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P A I N M E C H A N I S M S

Some aspects relating to inhibitory processes and their role in the clinical situation

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requirement for the degree of
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"The Physician's devotion to relieving pain is measured by his resistance to admitting defeat in his struggle against pain."

SZASZ (1968)

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INTRODUCTION

There is evidence in the literature of a growing awareness of the role of inhibitory processes in what constitutes pain. There are many biological mechanisms involved in the transmission of pain from damaged or inflamed areas in the body. Because of this interest it is the intent of this document to review, as far as present knowledge permits, some of the physiological principles that govern the transmission of noxious sensory information from the peripheral receptor sites to the central nervous system (CNS) and to examine the known inhibitory mechanisms and their relationship to the overall physiological syndrome described as pain. The collated information is applied to the dental situation wherever possible. From the evidence that follows, it can be clearly educed that there are two sets of peripheral nerve fibres that are differentially sensitive to noxious stimulation of the skin. Bright sharp pricking pain is served by certain fibres of the delta type, whereas the protracted burning quality of pain is conducted by certain C fibres. For the dual modality of pain to be evoked, impulses must be carried

by both sets of nociceptive fibres. Pain per se does not rely on impulses conducted by other sensory nerves although the total perceptual experience of which pain is a part is largely dependent on the input of information from other sensory receptors. It is the physiological variability of these nerve fibre terminal receptors in the skin and their different responses to a wide variety of stimuli that make the sensory experience of pain an interesting but complex study.

Since the receptor mechanism for pain is actively debated, special consideration is given to factors which influence the reception of noxious impulses (nociception) to the action of endogenous chemicals released at receptor sites as a result of tissue damage or inflammation, and to the special mechanisms that affect receptors in the dental pulp. The detailed nature of central transmission mechanisms and central transmitter substances is dealt with elsewhere, KRNJEVIĆ (1974).

There are 3 current physiological models proposed for the transmission of pain:

(1) the specific or classical theory,

(2) the pattern theory,

(3) the gate control theory which provides an alternative hypothesis as well as a basis for further examination of the problem of pain, NATURE (1973).

In each case the neural substrate remains constant, but according to the different protagonists there exist definitive variations in which "pain" is carried from the periphery to the spinal cord.

The problem of pain is further complicated by the variety of local, reflex, and behavioral reactions that become apparent when noxious impulses travel from receptors to the spinal cord and are projected along diverse pathways to reach higher interpretative centres in the CNS. The diffuse nature of these central tracts and the interactions that occur at multiple synaptic interconnections along various neural pathways tend to cloud the interpretation of evidence derived from experimental sources. Further, it is difficult to equate the physiological results of testable aspects of pain in the laboratory animal with the real issue of pain as it occurs in human circumstances.

In order to understand the physiological and clinical implications of pain, sufficient information is

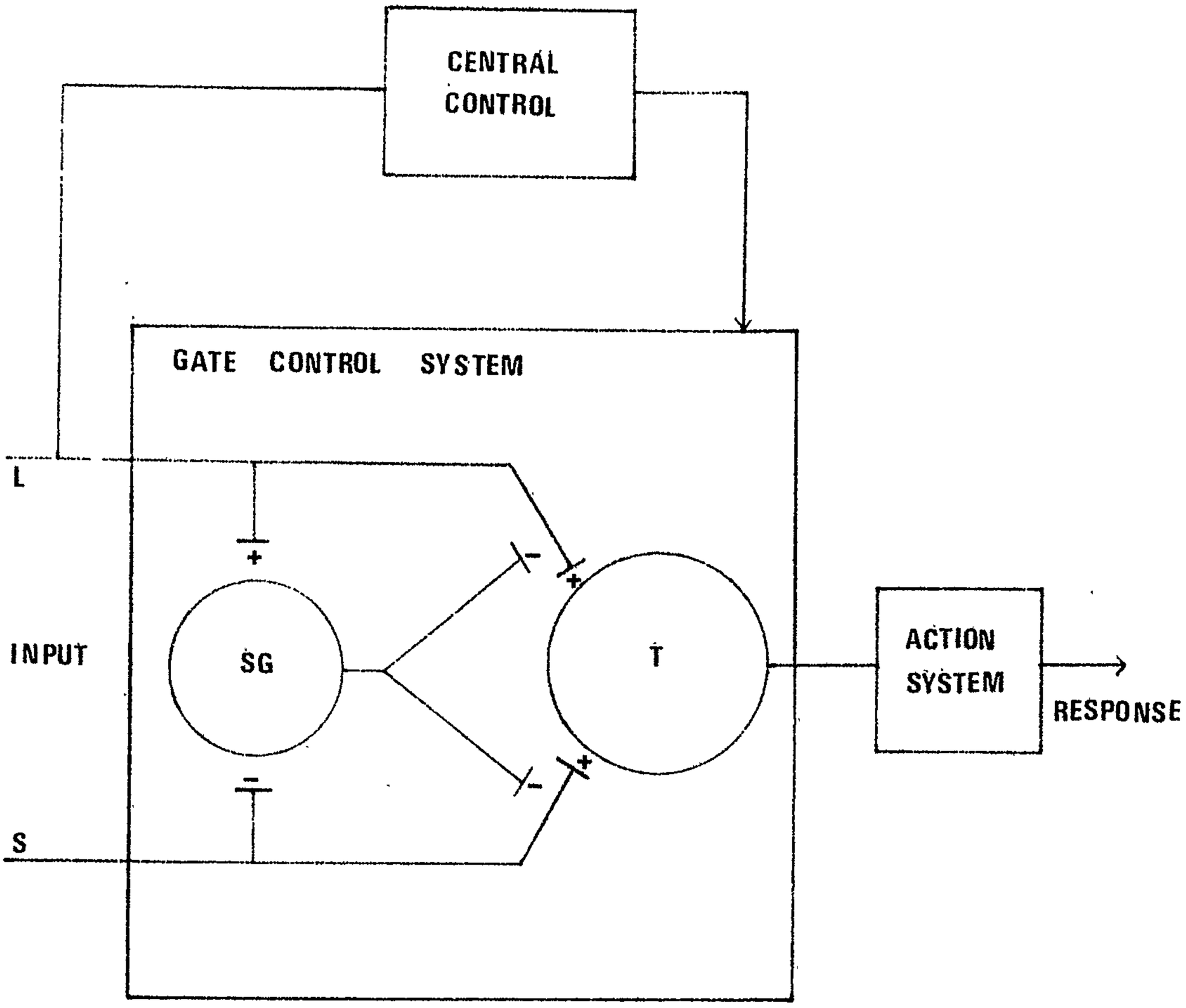

FIG NO 1 AFTER MELZACK AND WALL (1965)

\+ EXCITATION

\- INHIBITION

SG SUBSTANTIA GELATINOSA

L LARGE DIAMETER FIBRES

S SMALL DIAMETER FIBRES

T FIRST CENTRAL TRANSMISSION CELLS

provided in the first chapter to enable an overall picture of pain to be conceptualized.

Against this background, three chapters follow to reveal the more definitive nature of pain mechanisms. After an extensive appraisal of inhibitory processes and the concept of intracerebral stimulation, the thesis arrives at its conclusions which emphasise the major role of inhibition in pain. In the interest of clarity, concise summaries are placed at the commencement of each chapter.

INHIBITORY PROCESSES

There is evidence of a growing awareness of the major contribution of inhibitory processes in pain mechanisms. It is clear, from other evidence, that the body is functionally organised to inhibit neuronal excitability at all levels in the CNS.

According to MELZACK & WALL (1965), a "gate" control form of inhibition operates at the first synapse in the spinal cord. (See Fig. No.1 p. 4). This "gate" is normally held shut by the ongoing activity in large myelinated mechanoreceptive afferents as well as by descending central control mechanisms.

Hence, tonic activity is blocked in small diameter afferents which are presumed to transmit pain. The

hypothesis is that inhibition is removed (i.e. the "gate" is opened) by abnormally severe excitation of the small diameter fibres such as that which would occur in the case of tissue damage. When the summation of impulses passing through the "gate" exceeds a critical level, perception and response occur.

If this hypothesis is assumed valid, then it follows that all sensory information about pain is capable of being inhibited before central interpretation. It is therefore worthwhile to examine where and how this desirable effect can be achieved. It is well known that friction or massage of a bruised or injured part tends to mitigate pain. In addition, electrical stimulation appears to afford relief of chronic pain by excitation of larger myelinated afferents serving areas in which pain is felt. Electrical impulses presumably replace or reinforce tonic inhibitory activity which was partially or totally destroyed by previous neuropathy.

This line of thought leads to the notion that pain is more likely a graded response due to a progressive lack of inhibition rather than an event caused specifically by nervous excitement. A corollary would be that the amount of pain experienced is inversely related to the

degree of inhibition that prevails at the time of stimulation, i.e. pain is less when the level of inhibition is high. The extreme view is that pain is always present unless naturally or otherwise inhibited. For example, removal of normally occurring low grade tactile and temperature inputs from the skin provides a basis for pathological pain states, MELZACK & WALL (1970).

THE CLINICAL SITUATION

In the dental situation, it is known that synthetic processes such as sedation and mood amelioration techniques inhibit nervous excitability. Perceptual modalities, namely, environmental influences, "psyche", cognitive thought, knowledge, and experience alter the response to pain. Additional influences and other affects associated with pain, such as anticipatory phenomena, clinical symbolism, attention and distraction, verbal empathy and rapport, and the psychological significance of oral interference in a close interpersonal relationship, reduce or enhance the "pain" experience. Thus, individual patients react in most part according to the subjective degree of central excitation or inhibition that prevails at the time of their experience.

Because of this delicate sensory balance between neuronal excitation and inhibition, the evidence presented includes current methods which interfere with sensory transmission, or strengthen inhibitory processes, or reduce perceptual awareness of noxious stimuli. The prevention of depolarization by local anaesthetic agents is mentioned only where there is a direct relationship involved with cell membrane mechanisms or with "clinical" pain. The obliteration of conscious pain by general anaesthesia is already well documented and therefore excluded here.

The work of other authors is acknowledged as it occurs, whereas the writer's contributions are not referenced.

CHAPTER I

SUMMARY

1. Discussion on the problem of pain is limited by its subjective nature, its complex neuroanatomical and neurophysiological aspects and by investigator bias which serve to alter its definition.

2. Pain is generally unpleasant. Pain can be protective but also destructive in nature.

3. Increased inhibition may elevate the threshold for perception of pain. Absence of inhibition may result in pathological pain.

4. The subtle difference between threshold perception and perceptual awareness indicates that 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. Amelioration of anxiety, apprehension, and anticipation of stress, together with the strengthening of inhibitory control by conditioning learning and reinforcement procedures, tend to reduce perceptual awareness and thereby increase tolerance of pain.

5. Attention, distraction, suggestion and hypnosis

tend to modify perceptual awareness of pain. Suggestion is often a cause of bias in reports on pain. The placebo effect is generally a measure of individual suggestability level.

6. Sedative and hypnotic drugs have little effect on pain per se but may act to dull perceptual awareness as well as relieve much of the anxiety and apprehension associated with pain. Cerebral depression by intravenous methods involves amnesia and hence the discipline of general anaesthesia. It is an oversimplification to equate anxiety and fear as the reaction component of pain.

7. The wide range of observable physical signs of pain are related to changes in autonomic activity largely governed by stress activated neurohumoral mechanisms engendered by the specific meaning placed on pain by each individual. The subjective level of vigilance may fluctuate according to the meaning of the noxious information. Adrenergic predominance in excited states may serve to dull perceptual awareness of pain. In the dental situation, hidden psychological forces may evoke physical signs of stress which may be incorrectly interpreted as the patient's response to pain.

8. Noxious stimuli counteract sleep mechanisms. Insomnia has been linked with constant pain. Sleep appears to be controlled by an adrenergic mechanism similar in character to the central analgesic mechanism postulated for morphine. Some of the pain relief attributable to morphine activity may be due to the restful sleep that ensues after morphine administration. Low grade electrical and mechanical stimuli which inhibit pain may also promote sleep.

PAIN

DEFINITION

The word "pain" suggests an unpleasant physical event. TABER (1962) states that "pain is a sensation in which a person experiences discomfort, distress or suffering". The Oxford Concise Dictionary defines pain as any mental or physical anguish or distress.

MERSKEY & SPEAR (1967) describe pain as "an unpleasant experience which we primarily associate with tissue damage or describe in terms of tissue damage or both". They propose that the word "pain" is often loosely used to describe physical events which are part of but do not fully constitute the pain experience. They suggest instead, that the word "pain" is used to best advantage when it refers to a psychological state. However, this definition of pain completely excludes many physiological variables including that of the protective function of pain first described by SHERRINGTON (1920) and embodied in the attempted definition by STERNBACH (1968). In addition, LIM, MILLER, GUZMAN and ROGERS (1966) see pain as a chemical sensation which adds to the total proprioceptive body image or "somesthesis", while FROST (1968) views pain as a mathematical type relationship or interaction between the soma and the psyche in

which the sensory and emotional elements of pain contribute in varying proportion.

SOULAIRAC (1968) gives emphasis to the behavioural aspect of pain. He sees pain as an "algic" behaviour phenomena dependent on the level of central nervous system vigilance for its interpretation as either "pain proper or suffering". According to SOULAIRAC this behavioural aspect of pain helps to explain the parameters of adaption, habituation, learning and conditioning in relation to pain. MELZACK & WALL (1965), (1968), describe pain as a "response phenomenon" derived from "gateway" alterations in nervous excitability.

It is evident from the literature that physiologists, biologists and behavioural scientists describe specific modalities of pain but there is little definitive agreement on many of its aspects, partly because of the nature of their professional interest, and partly because pain is never without "emotional colouring", LIVINGSTON (1953).

GENERAL ASPECTS

There are many general factors that contribute to the overall concept of pain and its biological mechanisms. Pain is the most common symptom which impels patients

to seek dental counsel. A patient in pain feels, thinks, and acts differently from a normal individual. It is his toothache and he must be rid of it, sometimes at any cost. Pain is an individual feeling state which tends to develop its own "personality", LIVINGSTON (1943).

It is difficult if not impossible to give adequate attention to every aspect of pain since pain is such a complex problem with so many aspects. It is not possible to see pain as an object or measure it accurately. Pain can exist without apparent cause, or it can be either partially absent, FOX and HUOTT (1974), or totally missing at birth and hence indifferently experienced by the person concerned, STERNBACH (1963), BURDEA (1971). Pain is something of learned reflex, a conditioned process and a perceptual experience.

Pain is cruel and unpleasant; it produces aberrant behaviour, distorts interpersonal relationships, causes anxiety, fear, loneliness and suffering, and interferes with most disciplines of life. Pain impairs concentration; it contributes towards tissue damage and pain is a common cause of suicide and requests for euthanasia. Pain is not just a simple sensory experience but "an affective reaction capable of being added to the

multiple internal or external sensory messages and which is sufficiently intense to attain a behavioural level", SOULAIRAC (1968).

Pain therefore causes widespread physiological upheaval - a 'disruptive personality'.

In the dental situation individual patients react in part according to the subjective degree of central nervous excitation or inhibition existing at the time of their experience. This delicate balance is readily upset by any painful or traumatic experience. Thus, pain alone may destroy the dentist-patient relationship. Hence, the treatment of pain requires a deep knowledge and understanding of the whole toothache experience which embodies in unity both the sensory and the emotional aspects of pain.

THE UNPLEASANT AFFECT

For most people, pain is an unpleasant affect. MERSKEY & SPEAR (1967) report that ARISTOTLE, PLATO and, later, AQUINAS all refer to the unpleasant affect of pain as its relationship to other subjective feelings such as hate, sorrow, mental suffering and pleasure. AQUINAS argued that pain and pleasure were dependent on the senses and hence were different from feelings of joy

and grief which seemed to stem from internal awareness and knowledge. He proposed that pain and pleasure could exist in relation to the same object but were contrary in aspect one to the other.

LEONARDO DA VINCI supported the belief that pain was the antithesis of pleasure since he depicted the two sensations as twins inseparably joined but facing in opposite directions.

This co-existence may explain how pain is used by

(1) Masochists as a means to obtain erotic pleasure and

(2) Sadists as a tool for pleasure,

MERSKEY & SPEAR (1967)

PAIN AND BODY PROTECTION

Protective effect

LIVINGSTON (1953) refers to the protective mechanism of pain where pain follows muscular and visceral reflexes as the third line of body defence. Pain, a common symptom of disease, functions "as an early warning system indicating tissue damage", DUNDEE (1967). Often this warning arrives too late, the damage has already been done and the tooth is lost.

It is generally held that, whatever the cause of pain, the response within the organism is one of preparation to take any necessary action to avoid or escape tissue damage.

The so called "flight and fight" syndrome.

Destructive effect

Pain itself may produce a destructive biological cycle by setting up "protective reaction patterns" characterised by physical and physiological changes symbolic of pain avoidance.

WOLFF & WOLF (1958) propose that persistent pain causes bodily impairment through this cycle. For example, the contraction of the trunk muscles, as a result of pain, is potentially lethal in patients suffering chronic bronchitis or bronchiectasis, BROMAGE (1967). LIVINGSTON (1943) states about pain " . . . it frequently exceeds its protective function and becomes destructive. The impulses which subserve it are not pain, but merely a part of its underlying and alterable physical mechanisms". In 36 experiments of 10 minute dental stimulation WOLF (1963) observed extension of pain and vasomotor disturbances to areas remote from the tooth. KAWAMURA (1968) describes a viscious cycle of pain derived from dental stimulation. (See Fig. No.2 p. 18)

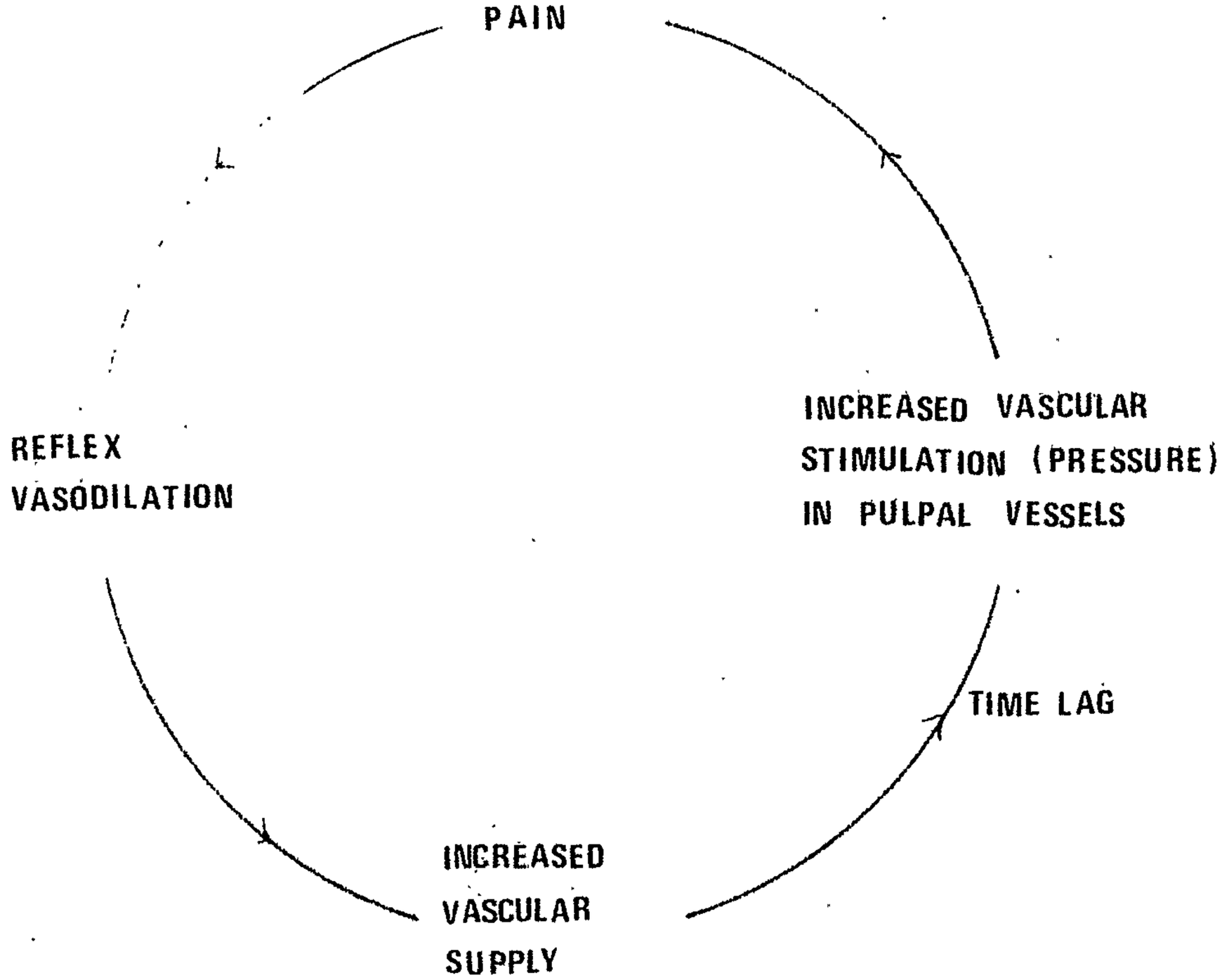

FIG NO 2 DENTO-VASCULAR PAIN CYCLE

PAIN COINCIDES WITH CARDIAC SYSTOLE

The far reaching effects of pain become more evident when recurrent deep pain from oral structures is left untreated, secondary "internuncial cycling" leads to intractable central pain which is unresponsive to peripheral therapy and which often requires referral to a neurologist for treatment, BELL (1967).

