remedies for what constitutes pain.

SURGICAL INHIBITION

When pharmacological methods fail to control pain, surgical intervention may afford temporary and, sometimes, permanent relief of intractable pain. Pain

pathways may be sectioned either peripherally or in the CNS. (See Fig. No.26 p. 193)

Surgical complications include anaesthesia dolorosa (painful anaesthesia), recurrent hyperesthesia, paresthesia (persistent numbness and swelling sensation) and various other symptoms in a range between itch and tingle to the return of the original neuralgic sensation in a more unbearable form than before, MASPES & PAGNI (1974).

OSMOTIC NEUROLYSIS

It is possible that techniques using icy hypertonic saline in solutions of 3500 m Osm/L to block pain carrying fibres, KING, JEWETT & SUNDBERG (1972), labelled "Osmotic Neurolysis" by HITCHCOCK (1969) on the basis of selective inhibition of sensory fibres, achieve their measure of success by interference with the sodium pump mechanism. MASPES & PAGNI (1974) suggest that interference with the sodium pump may result in a change in the nature of the afferent impulse barrage sufficient to alter its "algogenic character". PATEL, KELEKAR & MHAMBRAY (1974) report good relief of intractable pain in 80% of their selected patients after an initial injection of hypertonic saline 8 grms. % concentration.

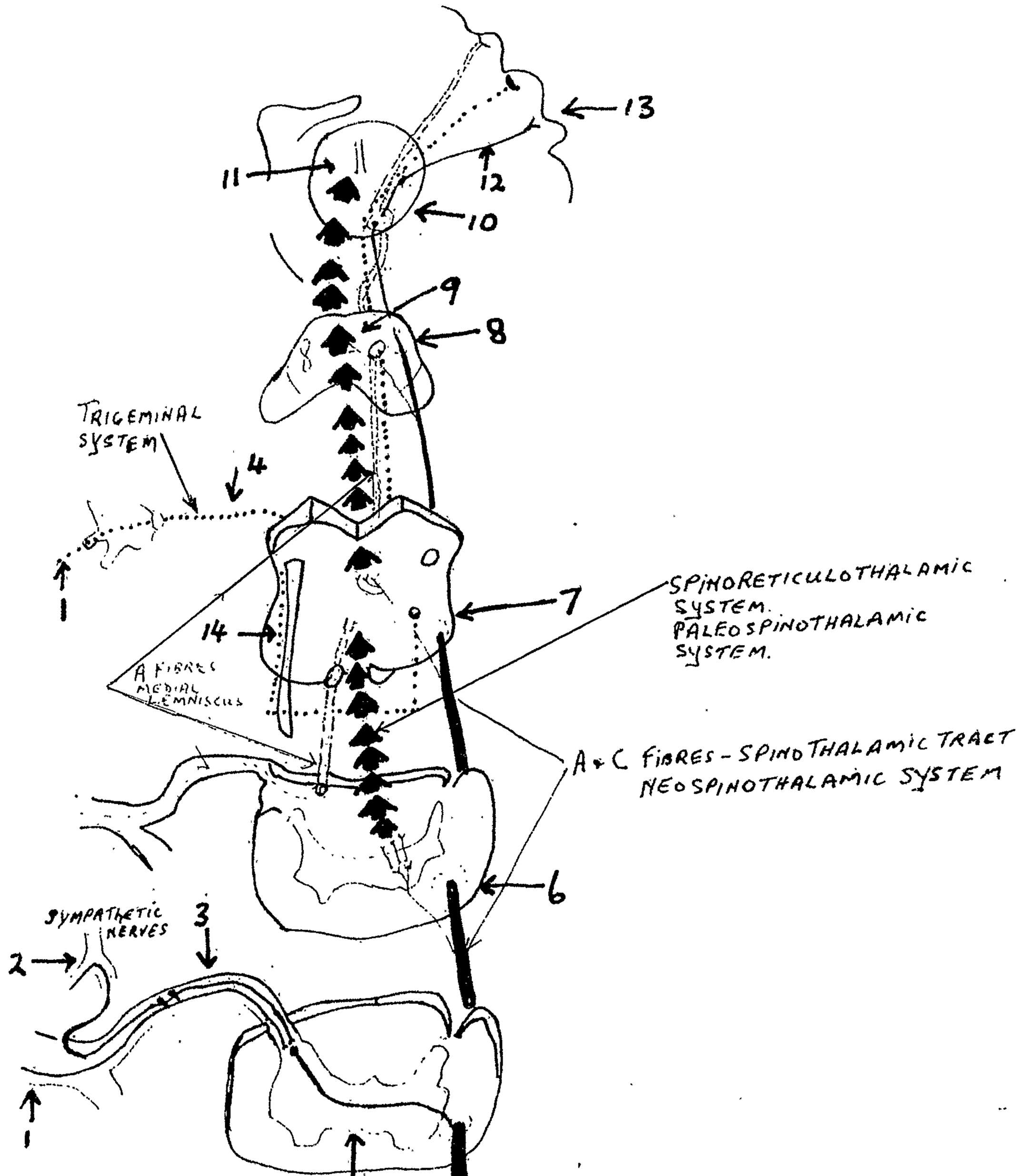


FIG. NO. 26. SCHEMATIC REPRESENTATION OF SITES AT WHICH PAIN PATHWAYS MAY BE INTERRUPTED BY SURGICAL INTERVENTION. [AFTER MASPES & PAGNI (1974).] SITES NUMBERED 1-14.