Secondary effects dependent on the type of neuronal excitation therefore include areas of hyperalgesia, referred pain, autonomic effects, and myospasm which may continue to cycle after the original pain stimulus had been removed, BELL (1968).

A reflex myospasm evoked by noxious stimuli may itself become painful due to the development of ischaemia and the release of endogenous pain producing substances such as substance p and lactic acid, LEWIS (1942).

The clinical diagnosis is made more difficult in instances when this soreness in the muscle becomes more severe than the original pain that provoked it, MOUNTCASTLE (1974).

(PHYSICAL MANIFESTATIONS)

It is evident from the literature that there is a range of physiological manifestations which are

interpreted as the individual's physical reaction to pain. These manifestations vary from person to person and in each individual from time to time. These reactions appear to be in part mediated by the "flight and fight" syndrome, and partly by the reaction of the adrenal cortex to "stress", both of which are under neural and chemical control through the hypothalamus, SELYE (1946), (1957). (See Fig. No.3 p. 21)

Physiological manifestations include:-

Pallor, flushing, increased or decreased heart rate and strength, increased or decreased respiration rate, variation in facial expression such as grimacing or complete lack of expression, eyeball reactions, erector pili reactions, mental excitation or depression, alterations to muscle tone, ocular muscle reactions, alterations to pupil size, crying, weeping and emotional phenomena such as belligerence and resistance, and alterations to the splanchnic vascular bed leading to syncope reactions.

The great variety of responses is an indication of the wide difference in individual interpretation and proprioceptive meaning, e.g. superficial or deeply located pain. The meaning placed on pain is a function

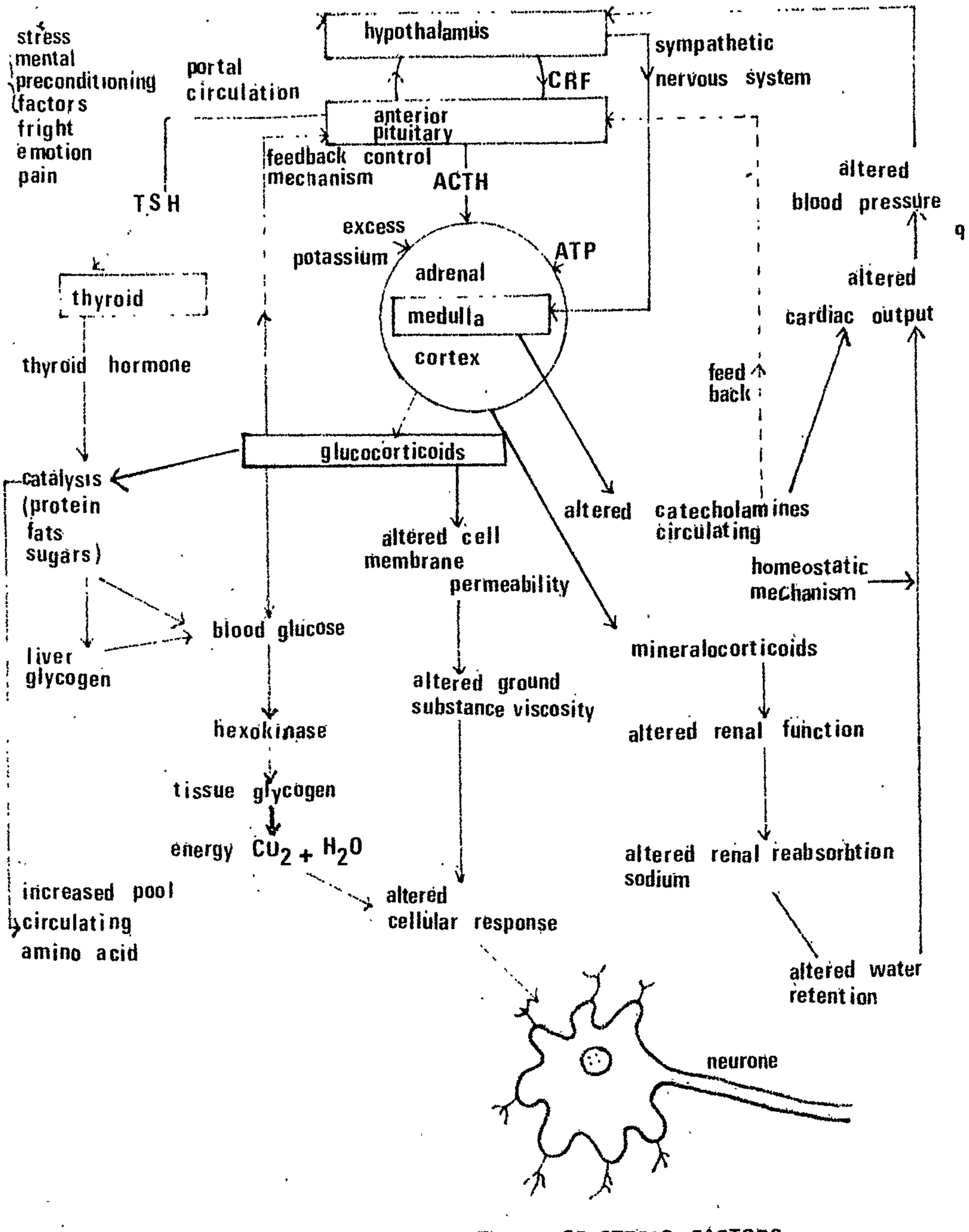

FIG NO 3 SIMPLIFIED REPRESENTATION OF STRESS FACTORS AND THEIR BIOLOGICAL EFFECTS

of central processes which determine the intrinsic level of alertness or "vigilance" of the body response to noxious integrated stimulation. (See Fig. No.4(a) p. 23)

ANATOMICAL MODEL OF AROUSAL SYSTEM

MOUNTCASTLE (1974) ascribes the transmission of pain to be essentially but not exclusively achieved by the neural elements of the anterolateral spinal tract. Apparently, afferent activity in the dorsal column exerts a "conditioning" effect via the lemniscal system without direct activation of the ascending pain pathways. In this model (see Fig. No.4(b) p. 24), the central projection on the forebrain of the lateral and medial components of the anterolateral column is achieved by 3 fibre systems, namely, the neospinothalamic system (lateral), the paleospinothalamic system (medial), and the generalized thalamocortical or spinoreticulothalamic system (medial). Sharp pricking pain or localised sensation is presumed to be carried by the neospinothalamic system which projects to the cortex via connections with the dorsal thalamus whereas burning pain or diffuse sensation (suffering) is carried by the phylogenetically older medial components of the anterolateral tract which projects upon

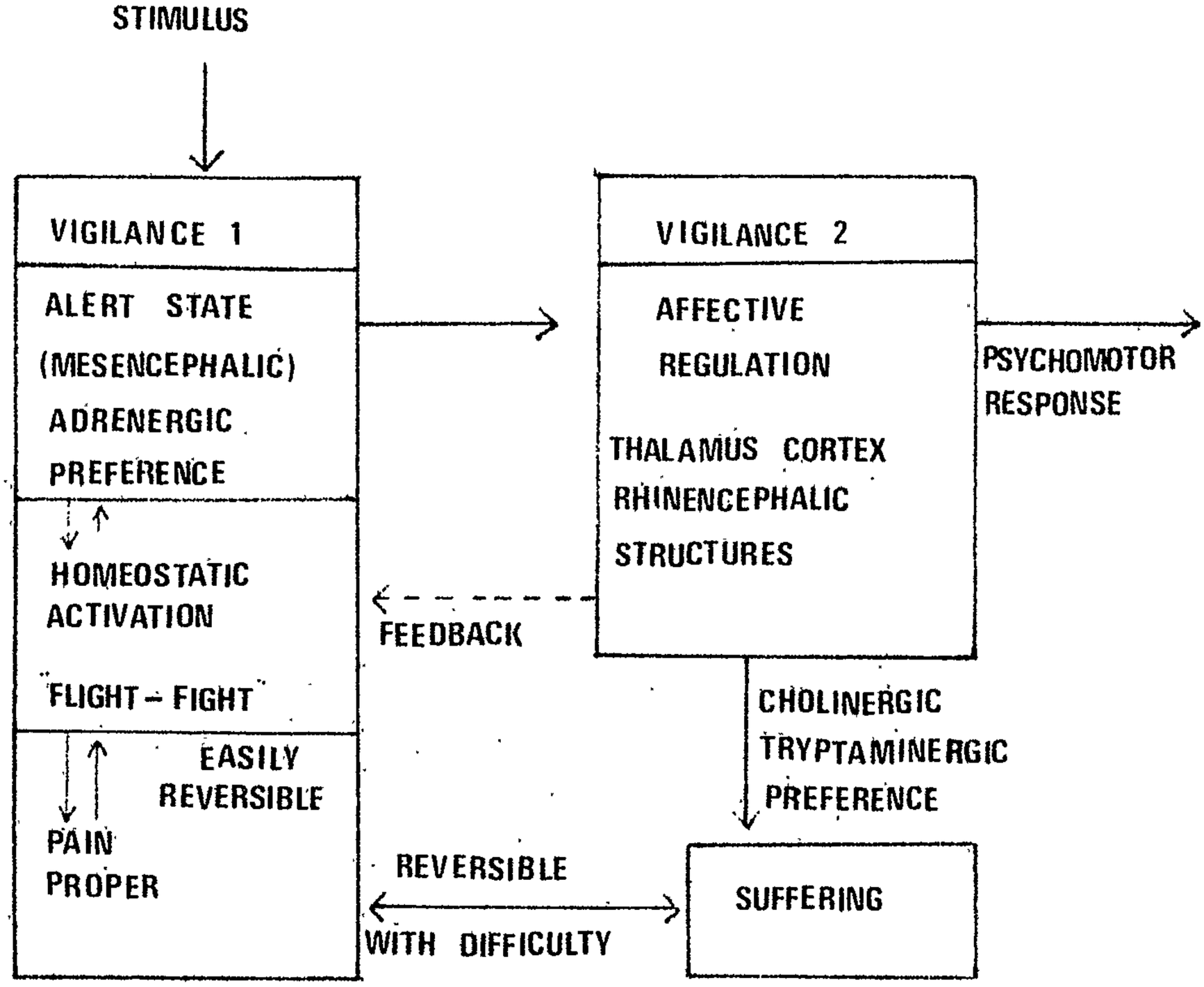

FIG NO 4(a) VIGILANCE. DERIVED FROM SOULAIRAC (1968)
(PAIN → SUFFERING ONLY AFTER PASSING FROM LEVEL 1 TO LEVEL2)

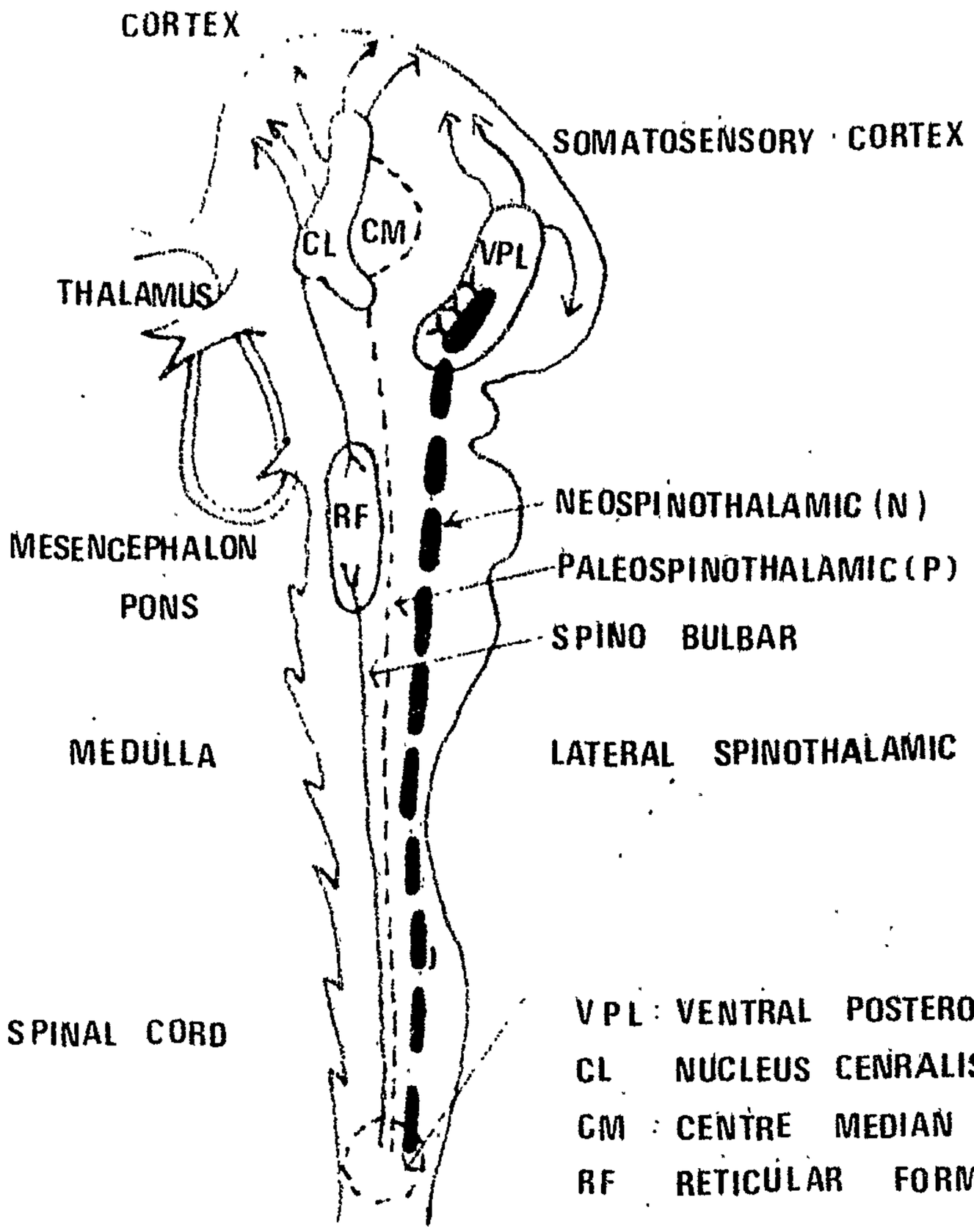

FIG NO 4 b

Simplified illustration of ascending fibre projections of the anterolateral system in man. Only one third of all fibres reach the thalamus. Projections of N, and P upon medullary and pontine nuclei and upon periaqueductal gray matter are omitted.

Modified from Mountcastle (1974)

the generalized thalamocortical system, the ventral thalamus, and the hypothalamus.

The medial system is thought to be responsible for arousal, affective reaction and autonomic activity. In this model, therefore, the alerting system is via the spinobulbar and paleospinothalamic tracts.

VIGILANCE

Observation of the physiological responses to electrical stimuli of different intensity in rats led CHARPENTIER (1968) to conclude that there are two separate systems of vigilance in dynamic equilibrium, one with the other, namely:-

1. Basal vigilance - classical reticulo cortical - predominantly adrenergic at pain perception threshold (PPT) level.

2. Affective vigilance - Rhinencephalic - predominantly cholinergic at high intensity stimulation approaching pain tolerance threshold (PTT).

CHARPENTIER suggests that these two integrative levels, together with alertness of the frontal cortex which is

presumed to be responsible for spatio-temporal analysis of stimuli and in intellectual integration, provide three distinct levels for the CNS integration of pain. (See Fig. No.5 p. 27)

The dental situation

It is of interest that many of the physiological reactions to the dental clinical situation seem to fit into the "flight and fight" pattern of responses or first level vigilance. Changes in autonomic activity are sometimes clearly evident in cases where a simple extraction inadvertently becomes a surgical manoeuvre with more meaningful sequelae. Clinical signs of sympathetic discharge evoked by sudden pain include a measurable increase in blood pressure, increase in radial pulse (tachycardia), pallor due to peripheral vasoconstriction, dilatation of the pupils, and increased sweat gland secretion. An interesting aside is that sweating may be accompanied by a measurable change in the electrical resistance of the skin - the galvanic skin reflex which can be used as an indicator of the "alarm reaction" or the affective state of each individual, MOUNTCASTLE (1974).

Physiological responses to pain are akin to those evoked by anger and fear as a result of changes in dynamic

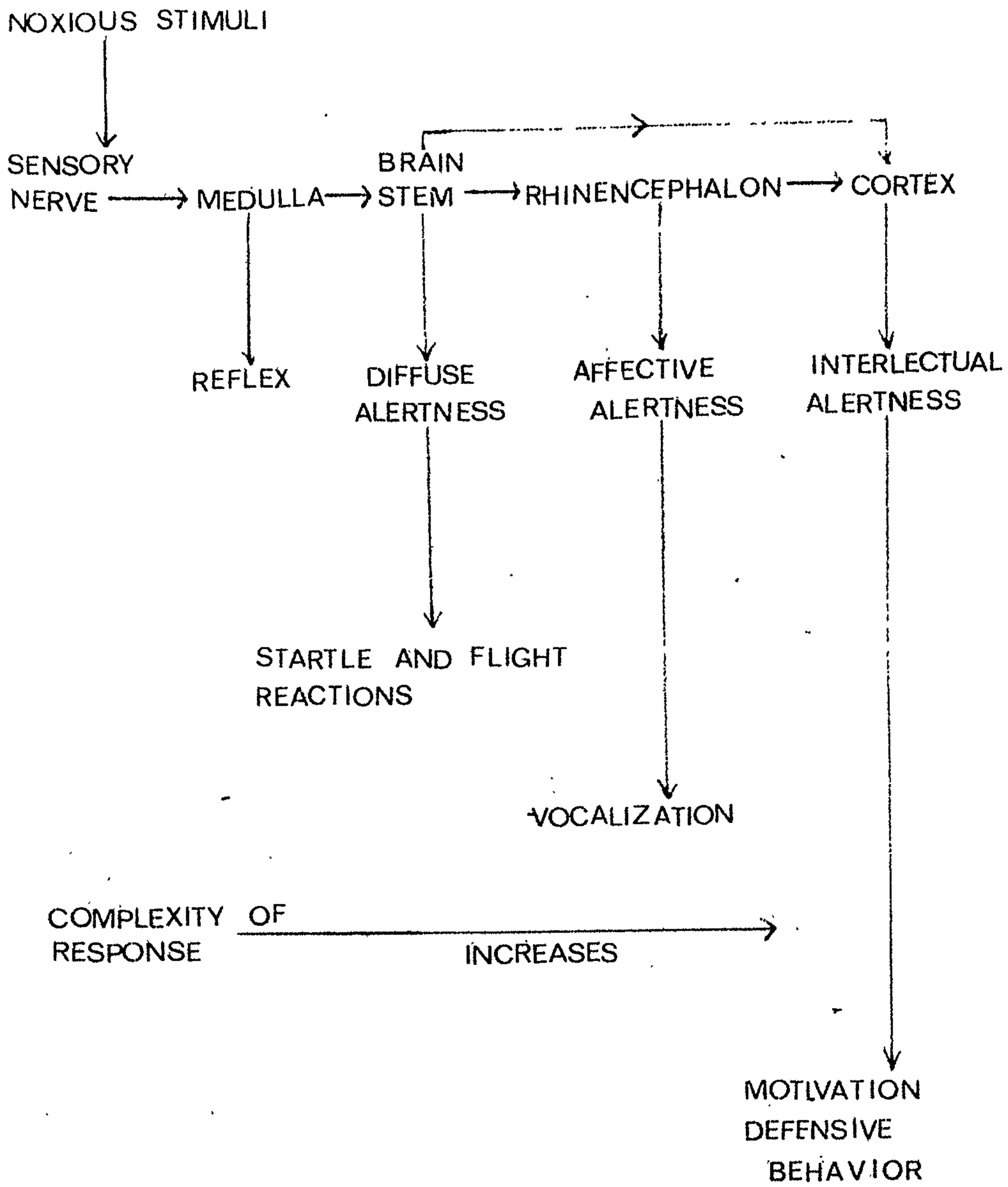

FIG NO 5 MODIFIED FROM CHARPENTIER (1968)
COMPLEXITY OF RESPONSE AS TRANSLATED BY NEURO ANATOMICAL LEVEL AFFECTED BY NOXIOUS STIMULI.

equilibrium of the para-sympathetic and sympathetic systems, STERNBACH (1968).

Increase in circulatory adrenaline due to peripheral sympathetic dominance helps to reduce blood flow after injury, STERNBACH (1968). This catecholamine release in excited states,such as fear experienced in battle, makes the individual less aware of the pain, DUNDEE (1967). Similarly, clinical experience reveals that highly excited young dental patients appear to suffer minimal pain when a deciduous tooth is removed without local analgesia.

MELZACK & WALL (1968) attribute this apparent lack of awareness to pain in excited states, such as fear and anxiety, to the influence of selective central control processes on sensory input,

i.e. the central control trigger is activated to close the "gateway" for pain.

Physical reactions are often misleading. In the final analysis one must rely upon the assessment by the patient that his pain is either greater or less as conditions change, HOUDE, WALLENSTEIN, AND BEAVER (1965).

CONVERSION SYMPTOMS

It is believed that many of the overt signs of pain may be related to hidden psychological factors associated with oral interference.

GIDDON (1966) suggested that noxious environmental stimuli in acute and chronic stress situations may be mediated by either volitional (somatic) or non volitional (autonomic or via the endocrine system) pathways to produce disease states such as acute necrotic ulcerative gingivitis. Other physiological manifestations, such as weeping and hysteria that may occur clinically in stress situations, may also be derived from psychological sources, as each individual attempts to maintain self security by adjusting to earlier levels of behaviour, CINNOTTI & GRIEDER (1964).

It would seem that the physical signs of dentally produced anxiety and fear may be due to physiologic conversion symptoms (fight - flight - syndrome) derived in part from psychological processes. When these physiological responses occur they are generally symptoms of stress derived from conscious or unconscious fear of oral damage, MARTIN (1965), (1967).

This notion is consistent with the proposal of

SOULAIRAC (1968) that central psychological processes may be responsible for the internal conversion of pain at first level vigilance to suffering at second level vigilance.

PAIN PERCEPTION THRESHOLD

WOLFF & WOLF (1958) held that the intensity of noxious stimulation required to elicit pain varied within very narrow limits (pain perception threshold, PPT) from person to person but that the meaning of the painful sensation (perceptual response) was subject to wide individual variation.

Despite other supporting evidence, MONHEIM (1965), the recent weight of opinion indicates that:-

1. PPT varies significantly with age and sex and follows a demonstrable circadian and circatriginton rhythm, the latter being an "expression of central rhythmic activity, presumably linked to hypothalamic - limbic circuits, common to both sexes and present also in old age, which in the young female is also revealed by the menstrual cycle and is not interrupted by pregnancy", PROCACCI, DELLA CORTE, ZOPPI, ROMANO, MARESCA, and VOEGELIN (1974).

2. Radiant heat and electrical stimulation are more acceptable methods of determining PPT than other methods

which include the submaximum effort tourniquet technique devised by BEECHER and his co-workers, SMITH, LOWENSTEIN, HUBBARD, and BEECHER (1968), BEECHER (1966).

3. PPT measurement is graded according to an individual's verbal response which is the "primary source of information about pain", KEELE (1966), BEECHER (1968).

4. Since there is only a semantic difference between PPT for pricking pain and PPT for burning pain, it is best to describe PPT as cutaneous pain threshold (CPT).

The fact that PPT can be elevated makes pain different from the other common modalities of the senses,such as sight, smell, vibration, touch and hearing.

PAIN TOLERANCE

It is clear that an upper limit of endurance or pain tolerance threshold PTT is reached when pain from an applied stimulus becomes unbearable. This level of tolerance is distinct from the pain reaction threshold (PRT) obtained only with radiant heat. PTT varies widely between individuals, and in the same individual from time to time, dependent on disease states such as diabetes, liver cirrhosis and advanced ischaemic

neuropathy, PROCACCI et al (1974). PTT is also influenced by personality traits, for example perceptual reducers, STERNBACH (1968), and other perceptual inputs, reviewed by GRAINGER (1972a), which alter the meaning of the experience.

MEASUREMENT OF PAIN

Whereas the threshold for perception of pain (PPT) may be measured with some degree of accuracy by radiant heat or electrical methods, the precise degree of pain experienced or the perceptual reaction so far remains immeasurable. In spite of over 20 years experience BEECHER (1968) found pain difficult to measure in quantitative and qualitative terms as a result of the following rationale:-

1. Interposition of psychic factors.
2. "Quantitative assessment of subjective magnitude".
3. Absence of "dependable facts".
4. Presence of "elusive variables".
5. Difficulty in linking observations made in animals with those made in man.
6. Pain threshold inadequate as an "end point" for investigation. Criteria

derived from subjects in slight
pain less reliable than data educed
from subjects at higher pain levels.

Using the submaximum tourniquet method, BEECHER claims some measure of success in that highly significant ($p<0.001$) dose response curves confirmed that pain responds dependently when 10 mg morphine is administered intravenously - pathological pain always being less in the presence of morphine.

Evaluation of mild analgesics using the same method indicates that aspirin-like drugs interfere with the sensory discriminative effect of pain but have little effect on the motivational affective system or "hurt" in pain, ADLER & LOMAZZI (1974).

A survey of direct and indirect methods of measuring pain experimentally, HUSKISSON (1974), indicates that measurement of pain relief using a visual analogue scale may be a more sensitive and reliable method of assessing response to medication than measurement of pain severity using a simple graphic rating scale.

As far as measurement is concerned, it would seem more accurate to employ the 22 step (2 steps = 1 dol) dol system of HARDY, WOLFF and GOODELL (1947), (1967), than

to use the 0 - 4 scale intensity method advocated by KEELE (1966).

FACTORS MODIFYING PERCEPTION

EMOTIONAL FACTORS

GRAINGER (1972a) pointed out the subtle difference between PPT and perception in pain mechanisms. This difference between the affect of pain and the effect of sensory disturbance is mainly due to the specific capacity of each individual to interpret the information supplied, WYKE (1958), LIVINGSTON (1953) - "Reaction to Pain", BEECHER (1962).

Emotional factors such as anxiety and fear are critical determinants of the nature and intensity of the pain experience, BEECHER (1956), (1959), particularly in the dental situation, GRAINGER (1972b), wherein the nervous system is sensitized, JORGENSEN & HAYDEN (1972), because of the increased psychological significance of oral interference, MARTIN (1965), GIDDON (1966), and stressful anticipatory phenomena, LAZARUS (1966), which may raise unconscious fears, MARTIN (1965) and (1967), capable of magnifying the pain experience, LEWIS (1957).

Experimental evidence, SHANNON & ISBELL (1963), SHANNON, ISBELL and HESTER (1963), supports the concept that the

mere threat of dental treatment is sufficient to arouse suppressed emotional responses measurable, at least in part, by significant changes in blood 17-Hydroxycorticosteroid.

In patients requiring oral surgery, the degree of stress is proportional to the severity of the operation but stress is greater before than during the procedure, SHANNON, SZMYD and PRIGMORE (1962). Hence, anticipation of an event often magnifies the actual experience in terms of stress, unless the meaning of the stimulus can be altered by conditioning, learning, and reinforcement, or by other means of varying the stimulus response relationship before, during, or after the event, MACKENZIE (1968).

LEARNING AND CONDITIONING

BEECHER (1962) held that experimental pain was regarded just as seriously by animals as pathogenic pain was regarded by man. MELZACK (1961) showed that dogs reared in isolation exhibited less sensitivity and awareness to painful stimuli such as a naked flame or pin prick. He attributed this response to the lack of past exposure to pain and therefore to insufficient knowledge and experience of its unpleasant affect. PAVLOV (1927) found that dogs could be conditioned to interpret painful

electric shocks applied to the skin and superficial structures as a signal to eat. In contradistinction, the same dogs, when given shocks of greater intensity to deeper bony structures, interpreted these noxious stimuli as a dangerous threat, and therefore reacted in a defensive manner and refused to eat. This extra-ordinary behaviour is evidence that the meaning of pain may be changed in certain circumstances. Reflexes, habits and motor acts largely depend on neuronal circuits laid down in early life as a result of learning, conditioning, and training, SAMPSON WRIGHT (1965).

Other factors

Data from other animal experiments, MAYER & LIEBESKIND (1974), indicates that electrical relief of pain (Stimulation Produced Analgesia) (SPA) is not causally related to reward or pleasurable sensations. Thus, relief of pain may not result merely by using rewards to divert attention from pain.

MEARES (1967b) proposed that pain could be so modified by auto-suggestion and self conditioning, that the pure sensation, i.e. pain without emotion or "hurt" in it, could be readily endured. The concept that emotional factors influence pain perception is further strengthened by the well known fact that prefrontal lobotomy

appears to eliminate or relieve the distress associated with pain without changing the patient's personality, MARTINEZ, BERTRAND, NEGRO, and PEREZ-CALVO (1975), - pain is felt but it no longer appears to be of any great concern. An interesting connection is that morphine appears to produce the same "dissociated" effect, GOODMAN & GILMAN (1966), also akin to the effect produced by the psychophysiological mechanism of hypnosis, WEST (1960), BENSON (1972).

SUGGESTION HYPNOSIS AND DISTRACTION

The amelioration of pain by suggestion hypnosis and distraction is well documented by BARBER & HAHN (1962), (1963), who showed that suggestion was just as effective as hypnosis in reducing physiological responses to noxious stimuli.

BARBER (1963) points out that suggestion alone may be the powerful factor that motivates pain relief and that hypnosis may play a secondary role in states of "hypnotic analgesis" for three (3) reasons, namely:-

1. The close interpersonal relationship may influence the desire of the patient to please and therefore motivation is increased to deny the existence of pain.

2. Some patients experience temporary amnesia to pain during hypnosis.

3. Pain is rarely abolished in operations where hypnosis alone is employed for pain relief.

These three factors also apply to hypnosedation techniques, SARA (1974), wherein relief of anxiety relies heavily on suggestion, personal attention, and communication of a confident attitude to the patient.

Hence, suggestion may enhance or reduce the perception of pain, often creating bias in scientific reports on pain.

DISTRACTION

"White Sound", GARDNER & LICKLIDER (1959) and other methods of audioanalgesia reviewed by MOROSKO & SIMMONDS (1966) have been shown to reduce perception and increase tolerance levels to pain. Success of these methods also rests heavily on suggestion since white sound used alone is ineffective, MELZACK, WEISZ and SPRAGNE (1963).

Suggestion can inhibit fear, LANG, LAZOVIK and REYNOLDS, (1965), especially when used in conjunction with

regulated hypnotic training sessions specifically designed to counteract individual anxieties, LANG (1966).

Recent evidence, MELZACK & PERRY (1975), suggests that chronic pain intensity may be reduced by up to 33% in most cases by combining "placebo effects" such as distraction, attention, suggestion and anxiety relief with "gadgetry" such as audio analgesia or EEG alpha training involving hypnosuggestive feed back signals. This indicates that pain can be autoregulated to an extent dependent on the amount of knowledge and control each individual can exert over his pain experience.

FACTORS MODIFYING PERCEPTION

OTHER PSYCHODYNAMIC FACTORS

Other psychic influences such as emotional status, present mental attitude, memory association, past experience, personality and cultural and social factors are closely linked with pain mechanisms, STERNBACH (1968), and influence the severity of post operative pain, LOAN & MORRISON (1967).

STERNBACH and TURSKY (1965) demonstrated significant cultural and ethnic variations in pain perception by administration of electric shocks to 60 paid housewives of different nationalities, namely, American (Yankees),

Jews, Italians and Irish. ZISKIN and MOULTON (1946), found that 92.86% of their patients who reported persistent orolingual pain actually suffered emotional disturbance. Other bizarre psychological disorders that may result in psychogenic pain for which there is no demonstrable pathological source have been well described by MERSKEY & SPEAR (1967).

STRUCTURAL FACTORS

SOMATO SENSORY APPARATUS

BOWSHER & ALBE-FESSARD (1962) describe two basic forms of somato sensory apparatus, namely, the "discriminative system" which is phylogenetically recent and the "non-discriminative" which is older and incompletely understood. LEE & ATKINSON (1964) refer to these two systems as:-

(a) Lemniscal - (Classical) - provides sensory discriminative evidence of pain.

(b) Extra-lemniscal - (Paramedial) - provides motivational forces, aversive drive.

These two systems are distinctly separate below the level of the cortex and act independently. MOUNTCASTLE

(1974) specifically relates the word "lemniscal" to the dorsal column system thereby excluding the direct application of this term to the transmitting apparatus for pain. The classical and paramedial systems embody the neural elements of the anterolateral tract described earlier. (See Fig. No.4(b) p. 24). Therefore, the word "lemniscal", when used in the context above, is actually a misnomer which serves only to indicate the semantic differences that may occur in various anatomical models of pain pathways. It is the anterolateral system which transmits pain, temperature and crude touch sensibility to the reticular formation and higher centres.

THE RETICULAR ACTIVATING SYSTEM (RAS)

The reticular activating system (RAS) in the brain stem has been implicated as a perceptual modifier of pain, GANONG (1971) since ascending pain carrying fibres communicate with or are channelled through the reticular formation, BOWSHER & ALBE-FESSARD (1965). Some primary afferent trigeminal fibres may enter the reticular formation directly, CLARKE & BOWSHER (1962), a factor previously confirmed by TORVIK (1956). Since sensory information appears to be collated at this level, and since pain is a potent arousal stimulus

experienced only when awake, the intensity of pain as a sensory and perceptual experience obviously depends on the activity of the RAS.

CORTICAL PERCEPTION

Cortical lesions and other experimental interruption of central pathways tend to decrease the appreciation of pain but do not abolish perception, GANONG (1971). This suggests that some perception takes place at a sub cortical level, although thalamic destruction produces abolition of pain on the opposite side of the body, WISE (1966a), and thalamic depression tends to elevate pain threshold, MONHEIM (1965). It is clear that cortical integrity is important in pain perception, LEE & ATKINSON (1964), and location of painful stimuli, VYKLICKÝ & KELLER (1973), but to attribute the sensation of pain to the crude interpretation of the thalamus and perception to the cortex is to take "too narrow a view of a complex functional interrelationship", WISE (1966a). Preliminary conclusions drawn from EEG changes in chronic pain sufferers, LEWIS, KIRSCH, LAQUE and GREENE (1975), also support the concept of a "thalamo-cortical activation model of pain". Since it is known that lesions of certain thalamic regions produce intractable pain ("thalamic syndrome")

it is likely that one function of the thalamus is to co-ordinate the flow of excitatory and inhibitory impulses along pain pathways at this level in the CNS.

THE PLACEBO RESPONSE

The use of chemically inert substances in clinical trials of pain relieving drugs is a well known technique. The response produced by these substances is variable. In the main, the question of the placebo response remains unanswered. Those who react favourably to placebos have been labelled as "placebo reactors", HOUDE (1974). BEECHER (1955) found that the average significant effect of placebos was 35.2 $\pm$ 2.2% in studies of 1082 patients. He noted 35 different tonic effects and showed that placebos were more effective in situations where there was increased stress. BLAIR (1965) recorded a percentage increase in pain perception threshold in ten dental students in whom he administered placebos. He observed the placebos raised the threshold of pain perception, especially when administered in an atmosphere of confidence, and found that in some instances placebos acted as psychotherapeutic agents. Psychological testing shows that placebo reactors are, in the main, well adjusted and normal people, LASAGNA, MOSTELLER, VON FELSINGER and BEECHER (1954), not consistently found in

volunteer groups, LASAGNA (1962). BEECHER (1960) showed that distress and anxiety resulting from pathological pain (34%) were relieved ten times more effectively by a placebo than stress derived from experimental pain (3.2%). He concluded that placebos as "active" drugs were more effective when stress was present and, therefore, the efficacy of placebos was directly proportional to the quantitative psychological stress. Hence, pathological pain is more stressful than experimentally contrived pain. There is no doubt at all that the placebo is active, WILSON (1962). BARBER (1960) showed that the confident approach of the operator influences the placebo response, since the patient believes that his pain will be less, or that the placebo actually works, SADOVE (1963). It is equally evident, however, that the same approach can achieve significant results without the use of the placebo. For example, the patient's pain is always less when it is known that treatment has commenced. An illustration is the reasonably common statement: "My toothache is gone, it left as soon as I arrived here".

Thus, the response attributed to placebos may be a measure of the level of suggestibility. HOUDE (1974) also suggests that placebos may be utilized to measure base line changes in pain intensity during courses of medication.

THE EFFECT OF SEDATIVES

Since it is only possible to reduce physiological "pain" syndromes of maximum intensity by 75%, WOLFF & WOLF (1958), it follows that any further attempt to diminish the perception of pain must naturally be directed towards its emotional dimensions.

It is generally accepted that hypnotics and sedatives have little effect on pain threshold except in doses which produce unconsciousness, FOSTER (1966), despite evidence to the contrary in 50% of cases, KEATS & BEECHER (1950). Intravenous barbiturates such as Pentothal Sodium and Methohexital (Brietal Sodium) administered in sufficient dosage abolish conscious appreciation and memory of pain, but at the level of surgical anaesthesia the transmission of sensory impulses from the site of stimulation to the brain is not completely impeded, SOMJEN (1967), i.e. operative pain is received but not interpreted or remembered. WILSON (1974) argues that the use of regional anaesthesia instead of light general anaesthesia involving nitrous oxide and muscle relaxants may avoid a harmful chain of events (exhaustion, wound pain, phantom limb, disturbances of water and electrolyte balance) liable to occur in the post operative period

as a result of the unimpeded passage of these noxious impulses.

The amnesic point is the critical determinant of an anaesthetic state since any drug which produces a state of diminished responsiveness and amnesia is an anaesthetic drug, WINTERS, MORI, SPOONER and BAUER (1967). Hence, the level of depression necessary to relieve anxiety and fear associated with pain should not exceed that point at which amnesia begins unless, for some other reason, amnesia is desirable.

INTRAVENOUS SEDATIVES

CLUTTON-BROCK (1960) suggests that mild doses of intravenous sedatives administered in the presence of pain may produce a state of "antanalgesia" wherein conscious appreciation of pain and reactivity to noxious stimulation may be heightened, presumably due to loss of central control. It is notable that intravenous antisialogogues produce the same atanalgesic effect, DUNDEE, NICHOLL and MOORE (1961), DUNDEE, MOORE and CLARKE (1964). WISE (1966b) proposes that this atanalgesic effect may explain the post operative restlessness often seen in children who have been premedicated with barbiturates.

It would seem that a paradox exists. On one hand, sedatives do not relieve existing pain. On the other hand, when pain is experienced it is often less due to the amelioration of anxiety and fear by prior sedation. The solution to the problem may be in the argument that sedatives reduce anxiety and fear but, at the same time, by virtue of their depressive action on conscious control, release unconscious elements which do not affect the level of pain to any extent but simply appear to magnify the pain experience.