SURGICAL RELIEF OF PAIN

TRIGEMINAL NEURALGIA

In the treatment of neuralgic conditions such as trigeminal neuralgia, surgical methods should be employed only after less radical methods such as gasserian blocks with absolute alcohol or phenol in pantopaque or glycerine vehicle, JEFFERSON (1966) are no longer successful, MASPES & PAGNI (1974).

Attacks of trigeminal neuralgia have also been successfully prevented by using a radio receiver implant to inhibit afferent "trigger" signals, SHELDEN, PUDENZ & DOYLE (1967) by using electrocoagulation techniques, PAWL (1975) and by "decompression" operations, TAARNHØJ (1954).

STEREOTACTIC PROCEDURES

Section of short polysynaptic axon pathways in the brain stem and the thalamus for relief of pain in terminal cancer are of little interest except as a final answer to the problem of pain when death is imminent, MASPES & PAGNI (1974).

CHAPTER VI

CONCLUSIONS

1. Inhibitory processes play an important part in what constitutes pain. Recent evidence indicates that there is a pain inhibitory system responsible for the regulation of ascending nociceptive information. This system operates at various levels and depends largely on the input of myelinated afferent fibres. The amount of pain experienced and, therefore, the behavioural response to pain, are inversely related to the existent degree of CNS inhibition.

The absence of central inhibition is likely to be responsible for painful neuropathies such as causalgia, post-herpetic pain, phantom limb pain, and amputation neuroma. Trigeminal neuralgia may be caused by the same afferent sensory deprivation mechanism, possibly derived from oral and dental sources.

Inhibitory processes also modify sleep mechanisms, the central action of narcotic analgesics and the message content of impulse patterns carried by afferent peripheral nerves.

2. The revitalization of afferent sensory input by electrical and mechanical means such as acupuncture and intermittent electrical current exploits the central process of descending corticofugal inhibition which appears to operate in the trigeminal as well as in other somatosensory pathways. It is not yet firmly decided whether pain arising from peripheral regions is temporarily relieved by electrical stimulation of the peripheral nerve related to the painful area or whether relief is afforded by peripheral nerve blockade of A δ fibres, although the latter appears more likely.

Other than the current methods available for intracerebral stimulation of inhibitory processes, it would be an advantage to seek and find chemical substances that would specifically activate either the large diameter afferent inhibitory system or those intracerebral inhibitory circuits responsible for the suppression and conscious control of pain.

Skill and training are prerequisites for the clinical use of acupuncture. Acupuncture in occidental patients should be limited to the simple extraction of monorooted teeth when there is known hypersensitivity to local analgesic agents.

3. Nociceptors are usually specific for either thermal or mechanical energy but not for both modalities. Chemoreception is not proven, but the release of chemical substances in the microenvironment may help to explain the mechanism of receptor sensitization following stimulation.

Since specialized receptors have been demonstrated as well as specific pain carrying fibres in the ventrolateral tracts, the pendulum of debate now swings in favour of VON FREY's original specific theory.

The nature of the inhibitory or facilitatory "gateway" in the first synapse with interneurones is still not clear. There may be several gates that operate at different levels, each gateway is not necessarily the same and some fibres may not be gated at all. The gate control theory is not tenable but should not be completely discarded.

4. Information about pain may be modified by changing its meaning and interpretation in the CNS through direct interference with central control determinants which dominate emotional and psychological content of pain. Drugs may inhibit transmission

of noxious impulses by general neuronal depression, synaptic interference, or by intervention directly or indirectly at receptor sites. The administration or sedative drugs strengthens inhibitory processes,at the same time reducing the chances of overt emotional reactivity. Over depression of the CNS by anaesthetic drugs tends to remove inhibitory control leading to emotional changes and physical manifestations that are in no way connected with the actual amount of pain experienced but merely an interpretation of latent psychological expression.

Sedatives should not be used as a substitute for suggestion, empathy and rapport, and other indirect methods of intracerebral stimulation of inhibitory processes, except in cases when these measures fail. Intravenous sedatives, narcotics and tranquillizers have little place in the routine management of dental patients.

5. There is no definitive evidence that any of the wide variety of pain producing substances (PPS) released in the microenvironment as a result of inflammation or pathological conditions is actually a prime cause of pain, but there is enough evidence to conclude that combinations of these substances

cause secondary or recurrent pain with spread of tenderness into the surrounding tissue.

Vasoactive substances such as bradykinin and serotonin (5 HT) may cause vascular and ischaemic pain by a direct accumulatory effect in the micro-vasculature. Ischaemic pain in migraine syndrome may be a result of a prostaglandin evoked "steal" from the internal carotid artery involving serotonin as a possible trigger substance.

Present evidence indicates that aspirin-like analgesics may act to suppress the elaboration of prostaglandins and other pain producing substances at the receptor site rather than to exert a direct effect on nociceptors. Further investigation of possible chemical antagonists to pain producing substances may provide better analgesics for the treatment of peripheral pain, including the "mystery" of toothache.

6. There exists in dentistry an opportunity to strengthen natural inhibitory processes supported by the elimination of known pain producing stimuli whenever possible. The restructuring of old neuronal circuits by infusion of new afferent inputs through conditioning, education, mood

amelioration, suggestion and other inhibitory stimulants may change the way in which the patient thinks, feels, and acts, before, during, and after dental treatment. These constructs enable the patient to gain a deeper knowledge, understanding and sense of control over the entire dental procedure. Reinforcement of inhibitory control at subsequent visits provides a central axis for the development of a more lasting dentist-patient relationship based on mutual trust and understanding.

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