The fact that sedatives sometimes inhibit synaptic activity in a generalized way, GANONG (1971), tends to preclude arguments for the release of corticofugal inhibition as a rationale for increased pain. Since effective anxiety relievers (e.g., tranquillizers, barbiturates, meprobamate) are not good analgesics, and since the defensive behaviour and withdrawal reflexes associated with noxious stimulation differ from reactions elicited by anxiety or apprehension, GOODMAN & GILMAN (1966) suggest that it is an "over-simplification" to equate anxiety and fear with the theoretical reaction component of pain. This evidence further indicates the complexity of the emotional response associated with pain mechanisms.

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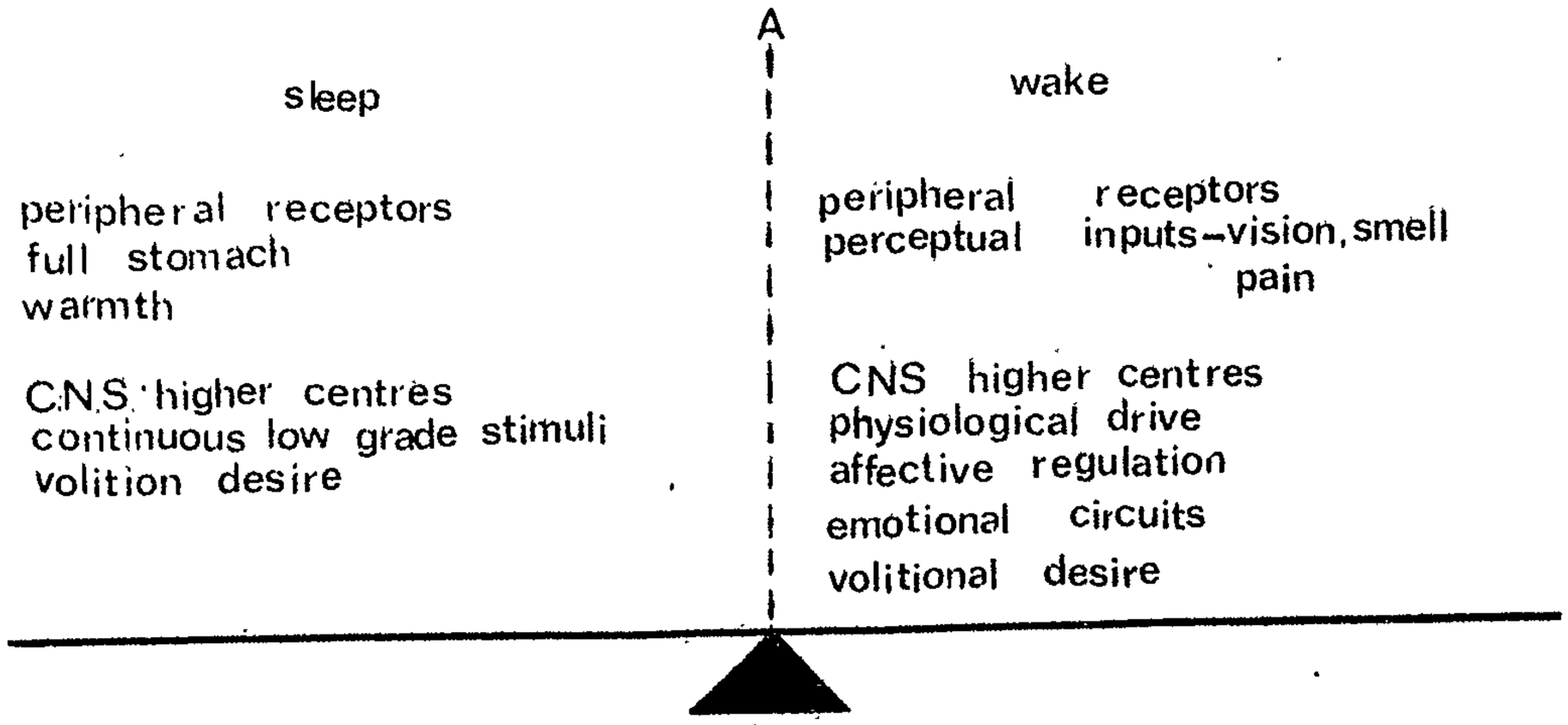
PAIN, SLEEP AND PERCEPTUAL AWARENESS

A sleeping individual is more easily aroused by pain than by any other sensory stimulus, LIVINGSTON (1953), presumably due to the potent excitatory effect of pain on the reticular activating system (RAS), DELGADO (1955), alerting impulses being projected to the neocortex by the non specific projection nuclei of the dorsal thalamus.

The RAS is sensitive to changes in the "spontaneous wake-sleep cycle "as well as to anaesthetic drugs, WINTERS et al (1967). Continuous stimulation of the wake system by emotional or sensory stimuli, such as pain, may cause insomnia. (See Fig. No.6 p. 49)

ROLE OF BIOAMINES

As far as sleep is concerned, this complex arousal system is influenced by the activity of the biogenic monamines, in particular, serotonin (5HT) and noradrenaline--The Neurohumoral theory (NHT), JOUVET (1967), (1969). Briefly, the theory suggests that serotonin from brain stem midline raphe nuclei stimulates light sleep whereas noradrenaline secreted within the locus coerulus of the pons is responsible for the onset of deep or paradoxical sleep. Both amines



A anatomical concept of wake – sleep balance.
B insomnia from emotional causes ——→
C insomnia due to pain - - - - - - →

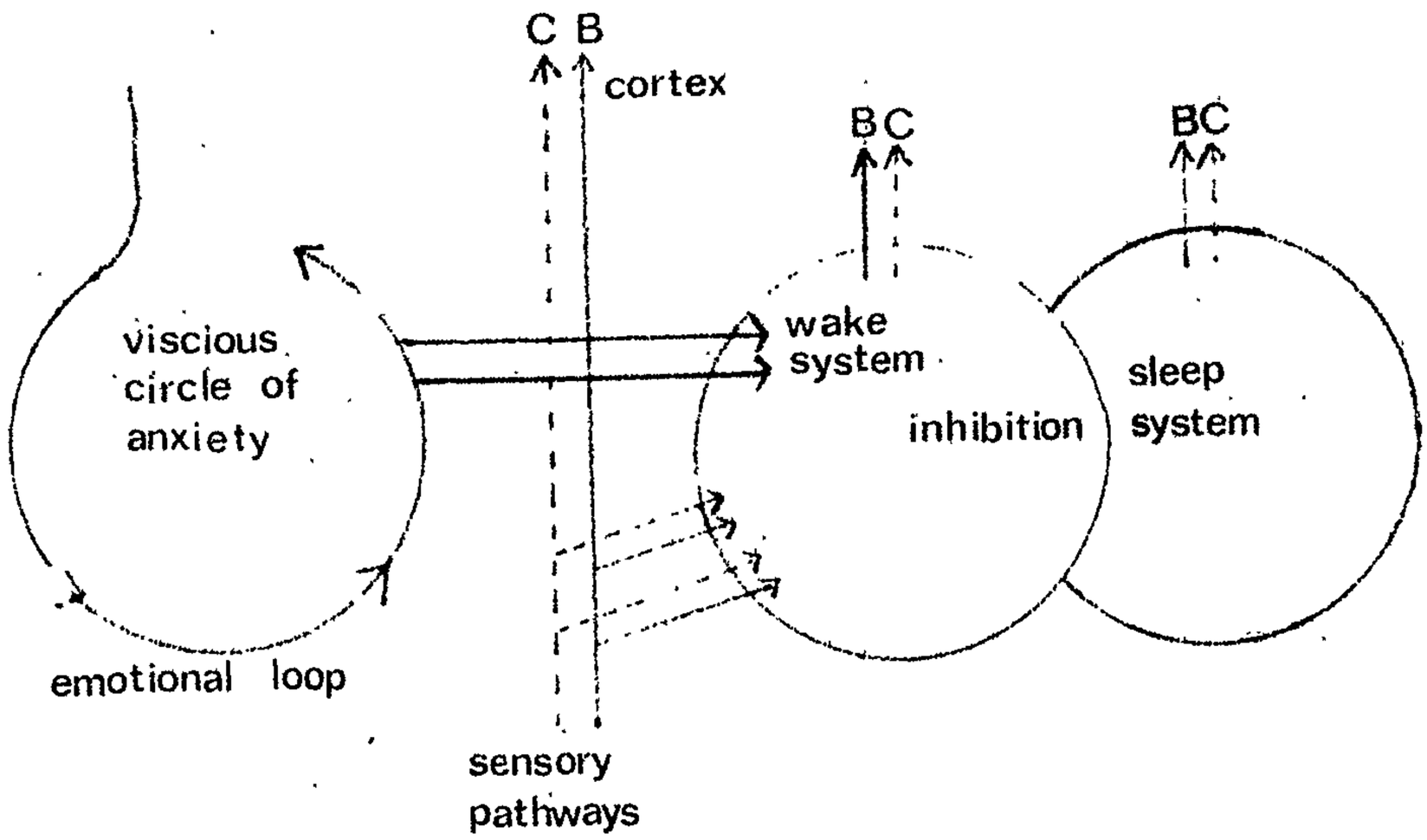


FIG NO 6 Insomnia
(derived from concepts of sleep) Laroche (1969)

are thought to modify the complex arousal mechanism of the RAS by their action on active and passive controls which "brake" or "accelerate" activity within the reticular system, JOUVET (1967).

The role of the bioamines in the two (2) major sleep states, namely:-

(a) Telencephalic, synchronised, light sleep characterised by slow wave electro encephalograph reading (EEG) and non rapid eye movement (N.REM).

(b) Rhombencephalic non synchronised deep or paradoxical sleep -- Rapid eye movement (REM) with EEG fast waves, have been investigated by GEORGE, HASLETT and JENDEN (1964), JOUVET (1969) and OSWALD (1968).

The evidence produced by this group of individuals places some importance on cholinergic mechanisms but generally refutes any specific relationship between acetyl choline and sleep states. Hence, the sleep mechanism may be adrenergic rather than cholinergic

although acetylcholine may trigger adrenergic neurones in REM sleep, JOUVET (1969) and there is evidence that an ascending cholinergic system may account for generalized arousal, KRNJEVIĆ (1967). There is no definitive evidence that any single biogenic amine is exclusively involved in the mechanism of any sleep state, OSWALD (1968). The connection of interest is the similar conclusion reached by PEPEU and NISTRI (1974) for the central mechanism of morphine induced analgesia. This coincidal evidence tends to confirm the clinical fact that pain is lessened by morphine induced sleep.

PERCEPTUAL AWARENESS

Thus, argument based on the NHT would indicate that perceptual awareness of modalities such as pain may depend on the maintenance of dynamic equilibrium between serotonin and noradrenaline, and their rate of exchange. This notion gains support from evidence that serotonin precursors promote light sleep whereas drugs which selectively depress serotonin levels in the brain produce a state of permanent wakefulness, JOUVET (1967). In addition, the RAS is stimulated by epinephrine in states of fear and shock, GANONG (1971), a similar monoamine mechanism presumably accounting for the over-alertness known as anxiety.

SLEEP AND THE RAS

On the other hand, depression of RAS activity and generalized cerebral depression by sedatives, hypnotics, tranquillizers, cellular anoxia, or by anaesthetic drugs may reduce or enhance the perception of pain, according to the depth of depression achieved. Drug induced sleep which differs from natural sleep in paradoxical content, HEUSER (1967), was thought to be due to selective depression of the RAS but it is now believed that there occurs generalized synaptic depression, GANONG (1971), as well as stimulation of a specific deactivation system or light sleep promoting mechanism caudally situated in the lower brain stem, OSWALD (1968). This mechanism appears to function independently of the cortex and forebrain, ZANCHETTI (1967), despite evidence to the contrary by JOUVET (1962) who suggests that cortical integrity is necessary for generalized deactivation of the RAS via descending cortico-fugal fibres, cortical feedback being thought responsible for arousal, GANONG (1971). A pacemaker activated mechanism located in the pons is thought to promote desynchronized sleep which, unlike synchronized sleep, relies purely on active processes, ZANCHETTI (1967).

THE ROLE OF INHIBITION

It is known that sleep may be induced by baroreceptor stimulation. It is also well known that low grade electrical stimulation of most parts of the CNS including large cutaneous afferents, in the absence of pain, may produce light sleep or synchronization which is easily reversible by increasing the frequency of stimulation. Et sequentia evidence indicates that impulses derived from large mechanoreceptive afferents may be involved in a process of corticofugal inhibition at the first cord synapse.

Hence, it is possible that low grade stimulation of these mechanoreceptive fibres may inhibit pain but at the same time promote sleep, a factor consistent with the general theory that inhibitory processes exert some control over both phenomena.

CHAPTER II

SUMMARY

1. A neurone fires when depolarization resulting from the sum input of EPSP's and IPSP's exceeds a critical level in the area of its axon hillock. The resultant action potential is all or none.

2. Subliminal stimuli do not normally initiate an impulse.

3. The cell membrane negative resting potential is maintained by the sodium-potassium pump in accord with the GIBBS-DONNAN Equilibrium and Nernsts' Law.

4. The cyclical rhythm of action potential may be impeded by interference with energy dependent sodium pump mechanisms such as oxidative phosphorylation or by unlocking membrane transport mechanisms which probably rely at least in part on the physico-chemical release of ATPase on the cytoplasmic side of the membrane. Interference at this level may alter the algogenic potential of an impulse.

5. Conduction of an impulse in nervous tissue is a physico-chemical process involving (1) electrical energy and (2) chemical changes within the nerve fibre energised by ATP derived from aerobic metabolism of glucose via the Krebs cycle.

6. Propogation is by electro-ionic interchange along the length of the nerve fibre. Myelinated nerve fibres transmit impulses at greater speed than unmyelinated fibres because of saltatory conduction.

7. Pain carrying fibres are small myelinated A delta fibres and smaller unmyelinated C fibres. Bright pricking and burning qualities of pain have been respectively ascribed to be carried by these two fibre systems. The difference in conduction speed between the two fibre types accounts for "double pain".

8. Sensory transmission of afferent impulses arising in branches of the trigeminal nerve is little difference from somato-sensory transmission at lower levels. The same mechanism of descending inhibition operates at the 1st cord synapse. Trigeminal reflex activity travels rapidly via intercalated neurones.

9. Synaptic transmission involves either the conversion of electrical energy to secretory activity with mediation across the junction by specific neurotransmitter substances, or the phenomenon of ephapse involving electrical jump of the junction. The coupling mechanism appears to be ATPase activated.

10. Excitation (Pna^{+}) or inhibition (Pcl^{-}) is determined by specific membrane permeability. The same mechanism

operates in the presynaptic fibre as in the post junctional synaptic membrane.

11. Synaptic junctions are particularly susceptible to the action of drugs, a factor that is utilized in the practice of general anaesthesia.

NERVE FIBRES

An important feature of pain mechanisms is the structure of sensory nerve fibres.

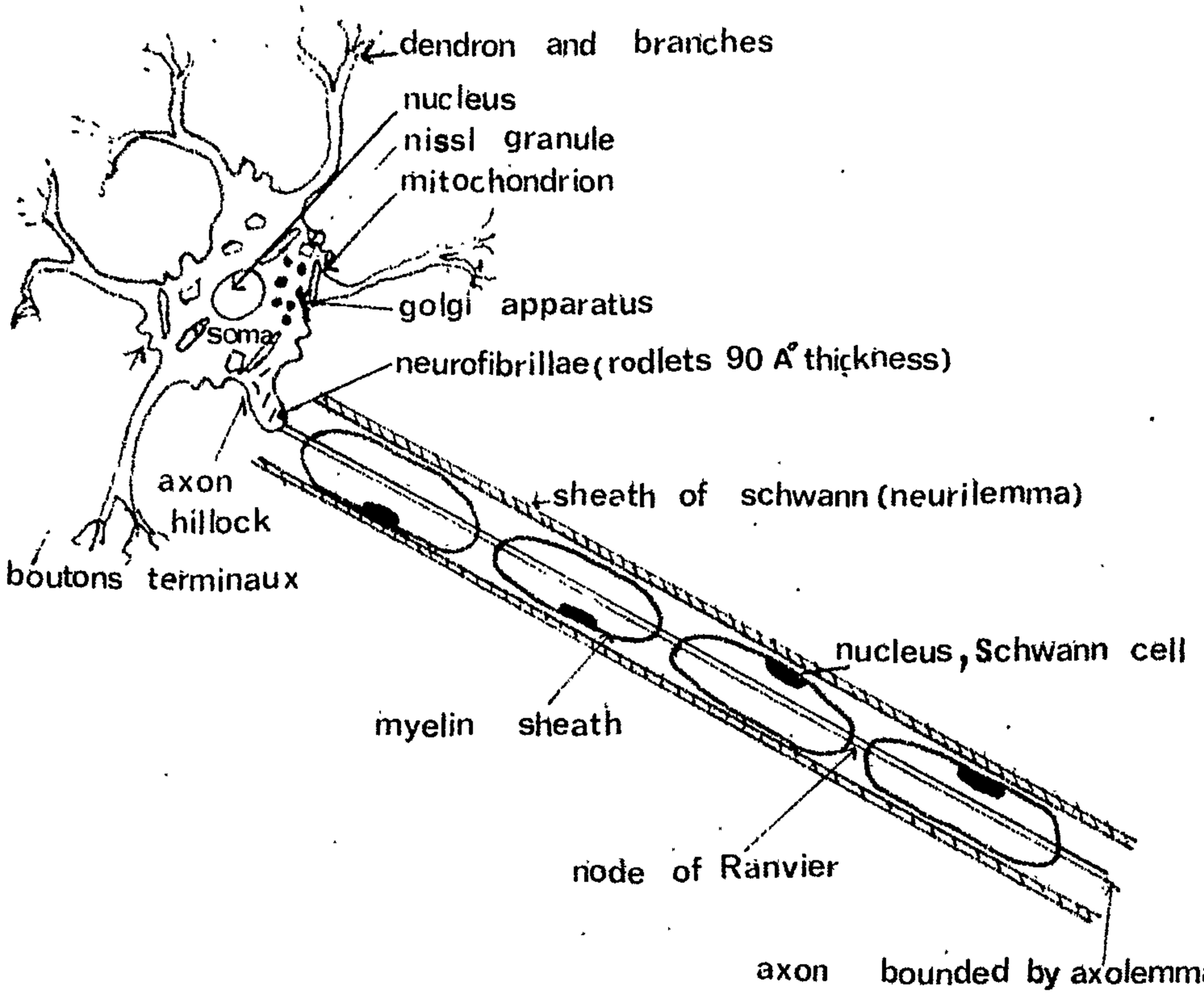
STRUCTURAL INFLUENCES

Each nerve pathway is a distinct unit: a nerve trunk is composed of many such units, MONHEIM (1969), "fascicles" of nerve fibre being bound together by connective tissue, ELFVIN (1968).

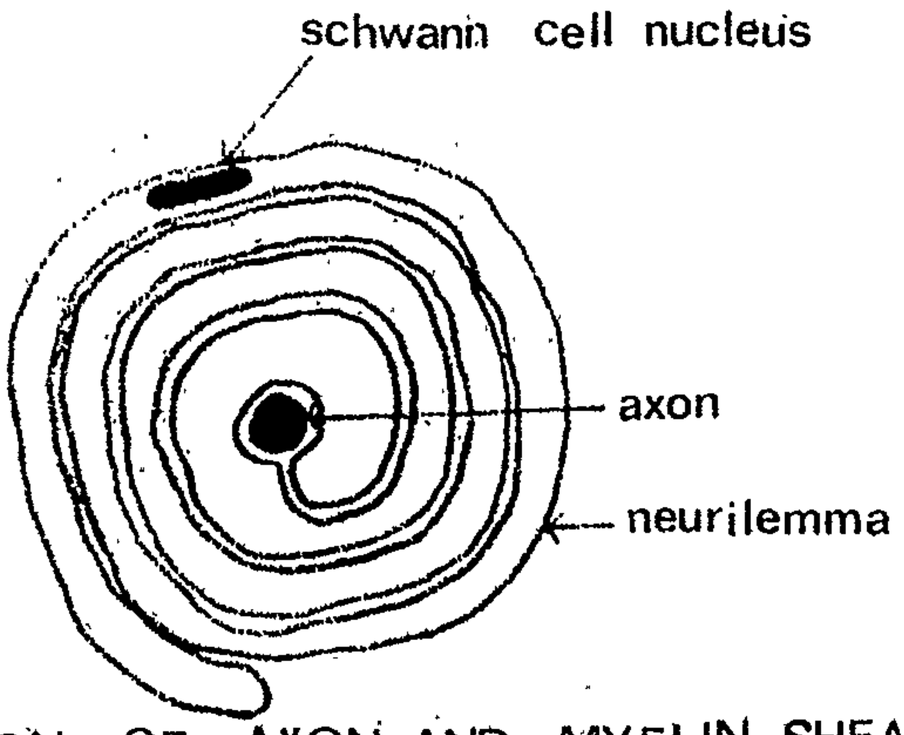
The concentric lipo-protein structure of myelinated nerve sheaths is well illustrated by ELFVIN (1968) who also describes the essential morphologic differences between myelinated and non-myelinated nerve fibres. The dendritic syncytium and the axonal connection to the soma are illustrated. (See Figs. No.7A and 7B p. 58)

In peripheral nerves the Schwann sheath contains more than one fibre, ELFVIN (1968). The peripheral nervous system is invaginated by the "Perineural Epithelium" which acts as a diffusion barrier to nutrients and other ionic substances, SHANTHA & BOURNE (1968).

The nerve cell membrane is best visualized as a dynamic mosaic structure composed of islands of specific protein embedded in a phospholipid matrix, SINGER & NICOLSON (1972).



A NEURONAL STRUCTURES



B CROSS SECTION OF AXON AND MYELIN SHEATH STRUCTURES

FIG NO 7

Any factor which changes the spatial relationship between the molecular layers of the membrane may alter its permeability, thereby facilitating the passage of larger ions otherwise unable to penetrate the neurilemma. (See Fig. No.3 p. 21)

CLASSIFICATION OF NERVE FIBRES

GASSER & ERLANGER (1927), (1929), and later GASSER (1943), classified nerve fibres by a fibre-size conduction speed relationship. On this basis, sensory nerve fibres are divided into A, B and C groups with five subdivisions of group A (myelinated somatic), namely, Alpha (α), Beta (β), Gamma (γ), Delta (δ) and Epsilon (ε). GANONG (1971) points out that touch and pressure sensations are carried by A β fibres 5 - 12 μm in diameter at a speed of 30 - 70 meters/sec., whereas pain and temperature sensations are carried by two distinct nerve fibre types, namely the small A δ myelinated fibres 2 - 5 μm in diameter at a speed of 12 - 30 meters/sec. and smaller unmyelinated C fibres 0.4 - 1.2 μm in diameter at a speed of 0.5 - 2 meters/sec. Nerve fibres serving the teeth are small myelinated fibres of the A δ type. Sixty four per cent of all fibres entering the dental pulp are <6 μm in diameter, none are >10 μm in diameter, ANDERSON & PEARL (1974). Dorsal root C fibres play the major role in

the conduction of pain impulses; small A fibres are involved to a lesser degree, ELFVIN (1968).

The bimodal nature (tactile-thermal) of the C fibres is still uncertain, LIM & GUZMAN (1968), but the difference in rate of conduction between A & C fibres introduces the question of double pain: a dual response associated with noxious stimulation.

DOUBLE PAIN

The phenomenon of double pain is generally described as being due to the difference in fibre size-conduction speeds between nociceptive fibres. The first pain is mediated by myelinated mechanical nociceptors, the second is mediated about one second later by non-myelinated axons, IGGO (1974).

As WOLF (1968) observes, the initial sharp response "bright pricking pain" is carried by the A δ fibres, whereas the dull protracted sensation "burning pain like cold pain" follows later via the C fibres. The separation time of the two responses is directly proportional to the distance from the site of impulse stimulation to the brain, WISE (1966a). In a series of animal experiments LEWIS (1942) used a needle, a hot plate, and a copper cylinder recorder to point out the distinction

between the two responses. The dual response theory was questioned by JONES (1956) who believed that double pain or "echo pain" was an "artifact". He cited the work of SINCLAIR (1955) who also supported the notion that the idea of two sets of pain fibres rested upon experimental observations and interpretations "not immune from criticism". Directly opposed to the view of SINCLAIR & JONES, BISHOP & LANDAU (1958) found that pain from C fibre stimulation is enhanced by the absence of the myelinated A δ pathway.

The short route travelled by pain carried in trigeminal fibres suggests that a dichotomy of response from stimulation of oral structures would be a difficult concept to believe, although MUMFORD (1968) suggests a stimulus response delay of 0.2 secs. useful in differential diagnosis of pain arising from the teeth. It is also of interest that if the gate control theory is held valid, only a single modulated response would be recorded centrally, according to BRAZIER (1972).

Despite the conflicting evidence, the concept of fast and slow pain is now tenable, GANONG (1971), and is substantiated by DYSON & BRINDLEY (1966) who were able to differentiate between the contributory roles of each axon type in human pain experience.

PAIN CARRYING FIBRES

TRIGEMINAL PATHWAYS

The nature of trigeminal pathways for pain is of special interest. The Perikarya (cell bodies, soma) of preganglionic trigeminal branches are located in the Gasserian ganglion. Afferent post ganglionic connections from these cells enter the spinal trigeminal nucleus via the spinal trigeminal tract fibres. The mediation of pain in the trigeminal system is generally ascribed to the most caudal part of the spinal nucleus which is continuous with, and similar to, the pars gelatinosa of the dorsal horn of the spinal cord, BRODAL (1972), BOWSHER & ALBE-FESSARD (1965) p. 65. (See Fig. No.8 p. 63)

The rostral portion, including nucleus oralis and the main spinal nucleus, is important in the mediation of non noxious stimuli, DARIAN-SMITH, ROWE and SESSLE (1968).

This does not preclude the possible transmission of pain or other sensory modalities via fibres connected with the other two sensory nuclei, namely, the principal (touch associated), and the mesencephalic (proprioceptive), since afferent trigeminal tract fibres branch to communicate with all three nuclei.

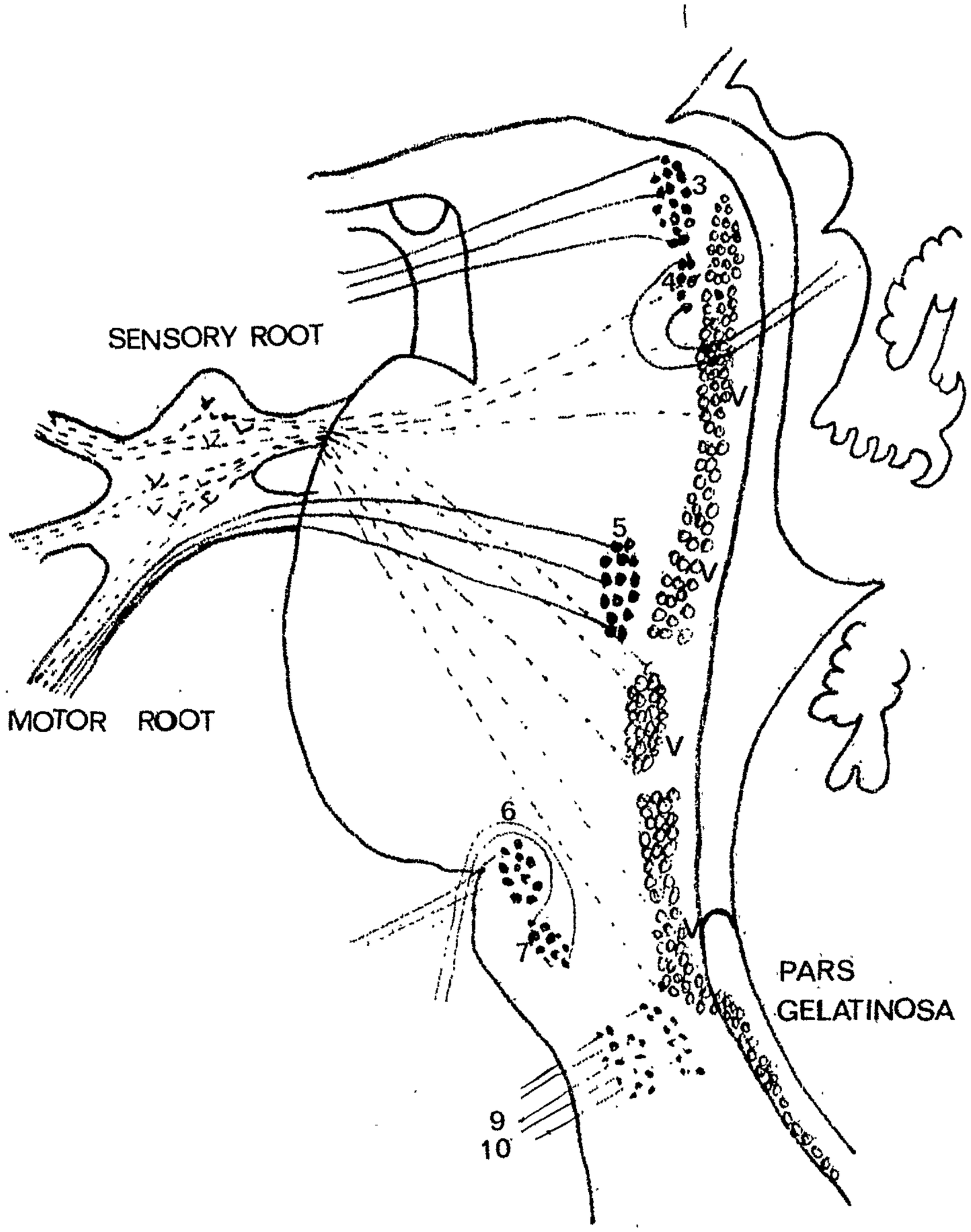


FIG NO 8

PRIMARY TERMINAL NUCLEI- SENSORY FIBRES Vth CRANIAL NERVE.

NUCLEI MOTOR NERVES

Since the mesencephalic - proprioceptive function is now well established, BRODAL (1972), the onus for noxious impulse transmission rests largely on the other soma which closely mimic in function the cells of the spinal cord, TORVIK (1956).

Experiments on stimulation of the dental pulp by KERR, HAUGEN and MELZACK (1955), and TORVIK (1957) have demonstrated that pain entering the trigeminal system is transmitted via six ascending tracts from the principal and descending trigeminal nuclei, namely, the trigeminal leminscus, the dorsal trigeminal tract, the trigemino - bulbo - thalamic projection, the central tegmental fasciculus, the trigemino - reticular pathway, and a pathway within the central grey matter. (See Fig. No.9 p. 65). It must be remembered that the above pathways constitute one of the possible anatomical models for the trigeminal system. This model is possibly derived from TORVIK's description of ventral crossed and dorsomedial uncrossed fibres which project from the ventral and smaller medial dorsal parts of the main sensory nucleus. Since pathways are difficult to trace, some authors disagree with the terminology used, preferring a 5 pathway system without dichotomy of the dorsal secondary trigeminal pathway of the central

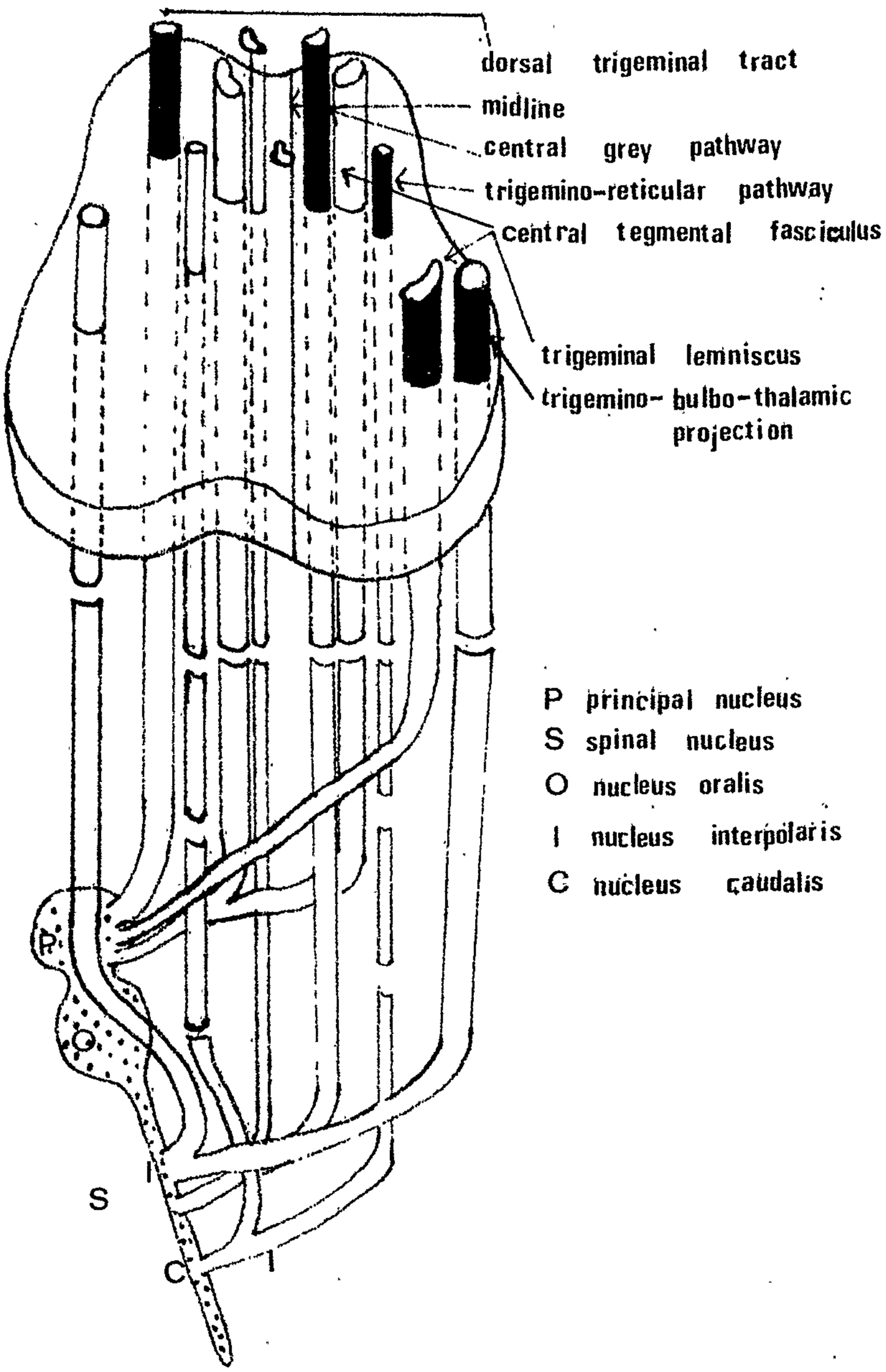


FIG NO 9

Diagrammatic representation of six secondary trigeminal pain pathways on one side After Dellow (1962)

tegmental fasciculus. The central tegmental fasciculus may inhibit incoming excitation in the other afferent channels, MELZACK, STOTLER and LIVINGSTON (1958). Nitrous oxide (N_2O) has a predilection for this pathway, HAUGEN and MELZACK (1957), an interesting connection with Langa's analgesic technique, LANGA (1968).

Descending signals from cortical cells inhibit impulse propogation at the first synaptic relay in the dorsal horn, HAGBARTH & KERR (1954), through a mechanism of presynaptic inhibition, ANDERSEN, ECCLES & SEARS (1962). Afferent impulses entering the trigeminal system are similarly inhibited, HERNÁNDEZ-PEÓN & HAGBARTH (1955), DARIAN-SMITH (1965).

Evidence that tactile information is progressively refined as it enters the trigeminal system from the periphery, DARIAN-SMITH et al. (1968), suggests that information about pain may be similarly diluted. Other evidence, MUMFORD & NEWTON (1971), (1974), tends to confirm convergence at nucleus oralis (first order interneurones) with loss of information at nucleus caudalis (2nd order interneurones) involving progressively fewer "pain" carrying fibres. This data suggests that each primary afferent fibre becomes less and less excitatory in effect at synapses with other neurones as it enters the CNS from the periphery, a factor

consistent with the concept of functional inhibition of noxious information. Thus, the transmitting apparatus for pain from the periphery to the CNS appears to function similarly in both the trigeminal and the cutaneous somato-sensory systems related to other parts of the body.

TRIGEMINAL REFLEX ACTION

Centripetal propogation of sensory information may stimulate different reflex actions, e.g. vasodilation, reflex muscle movement, derived from direct synapse with afferent motor units which transmit back to the periphery. Similar reflex activity may occur on stimulation of trigeminal nerves, although there is evidence which suggests that impulses are not transmitted by direct connection or synapse but by intercalated neurones, possibly cells of the brain stem reticular formation, which then activate the motor trigeminal nucleus, BRODAL (1972). However, this does not apply to the mesencephalic trigeminal nucleus fibres from which synapse directly with motor cells, BRODAL (1972).

MEMBRANE MECHANISMS

Examination of cell membrane mechanisms may reveal the nature of the link between physico-chemical changes at

cell membrane levels and pain mechanisms.

MEMBRANE RESTING POTENTIAL

Under normal conditions a nerve fibre plasma membrane is negatively charged inside with respect to the outside, (i.e. polarized). This electrical difference of about -60 mv., known as the membrane resting potential, is a function of the concentration gradients of diffusible ions across the membrane, the ionic flux being in accord with the GIBBS-DONNAN effect, SAMPSON WRIGHT (1965).

Entry of sodium ions (Na^+) into the cell or nerve fibre is inhibited by the resting membrane, whereas potassium ions (K^+) and chlorine ions (Cl^-) are distributed on both sides of the membrane, the greater number of K^+ remaining within the cell.

The potential difference between the two sides of the nerve cell or axon membrane which equalizes the flow of ions entering or leaving the cell is determined by NERNST's law, HODGKIN & HUXLEY (1945), (1952a) and (1952b).

The electrochemical potential is the sum of the potential energies both concentration and electric. Hence,

ionic equilibrium is largely dependent on specific variations in (1) osmotic pressure, (2) chemical potential, and (3) electrical potential, as well as being subject to changes in hydrostatic pressure and active ionic transport by the membrane itself. At equilibrium the ionic flux is zero.

THE SODIUM PUMP

The intrinsic cellular mechanism responsible for active ionic transport is known as the "sodium - potassium pump", ECCLES (1957).

The inflow of Na^+ and the approximately equal efflux of K^+ associated with a nerve fibre action potential are juxtaposed by the active extrusion of sodium by the pump in the recovery phase. The energy for this manoeuvre is thought to be supplied by adenosine triphosphate in the presence of arginine phosphate, KEYNES (1961), or an acyl phosphate, CALDWELL (1970), DAHMS and BOYER (1974), the pump itself being actively maintained by mechanisms of oxidative phosphorylation.

The cyclical relationship between Na^+ and K^+ following nerve stimulation is well described by HODGKIN & KEYNES (1955), HODGKIN (1958) and HODGKIN (1964). (See Fig. No.10 p. 70)

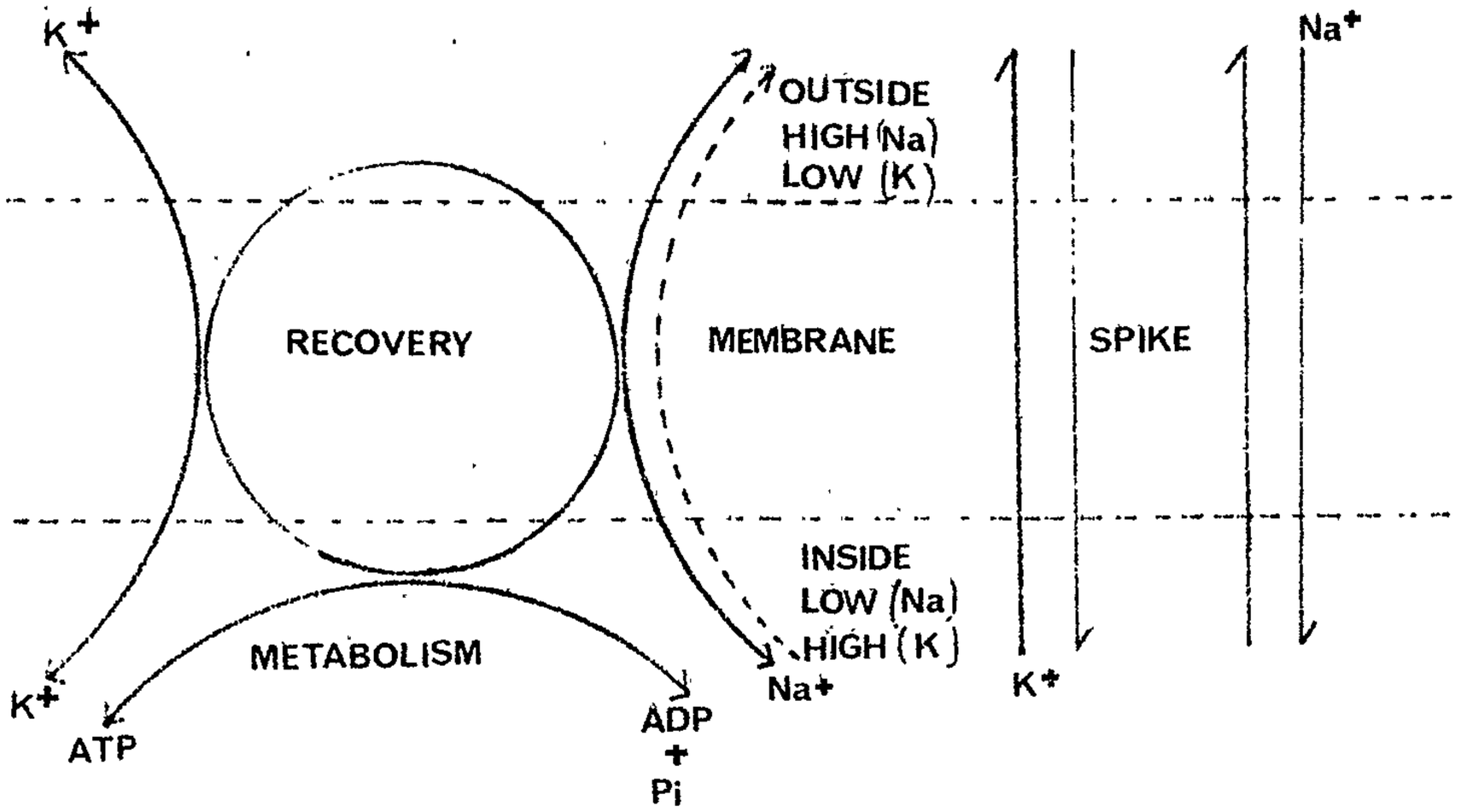


FIG NO 10

CYCLICAL SPIKE-RECOVERY MECHANISM MODIFIED FROM HODGKIN AND KEYNES (1955)

The energy linked movement of Na^+ and K^+ against the chemical gradient is thought to be achieved by the action of a specific but independent carrier, SOLOMON (1952), GLYNN (1956), capable of structural modification to enable interchange by displacement of either Na^+ or K^+, SHAW (1955), at a rate proportional to the concentration of ATPase in the cell membrane, GANONG (1971).

A possible functional energy mechanism for the sodium pump is described by EYRAUD, LENOIR & JENIN (1972). (See Fig. No.11 p.72). According to EYRAUD and his colleagues, the membrane consists of a series of "générateurs électriques" which alternate anode and cathode in accord with the specific enzyme present at selected sites along the membrane: "Catylseur sélectif adsorbé sur la plage correspondante". Fuel cell energy is supplied by dissolved oxygen and an extracellular energy source possibly involving glucose metabolism. Passage of current is facilitated, at least in part, by the involvement of multivalent metallic atoms of multiple valency (e.g. Fe_2 Fe_3) available from cytochromes fixed in the membrane. The system is presumed to apply to other tissues with mosaic membrane structures, e.g. Henle Tubules.

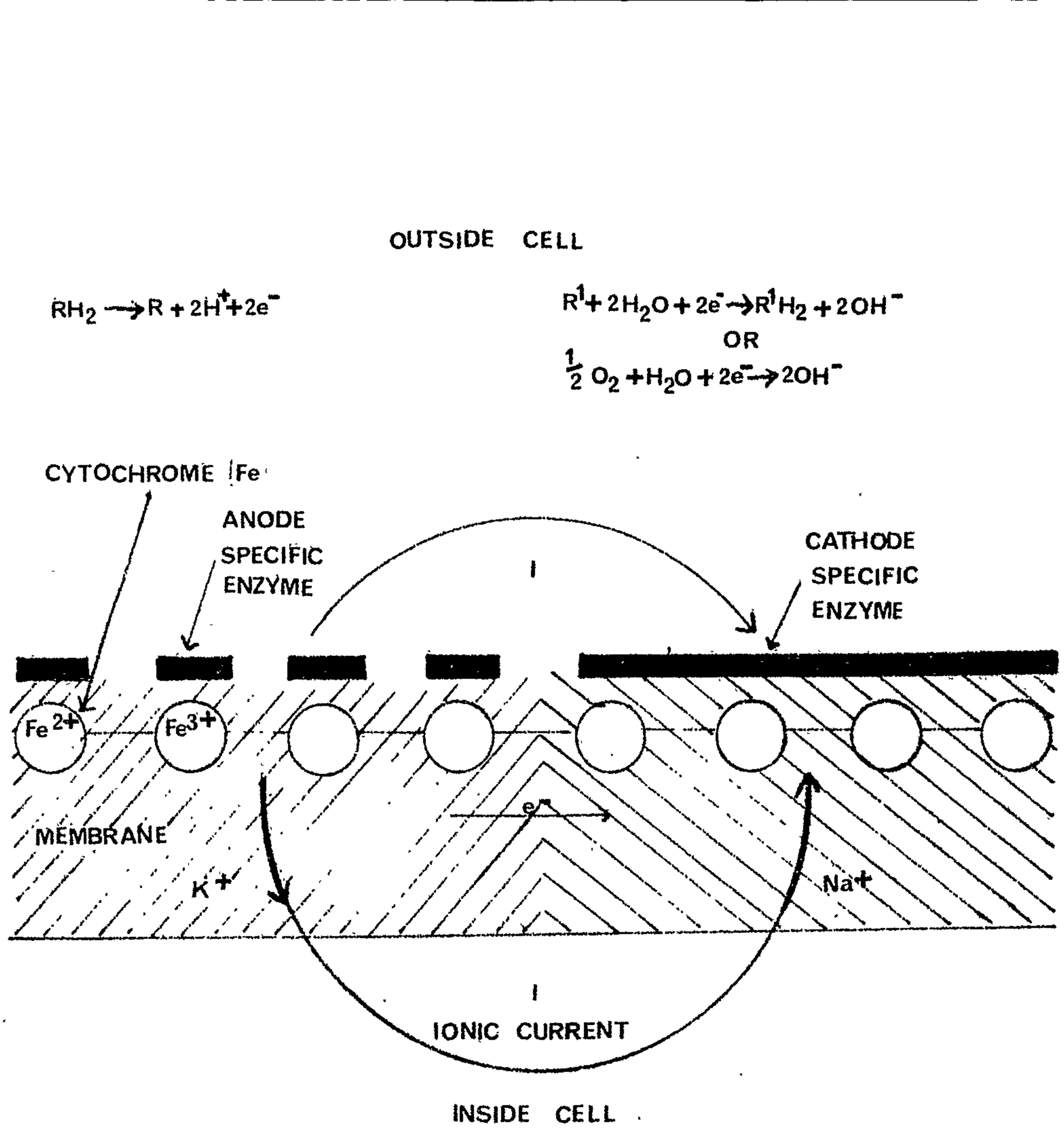


FIG NO 11

FUEL CELL THEORY, AFTER EYRAUDet Al (1972)

No carrier is involved. Ion movement is by current generated by fuel cell anode-cathode reaction. Energy supplied by extracellular reactions; RH Molecules are oxidised and dissolved oxygen is reduced.

ENERGY FOR TRANSPORT

The level of ATP sufficient for active ionic transport is maintained by the presence of glucose under aerobic conditions, QUASTEL (1969). Biological oxidation of glucose via the well known pyruvate - citric acid cycle yields 38 ATP mols from the complete oxidation of 1 mol glucose, 2 mols of ATP are formed by glycolysis to pyruvate and the remainder in the process of respiration. Other aspects of cellular metabolism including:

(i) the role of the mitochondria in ATP production;

(ii) the detrimental effect of anoxia;

(iii) the release of metabolic energy by ATPase are succinctly documented by FOURCADE & DESCOTES (1974).

CELL MEMBRANE MECHANISM

It is apparent that there is a close relationship between the energised "pumping" movement of Na^+ out of and K^+ into the cell with membrane localized

adenosine triphosphatase (ATPase). ATPase is activated by intracellular Na^+ and external K^+, whereas internal K^+ appears to be a competitive inhibitor of intracellular sodium in the action of Na^+/K^+ activated ATPase, POST (1968).

The ratio of $\frac{\text{conc intracellular } K^+}{\text{conc extracellular } K^+}$ is a major chemical factor in the excitability of nervous tissue as well as the conduction of sensory impulses, VAUGHAN & LUNN (1973).

The influx of K^+ against the concentration curve is determined by the equation:

$$K^+ \text{ influx} = \frac{\alpha \quad (Ko)}{\beta + (Ko)} + \gamma \ (Ko)$$

where Ko = concentration K^+ outside the cell and alpha, beta and gamma are constants, SHAW (1955).

When all three ions are in hydrated form, the apparent radius of Na^+ is approximately 1½ x that of Cl^- and K^+, CONWAY (1952), CREIGHTON & KOEHLER (1943) p. 140.

Excitability depends on Na^+ influx and K^+ efflux, suggesting that the mechanism which stimulates sodium conductance through the expanded pores or membrane channels also initiates action potential. Why does the cell membrane suddenly become specifically permeable to Na^+? Is there a simple physical reason linked to a

change in the special relationship of the molecules of the membrane structure? It is known that the difference between active transport and passive diffusion rests on the capability of energy linked chemical mechanisms in the cell to create favourable concentration gradients for ionic movement across the plasma membrane. This suggests a possible physiochemical trigger mechanism for the cyclical rhythm of action potential. If the size of the pore opening is equal to or greater than Na^+ size, it is logical to assume that substances with the exact molecular structure as the pore opening may physically block Na^+ influx. Local anaesthetic solutions are thought to work in this manner.

When this notion is combined with the "lock and key" nature of enzymes at receptor sites, the possibility arises that enzymes may play an important role as physical blockers of the membrane to Na^+. For example, it is believed that enzymes are built into membrane structure possibly in the "thick cytoplasmic opaque layer" on the cytoplasmic side of the plasma membrane, ELFVIN (1968). The carrier mechanism advocated by SHAW, GLYNN & SOLOMON also appears to be enzyme activated.

From previous evidence, the presence of Na^+ inside the cell activates membrane localised ATPase. The release

of ATPase from its membrane site to catalyse energy reactions may open the gateway to Na^+ thereby assisting in sodium conductance through the membrane.

DEPOLARIZATION

It is clear that the electrotonic state of the membrane is largely dependent on the concentration gradients of K^+, Cl^- and Na^+ across the membrane. A special transient increase in membrane permeability to Na^+ (Pna) produces depolarization (excitability), whereas a similar change in permeability specific for Cl^- (Pcl) with associated K^+ leakage results in hyperpolarization (inhibition), BRAZIER (1969a). Depolarization is the trigger for the following action potential, WALL (1974), but an action potential is not always the response to depolarization, e.g. the axon may be fired but not the soma or dendrites because of their higher threshold. (See Fig. No.12 p.77). The response of the nerve depends on its electrotonic state (chronaxie) at the time of stimulation. Normally, inadequate stimuli may produce a response in the presence of predisposing factors, e.g. fear and anxiety which seem to sensitize the nervous system, JORGENSEN & HAYDEN (1972). Factors which prevent depolarization also inhibit action potential, e.g. the cation portion of local anaesthetic

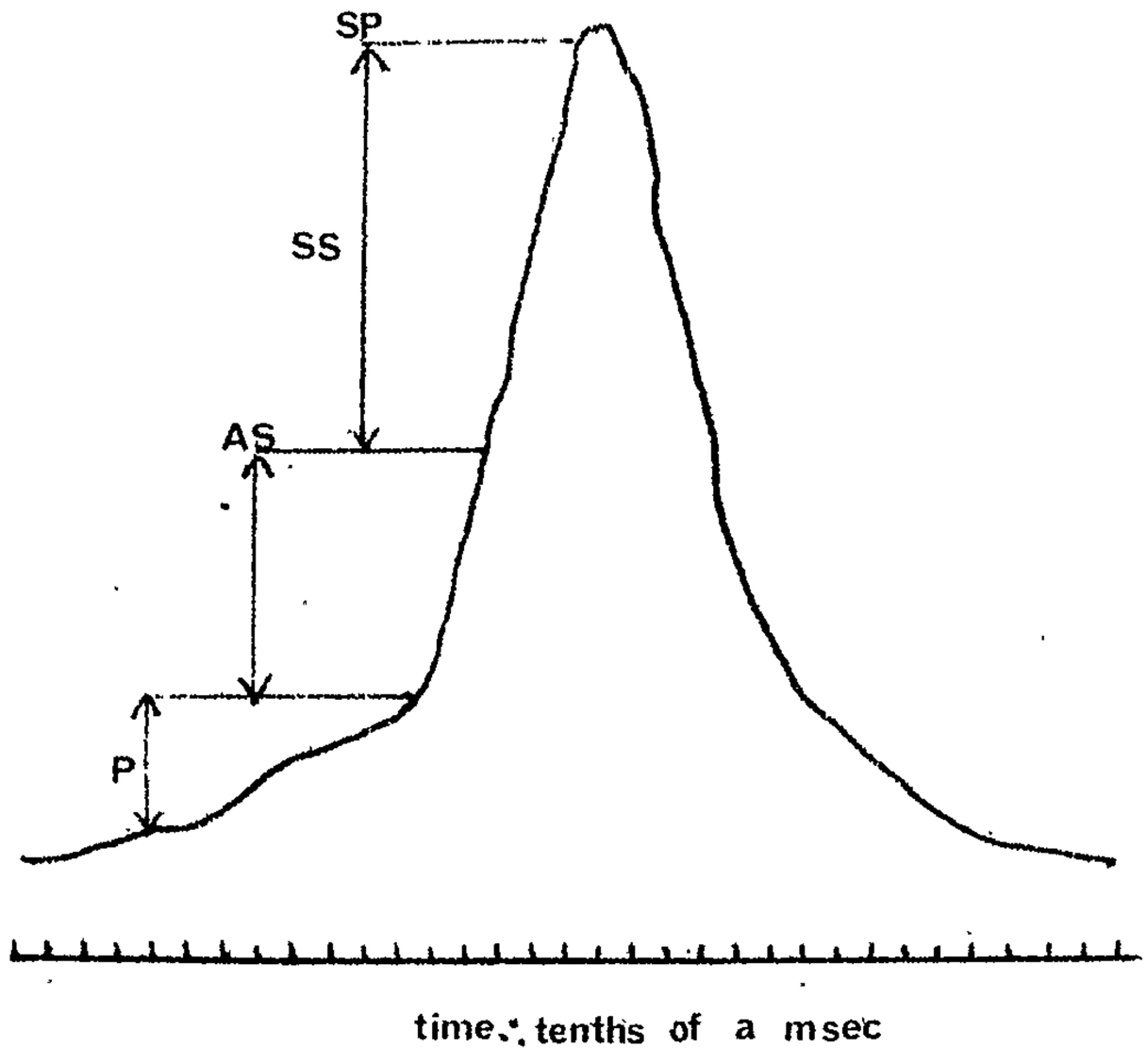


FIG NO(12)

Graded excitability - cat motor neurone. After Brazier(1969)

SP: Spike peak

SS: Soma spike

AS: Axon spike

P : Post synaptic potential

agents, KRAMER & SCHMIDT (1968). Thus, the logical way to prevent pain in the clinical situation is by the use of local anaesthetic agents or substances which will block "permselective channels" in the nerve cell membrane. This interference with the sodium pump mechanism prevents Na^+ influx and subsequent depolarization of the membrane, i.e. the nerve becomes incapable of firing an action potential.

ACTION POTENTIAL

The measurable changes in electrical potential within a nerve fibre membrane after stimulation are illustrated by "action potential" (See Fig. No.13 p. 79). The sum input of action potentials carried by different diameter nerve fibres within a nerve trunk varies according to the number of fibres and their specific conduction velocities. The total response is known as compound action potential, BRAZIER (1968) (pp. 43-49). A brief specific increase cell membrane permeability (Pna^+) takes place at the peak of action potential; reversal of this reaction provides a physiological explanation for "overshoot" and subsequent (5 m sec.) repolarization concomitant with re-excitability along the nerve fibre, BRAZIER (1969a), as the plasma membrane attempts to recover through its accommodative processes

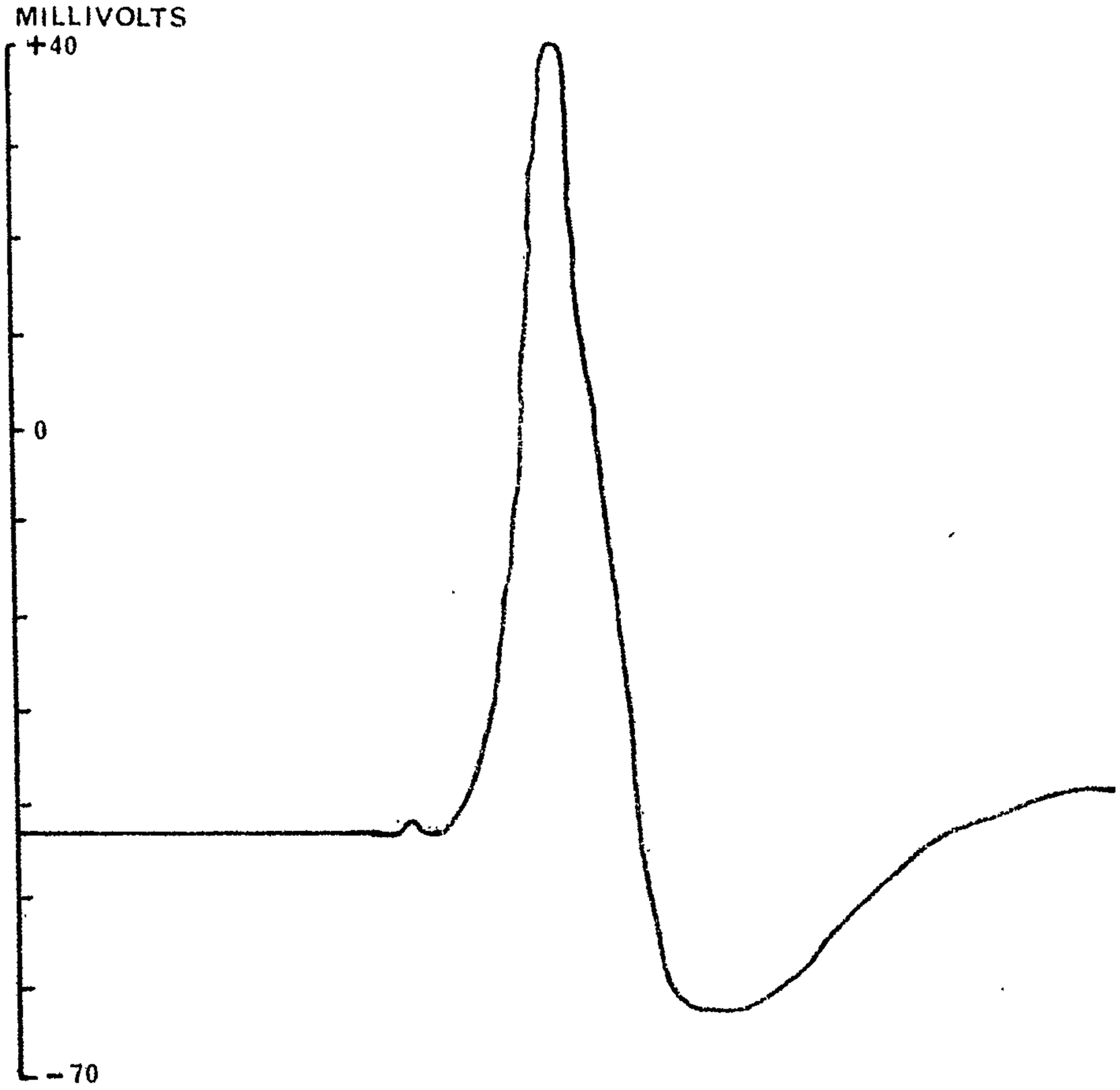


FIG NO 13 AFTER HODGKIN AND HUXLEY (1945).

ACTION POTENTIAL RECORDED BETWEEN INSIDE AND OUTSIDE OF AXON (SQUID).

and through electrotonic dilution along the nerve fibre. Immediately after peak action potential there is a refractory period in which the nerve will fail to respond to any kind of stimulation, BRAZIER (1968) p. 35. Just before equilibrium is established, the cell membrane becomes hyperpolarized (positive after potential), a factor which tends to limit the firing rate and to control the rhythm of action potential. Recovery takes place by active expulsion of Na^+ across the plasma membrane.

IMPULSE INITIATION

A nerve cell fires when there is sufficient change in the electrical potential of its membrane. The degree of depolarization is derived from and proportional to the summation of EPSP and IPSP (excitatory and inhibitory postsynaptic potentials) input from impinging synaptic connections. The level of depolarization becomes critical at the axon hillock where threshold is lowest and which is thought to be the site of impulse initiation from the cell, BRAZIER (1969a), ECCLES (1957) p. 49. Neuronal activity is complicated by the convergence of many synaptic contacts upon a single neurone which may also transmit impulses along many divergent synaptic pathways, GRUNDFEST (1969).

It is known that a stimulus of supra threshold intensity fires a nerve at maximum quantum only. Sub-threshold stimuli do not normally trigger action potential - the "all or none law", GANONG (1971).

The fact that this principle applies only to propogated action potential and not to all other responses recorded at receptor sites demonstrates the high degree of flexibility within the nervous system, BRAZIER (1969a).

Once a nerve fibre fires, i.e. an action potential is established, the impulse is conducted along the nerve fibre towards the central nervous system by a mechanism of ionic transfer known as "propogation".

The mechanism for propogation was first described in definitive terms by ECCLES in his gateway theory of active ionic interchange, not to be confused with the unrelated synaptic control mechanism described by MELZACK & WALL, (1965).

PROPOGATION

It is clear that the initiation of an impulse is a chemical mechanism in so far as it is closely linked to the energy requirements of the sodium-potassium pump, whereas impulse propogation is largely a physical mechanism relying on electrical conduction

along the nerve fibre. Thus, the physio-chemical conduction of a "pain" impulse from the afferent receptor to the CNS is accomplished by electron (energy) transfer as a result of ionic exchange (K^+ out of the cell and Na^+ in). Therefore, conduction in nervous tissue is the consequence of the unidirectional passage of electric currents from the active region to the inactive area ahead of the impulse. The speed of conduction is greater in myelinated nerves because of saltatory (node to node) conduction, whereas in unmyelinated fibres the impulse proceeds by simple ionic interchange along the entire length of the fibre. (See Fig. No.14 p. 83). The amplitude and velocity of an impulse is constant regardless of the strength of the original stimulus; the larger the nerve fibre the greater the speed of conduction, GANONG (1971). The source of energy for impulse propogation is derived from the intrinsic metabolic process within the nerve fibre, not from the energy supplied by the stimulus. The impulse travels to the synapse where electrical energy is converted to secretory activity by an unknown coupling mechanism which initiates the release from the nerve end boutons, transmitter chemicals, normally stored in the vesicles apparent in the boutons.

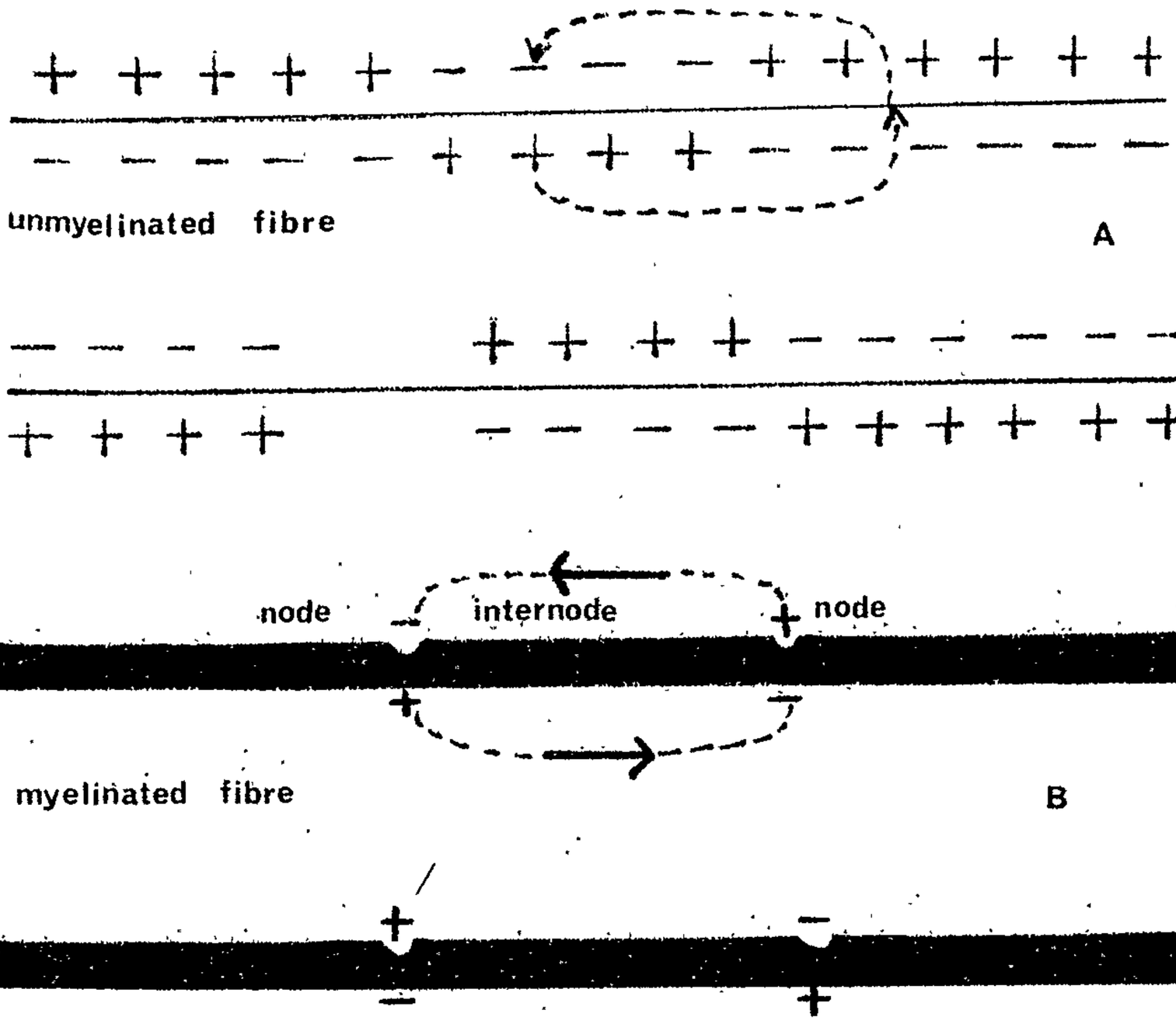


FIG NO 14

Modified after Hodgkin (1958)

Impulse propogation along a nerve fibre.

Local circuit theory.

Saltatory conduction.

SYNAPTIC TRANSMISSION

Synaptic transmission is a particularly interesting aspect of pain mechanisms.

"Pain" impulses are propogated along a one way system of synapse involving mediation by a specific chemical transmitter substance released at nerve ending bulbs (boutons terminaux) proximal to the synapse.

Impulse conduction speed is slower when multi synaptic changes are involved due to the delay of 0.5 - 0.6 m sec. required for transmission from the presynaptic cell to the post synaptic nerve fibre, GANONG (1967). Synaptic latency varies with the type of tissue and its excitability, e.g. latency is greater in smoother than in voluntary muscle, AMBACHE (1967).

When presynaptic stimulation ceases, specific enzymes function to deactivate transmitter substances, thereby inhibiting any further excitation of the post synaptic cell.

This hydrolytic mechanism operates by lowering the level of depolarization previously induced by synaptic excitation, AMBACHE (1967).

MECHANISM OF TRANSMITTER RELEASE

Measurement of ATPase activity in rat cortical

synaptosomes and other experimental work involving the CNS and peripheral nerves by GILBERT, WYLLIE & DAVISON (1975) indicates that ATPase may be a "possible trigger" for the release of neurochemical transmitter substances such as acetylcholine and noradrenaline from synaptic vesicles.

It is already known that Ca^{++} influx and other ionic changes not Ca^{++} dependent may influence the release of acetylcholine (ACh), e.g. Ca^{++} facilitates ACh release, MOUNTCASTLE & BALDESSARINI (1968) (see Fig. No.15 p. 86) and Mg^{++} inhibits this process, WYLIE & CHURCHILL DAVIDSON (1966). KRNJEVIĆ (1974) also suggests that the prostaglandins may play a signif-icant inhibitory role in transmitter release at the presynapse and may influence excitability by binding Ca^{++} at synaptic membranes.

TRANSMITTER SUBSTANCES

Some neurochemical transmitters have been identified, e.g. ACh for the recurrent branches of motor neurones, KRNJEVIĆ (1974), and for certain interneurones such as Renshaw cells, ECCLES (1967), ECCLES, ECCLES & FATT (1956).

Gamma aminobutyric acid (GABA) and glycine may be major central inhibitory transmitters, glycine may be the

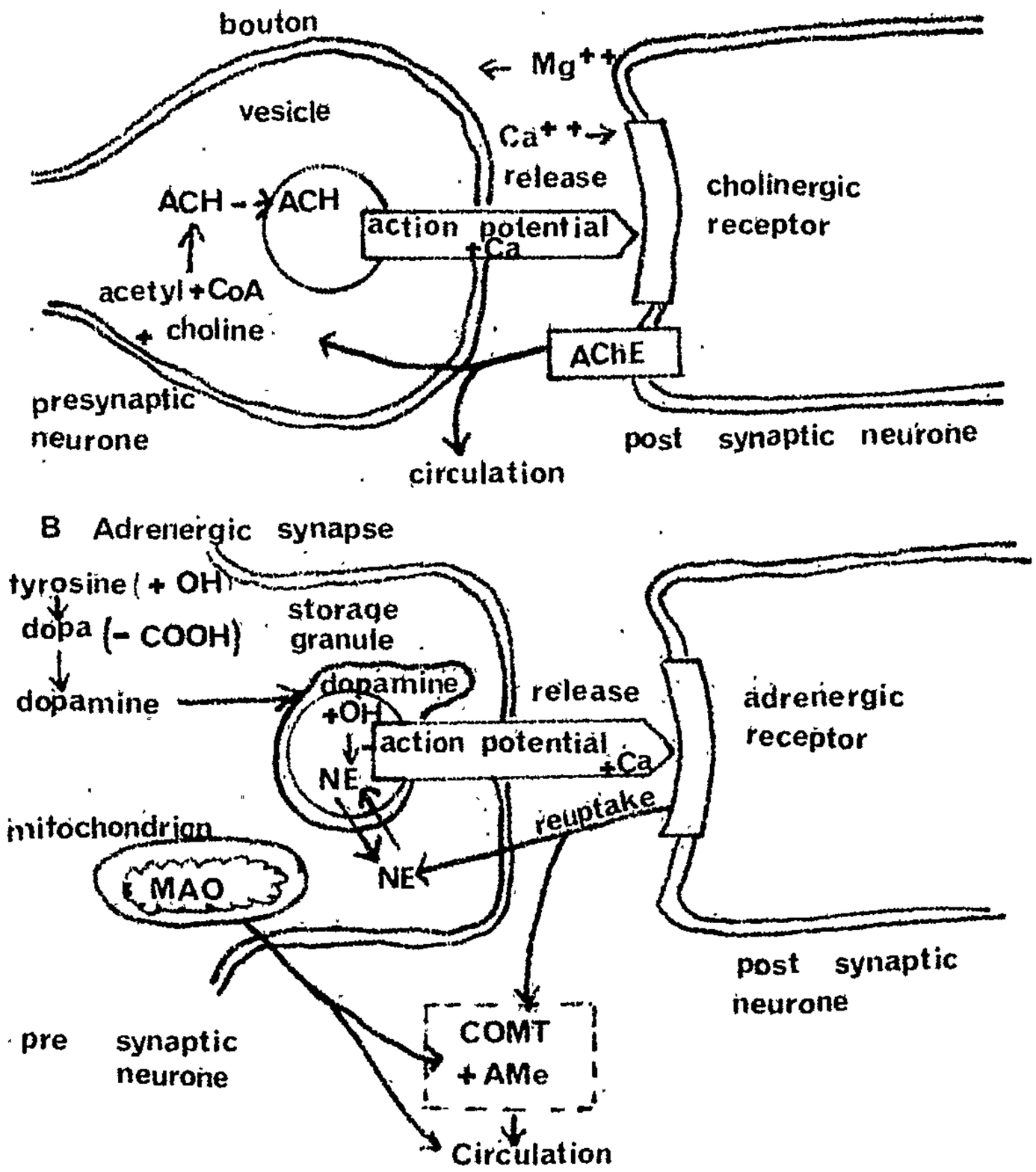


FIG NO 15 Synaptic transmission.
From Mountcastle and Baldessarini (1968)

transmitter substance released by Renshaw cells on motor neurones and interneurones of the "direct" inhibitory pathway, JOHN CURTIN report (1973), GAME & LODGE (1975). "Mutual inhibition" between Renshaw cells is also likely to be glycine mediated, GAME, LODGE & CURTIS (1975). Aspartic and glutamic acids have been strongly suggested as central excitatory transmitters, DUGGAN (1974). ACh and norepinephrine have been labelled as central transmitters at synaptic junctions, SALMOIRAGHI & WEIGHT (1967). The excitatory and inhibitory amino acids have also been implicated, KRNJEVIĆ (1967), but "There is still only suggestive evidence available for most pathways", KRNJEVIĆ (1974).

There is no "complete proof" that any of the postulated synaptic transmitter substances including ATP, 5HT, histamine, glutamic acid, GABA, glycine and other monoamines such as dopamine and noradrenaline reviewed by KRNJEVIĆ (1974) are actually responsible for transmission at synapses since none fulfil the ideal requirements and more than one transmitting substance may act at any given time. The same transmitter may affect the post synaptic cell in a different way, e.g. the muscarinic and nicotinic actions of ACh.

An interesting connection in the neuro transmitter link is the possibility that nerve cells may communicate with target cells by release of "mysterines" or neurotrophic substances which in the long term may influence the structure or function of either cell, DRACHMAN (1974a). For example, cholinergic transmission is a necessary requirement for trophic influence in the maintenance of muscle, DRACHMAN (1974b). The definitive nature of neurotrophic substances remains unknown, LENTZ (1974). These contribute to "growth, maintenance and regression either of nerve cells as a whole or of an extra-somatic element (for example, the dependence of the axon on trophic influences from the soma)", ECCLES (1974).

ADRENERGIC AND CHOLINERGIC FIBRES

Peripheral nerve fibres are known to be either cholinergic or adrenergic at effector cell synapses. All post ganglionic sympathetic fibres are adrenergic except those serving sweat glands, BRODAL (1972), whereas preganglionic sympathetic fibres release ACh on the passage of an impulse. Both preganglionic and postganglionic fibres of the parasympathetic system are cholinergic, as are the motor fibres to skeletal muscle and the prior mentioned Renshaw cell connections, BRODAL (1972).

TRANSMITTER SYNTHESIS

In vertibrates, transmitter substances are stored in vesicles 20 - 40 µm in diameter, HORRIDGE (1968) demonstrated histochemically at the boutons.

ACh synthesis takes place in the mitochondria which migrate via the axoplasm to supply nerve ending vesicles with ACh. Axoplasmic vesicular migration is still debated, KELLY (1967). It is generally accepted that noradrenaline is stored in granules in adrenergic neurones, VON EULER (1969) and chromaffin cells of the adrenal medulla, the latter cells also storing adrenaline, VON EULER (1966). The exact site of catecholamine transmitter storage at synapses awaits a firm decision between granulated and small non-granulated vesicles, KELLY (1967).

RELEASE & TRANSFER

Secretion of a particular neurochemical substance is triggered by the summation of EPSP's and IPSP's that impinge upon the presynaptic cell. The conversion of excitatory electrical energy into chemical energy is facilitated by an unknown coupling mechanism. Transmitters are released by way of fusion of the vesicular membranes with the presynaptic cell membrane, KELLY (1967).

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Once released, a neurotransmitter must diffuse across the synaptic space towards the post synaptic membrane subject to several factors, namely:-

(1) reabsorption at the presynaptic membrane,

(2) absorption by inert tissue,

(3) spread by diffusion into nearby tissue spaces,

(4) enzymatic destruction, GRUNDFEST (1969).

UPTAKE

The inhibitory or excitatory nature of each mediator is dependent on the uptake coupling mechanism in the post synaptic cell which favours the movement of specific ions across the post synaptic membrane via special ion "permselective channels", GRUNDFEST (1969), ECCLES (1957) (pp. 220-221), e.g.:-

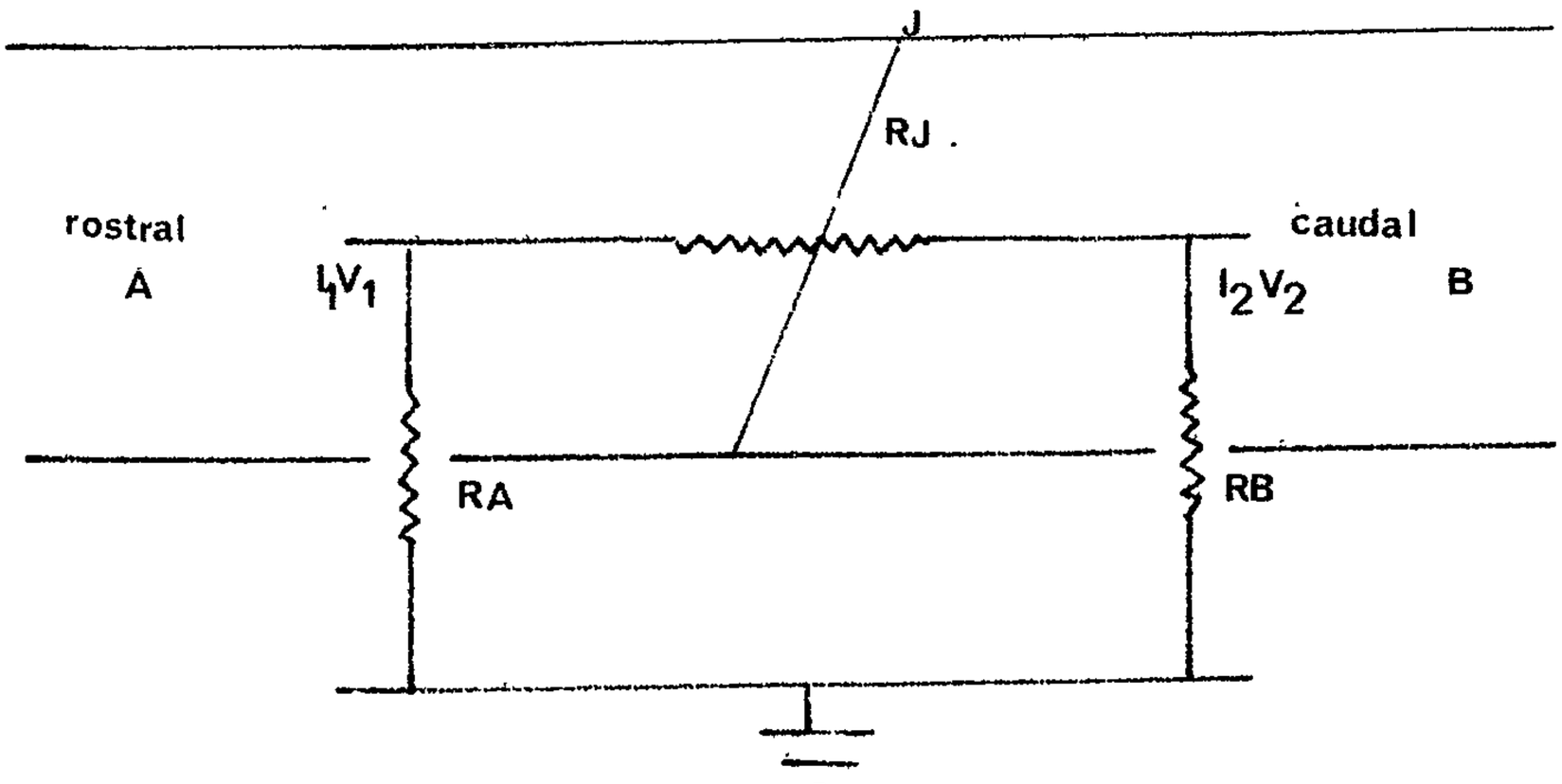
(Cl^- : Inhibitory)

(Na^+ : Excitatory)

Hence, there is no difference in the physiochemical mechanism of ionic transfer at the receptor site or nerve fibre from that which occurs at the post synaptic cell membrane.

EPHAPTIC TRANSMISSION

The electrogenesis of the spike potential from one nerve fibre to the next by "jumping the gap" is known as Ephapse (artificial synapse). Ephaptic transmission usually occurs at "tight junctions" between cells particularly epithelial cells with low coupling resistance, LOEWENSTEIN (1966) and in junctions which "lack visible extracellular cementing materials", KELLY (1967). Ephaptic junctions are thought to be highly differentiated replicas of these "ancestral epithelial precursors", GRUNDFEST (1969). The lower resistance of the pseudojunctional area (J) relative to the membrane resistance of either abutting end (A or B) (see Fig. No.16 p. 92) permits current flow in either direction and the same current effect in either segment. Thus, the general spread of unpolarized current by ephatic transmission is the same, regardless of the particular function of the cells involved. There are other forms of ephapse involving polarized junctions. (See Fig. No.16 p. 92). Ephaptic transmission in nerve fibres does not occur in damaged tissue except at the time immediately following injury or nerve transection, WALL (1974).



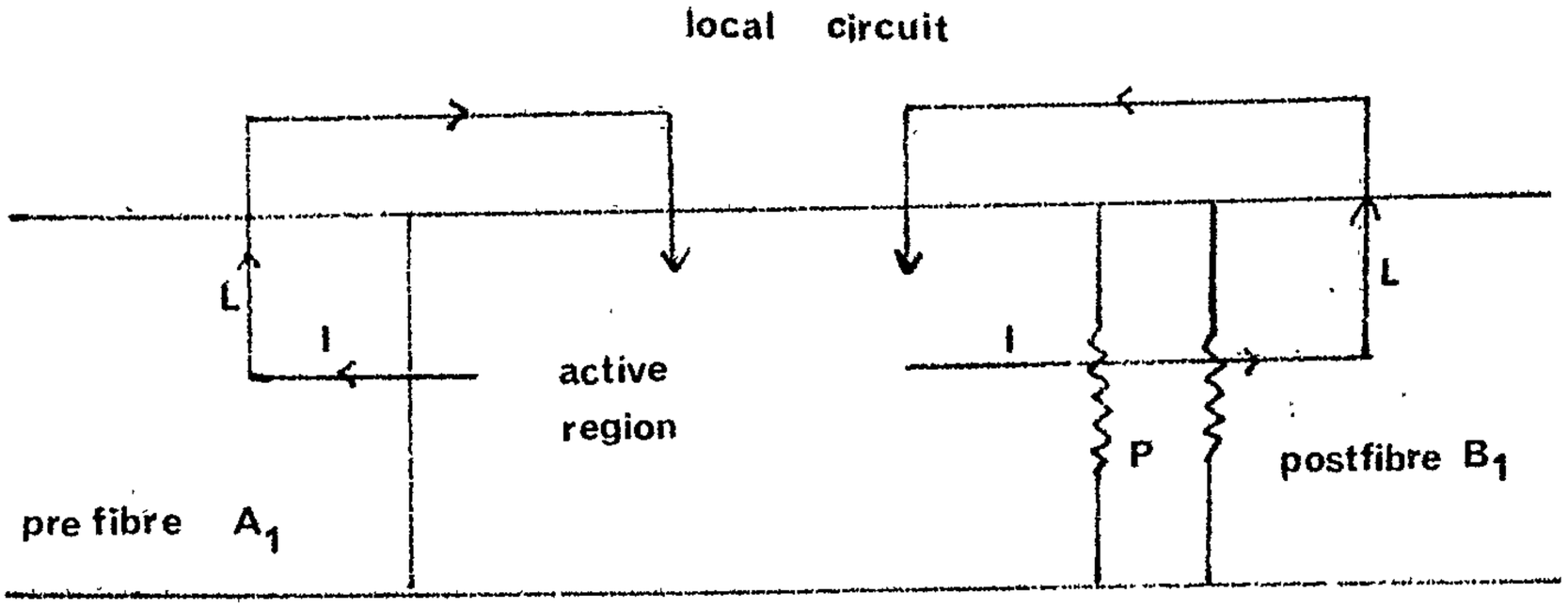


FIG NO 16 From Grundfest (1969)

J : Unpolarized ephaptic junction
P : Polarized ephaptic junction
L : Local circuits
I : Current $A_1 \rightarrow B_1$ (not reversible)
$I_1 V_1$ $I_2 V_2$: Reversible currents and spikes

Thus, it seems that pathological pain such as causalgia is unlikely to be caused by ephapse, WALL (1974), but there is no reason to preclude the electrogenesis of action potential between closely approximated axons when stimulation of one may trigger a response in the other. A connection of interest is that ephapse in the dural canal in the nerve fibre section between the ganglion and the superior border of the petrous temporal bone has been suggested as a possible cause of trigeminal neuralgia, GARDNER (1962), (1970).

EFFECT OF DRUGS AT SYNAPSES

WALL (1967) suggests that there are seven "known or suspected points" which overall govern the character of input and output at synapses, namely:-

1. Impulse transmission in the incoming axons -
    - (a) Blockade
    - (b) Depolarization
    - (c) Hyperpolarization
2. Repetitive firing in the terminal arborization.
3. Chemical transmission at junction points -
    - (a) Synthesis
    - (b) Release

(c) Transfer

(d) Reception

4. Electrical transmission at junction points -

(a) Release (presynaptic membrane properties)

(b) Transfer (extracellular impedance)

(c) Reception (postsynaptic membrane properties)

5. Propogation from contact point to axon hillock -

(a) Electrotonic

(b) Impulses travelling in dendrites

6. Threshold variation at points of impulse initiation.

7. Repetitive postsynaptic firing -

(a) Generated by bombardment of external origin

(b) Generated by intracellular mechanism.

Drugs may affect synaptic transmission at one or many at the same time of these points, WALL (1967).

THE EFFECT OF DRUGS

SYNAPTIC INHIBITION

Inhibition at synapses is either by release of inhibitor substances at the synaptic junction (post

synaptic inhibition), or by interference with the release of excitatory transmitters from excitatory presynaptic terminals (presynaptic inhibition), BRAZIER (1969b).

The activity of synaptic neurotransmitters may be modulated by drugs thereby inhibiting the transfer of electrical energy to chemical energy (i.e. secretory activity) at synapses.

EXAMPLES OF DRUG INTERFERENCE

For example, the knowledge that ACh mediated transmission is antagonised by acetylcholine-esterase at neuromuscular junctions (end plates) has been utilized in the practice of anaesthesia where muscle relexant ACh competitors tubocurarine and hexamethonium, BURN (1965) and antagonists (depolarizers such as suxamethonium) are administered prior to intubation, WYLIE & CHURCHILL-DAVIDSON (1966). In the case of tubocurarine, transmission can be restored by anti-cholinesterases (eserine and neostigmine) which ensure a flood of ACh at the end plate sufficient to overcome the competitive block.

Drug interference at synaptic junctions also includes inhibition at motor and autonomic synapses and, hence,

a diminution of the physiological responses generally attributable to noxious stimulation. Neuromuscular synapses are especially vulnerable to the action of volatile anaesthetics, KARIS, GISSEN & NASTUK (1967). The knowledge that synapses are more sensitive to drugs and anoxia and that transmitter substances may be specifically inhibited, tends to rationalise the use of drugs to prevent pain, since the brain embodies polysynaptic pathways rather than single nerve fibres, GANONG (1971).

CHAPTER III

SUMMARY

1. There is no receptor specific for pain per se but that there are several specialised classes of receptors which function in the transmission of noxious impulses from the periphery to the central nervous system.

2. These receptors signal peripheral disturbance and transmit information from changes in the tissues due to injury, ischaemia, hypoxia, acidosis or the development of inflammation.

3. Receptors generally respond preferentially to either mechanical or thermal energy but seldom to both.

4. Pulpal receptors may rely on a hydrodynamic link in the dentine.

5. Encapsulated afferent A δ myelinated nerve endings are generally mechano-sensitive. The wide variety of these receptors in the skin indicates a polymodal sensory response to mechanical stimulation not just the response of any single receptor.

6. The release of chemical substances at receptor sites may help to explain the mechanism of receptor sensitization that occurs after stimulation.

7. The classical theory assumes direct transmission of pain by specific fibres and tracts connected to a specific pain centre. It is physiologically strong but incapable of psychological extension to any great degree. To rationalize this approach, pain has been divided into sensory and emotional elements.

8. The pattern theory describes the non specific coding of sensory information into spatial and temporal patterns modified at spinal levels before final interpretation in the CNS.

9. The gate control theory attempts to consolidate the best characteristics of the other two theories with special emphasis on the convergence interaction and control of afferent sensory input at the first synapse in the spinal cord. The theory is capable of extension to explain pain mechanisms of dental

origin, pathological pain, and the mechanism of acupuncture analgesia. Many testable aspects of MELZACK & WALL's theory have so far proven to be incorrect, but the theory can not be entirely discarded.

10. Cells of rexed lamina 5 may be special intermediaries in the transmission of pain from pathological and referred sources. Specific pain fibres have been demonstrated in the ventrolateral tract.

11. Afferent input may be modulated at the 1st cord pre synapse by the central influence of stored emotional and perceptual data mediated via paramedial and neospinothalmic projection systems. Some post synaptic interaction may also occur. The synthesis of information carried by corticofugal, discriminative, and motivational systems may determine the character of the final response to pain.

NOCICEPTION

Cutaneous pain impulses of threshold intensity are detected by densely entangled networks of fine nerve endings (intercommunicating syncytium), LIVINGSTON (1943).

Individual receptors may be encapsulated or non encapsulated free nerve endings, which form a "mosaic" pattern in surface skin with little overlap in their receptive fields, IGGO (1960), (1974). Noxious stimulation of an area supplied by these nerve fibre afferents produces a wave or pattern of impulses derived from the simultaneous activation of numerous sensory receptors, LIVINGSTON (1943) related to the variability of the physiological properties of each receptor, MELZACK & WALL (1962), such as specific energy related thresholds, stimulus response curve, after discharge, and rate of adaption.

FIBRE SPECIFICITY

The concept that there are receptor units specific for pain is not generally accepted, DUNDEE (1967), although pain is not produced by overstimulation of other receptors, GANONG (1967), (1971), unless as BRAZIER (1972) suggests, there is some chemical irritation as a result of tissue distortion. MELZACK & WALL (1965)

support the idea that there exists a small number of highly specialised nerve fibres which respond only to intense stimulation, but they suggest that these fibres are not necessarily specific pain fibres - pain is only the outcome of stimulation of these fibres. To believe that there is a direct connection between a "pain receptor" and a brain centre where pain is felt is a "psychological assumption", MELZACK & WALL (1970). This notion is supported by IGGO (1974) who denies the existence of a "single universal pain receptor", but at the same time he accepts that there are peripheral cutaneous receptors which respond in a special way to a wide range of thermal, mechanical and electrical stimuli.

Individual receptors respond differently to the same external stimulus, DARIAN-SMITH (1966).

RECEPTOR TYPES

IGGO (1974) describes three functional groups of cutaneous receptors, namely, mechanoreceptors, thermo-receptors and nociceptors with sub groups related to extremes of temperature and mechanical stimulation.

The MECHANORECEPTORS are served mostly by A type myelinated afferents which are sensitive to low grade tactile stimuli (brushing, stroking) but possess a

higher threshold to thermal stimulation. These receptors present themselves histologically as different nerve endings in hair follicles or encapsulated receptors (Pacini corpuscles, Ruffini endings, Merkel touch spots or epidermal endings) classified by DARIAN-SMITH (1966) as rapidly adapting hair cells, touch receptors, and pressure receptors. (See Table No. I p. 103)

THERMORECEPTORS: exhibit sensitivity for small changes in temperature but are less affected by mechanical stimulation (higher mechanical threshold).

NOCICEPTORS: Afferent discharge is evoked only if noxious stimulation is of sufficient intensity to cause tissue damage. These receptors are sensitive to extremes of temperature (>45^{o}C, <10^{o}C), and severe mechanical stimulation. IGGO & OGGOWA (1971) have demonstrated the existence of specialised skin nociceptors sensitive to severe thermal stimuli. They renamed these receptors "thermal nociceptors".

THERMAL NOCICEPTORS

Myelinated and unmyelinated afferent fibres serving heat and cold (<3^{o}C) sensitive receptor units have been isolated in primates. These afferent units are

TABLE NO. I

CUTANEOUS NERVE TERMINATIONS

Skin Type	Free Nerve Endings	Terminals with Expanded Tips	Encapsulated Endings
Glabrous skin			
a. Epidermis and dermal papillae	+	Merkel's discs	Meissner corpuscles
b. Subpapillary dermis	+	+	Pacinian corpuscles
Hairy skin	+	Pinkus hair disc (aggregations of Merkel's disc)	Laminar network associated with follicle
Deep fibrous Structures	+	+	Pacinian corpuscles

From DARIAN-SMITH (1966)

also sensitive to mechanical pressure, IGGO (1959).

The presence of similar myelinated afferents in man could,in part, explain the phenomenon of "fast pain" where impulses from very hot objects are carried by rapidly conducting myelinated afferents serving thermal nociceptors. BESSOU & PERL (1969) observed that gradual heating of the skin to temperatures >60^{o}C or rapid skin contact with objects at higher temperature (>75^{o}C) produces partial inactivation of receptor units. More moderate temperature increases, applied gradually, produce enhanced responsiveness with lower threshold to further thermal and mechanical stimulation.

This enhanced thermal and mechanical sensitivity was found to persist for some time and may be due to inflammatory changes in the skin directly resultant from the elevated skin temperature. A simple illustration is the hypalgesic skin of facial sunburn where threshold to mechanical stimulation is lowered so that normally innocuous pressure causes afferent discharge from nociceptors in the skin surface. Initially, stimulation of an afferent fibre lowers its threshold to further stimulation by an unknown mechanism. This "sensitization" takes place in a few seconds and

therefore is not necessarily due to the inflammatory reaction which takes some time to develop, WALL (1974).

CHEMORECEPTORS: It is believed by some authors that irritant chemicals released at the receptor site may sensitize nerve endings and cause pain.

LIM (1967) describes pain receptors as finely entangled unmyelinated end fibres which occupy connective tissue spaces near capillaries and venules. He produces evidence to indicate that these receptors for pain are chemoreceptive and not nociceptive, since pain results from the application of synthetic and natural bradykinin at the receptor site. He states, however, that "this does not rule out the classical causal relationship between nociception and pain, but indicates that axons and receptors are stimulated accidentally and unspecifically as they lie in the path of injury". The chemoreceptive nature of nerve fibre receptors is keenly debated by IGGO (1974) who casts much doubt on the viability of LIM's theory.

OTHER NOCICEPTORS

BURGESS & PERL (1967) also describe a class of myelinated mechanical nociceptor which responds only to severe mechanical pressure and which does not respond to severe thermal stimuli or to solutions of strong acids and chemicals such as bradykinin introduced by

intra-arterial or intradermal techniques. These fibres cease to respond to mechanical stimulation when the stimulus is removed (i.e. stimulus locked). However, MELZACK & WALL (1970) argue that these small A δ nociceptors are most likely to represent the upper limit of a whole range of "receptor fibre thresholds" rather than a fibre of a specific modality class. BESSOU, BURGESS, PERL & TAYLOR (1971) describe a C type mechanoreceptor which responds to severe stimuli and conducts at velocities <30 meters/sec.

BRAZIER (1972) cites the description of this specialized minority fibre class of mechanoreceptor by CHRISTENSEN & PERL (1970), pointing out that the question of specific pain fibres now remains in the balance.

It is notable that all three groups of lamina I neurones described by CHRISTENSEN & PERL (1970) receive inhibitory inputs as well as excitatory connections from afferent receptors. It is likely that Rexed lamina I receives an input directly from dorsal root C fibres. Neurones in this lamina could form a "specialized sensory nucleus" with sensory discriminative power, CHRISTENSEN & PERL (1970). Thus, the high degree of specialization, as well as the discovery of fibres which respond only to noxious stimuli, suggests that the concept of pain as a specific

sensation is more real than general evidence would at first appear to indicate.

ORAL RECEPTORS

It is generally accepted that oral structures are more sensitive than skin since oral epithelial extensions of nerve fibrils reach most mucous membranes, GROSSMAN & HATTIS (1967). This difference in relative sensitivity is also connected to the clinical facts that carious and filled teeth are more sensitive to thermal changes than skin, and that skin is fairly well insulated by its outer horny protective layer. The number of oral nerve endings diminish progressively anteroposteriorly, especially in the tongue and palatal tissue, GROSSMAN & HATTIS (1967). This anatomical fact tends to substantiate the clinical and experimental knowledge that the localization of oral and dental pain becomes progressively more difficult from the incisor to the molar area, FRIEND & GLENWRIGHT (1968). Sometimes the source of pain is found on the opposite side to the symptom, HARRIS (1973). An interesting connection is the consistent appearance of greater numbers of receptor units in the epithelium overlying the palatal rugae than in the troughs between them. This histological evidence confirms the clinical fact that

insertion of a needle (local injection) in the trough area is less painful than a similar injection into the crest of the rugae.

DENTAL RECEPTORS

Instrumental stimulation of a tooth in the clinical situation reveals that dentine and pulp respond to both thermal and mechanical stimulation. Sensory information from enamel converges physiologically at the dentino-enamel junction due to receptor field overlap in the pulpal tissue, MUMFORD & NEWTON (1970), as well as resulting from convergence from the first to subsequent neurones in the trigeminal pathway, MUMFORD & NEWTON (1971). Pain or prepain sensations are the only response evoked by tooth pulp stimuli including electrical stimuli, MUMFORD (1965), BROOKHART, LIVINGSTON & HAUGEN (1953). DELLOW (1962) suggests that dentinal pain is conducted via "pseudo synaptic connections" from odontoblasts to pulpal receptors, a large fibril network existing at the dentino enamel junction. But the evidence of BRÄNNSTRÖM (1963), ANDERSON, HANNAM & MATTHEWS (1970) indicates that there is an "hydrodynamic" link between the dentinal tubules and the afferent receptors in the pulp. Apparently "pain" is the outcome of any stimulus, thermal

mechanical or osmotic, which causes displacement of the fluid content of the dentinal tubules. Clinical measures such as intermittent burring, air blast, and suction also provoke fluid movement; outward flow is more likely to cause pain than inward flow, MUMFORD (1973). Clearly the rate of flow is important; substances with higher osmotic pressures are more likely to cause pain. However, fluid flow through the dentine may not be the only mechanism by which stimuli produce pain when applied to dentine, since water at body temperature causes fluid flow but not pain, and other "hot stimuli" may have a more direct effect on nerve terminals, HORIUCHI & MATTHEWS (1973). Fluid movement also takes place as a result of increased intra-pulpal pressure in pulpal inflammatory conditions, SCOTT (1975). Pulp extirpation fails to eliminate the response of the tooth to pressure and vibration, indicating that the bulk of mechanoreceptors are external to the tooth in the periodontium. This clinical evidence is confirmed histologically by GRIFFIN & HARRIS (1974) in part one of their four part treatise, and documented by DARIAN-SMITH (1973) who cites previous work of HARRIS & GRIFFIN (1968) on the three fibre types in pulpal tissue and WILSON (1968) on fibre size and its relation to pain sensation from the pulp and periodontal tissue. It is notable that pain is thought to be transmitted by beaded

myelinated nerve endings with axonal expansions as well as by fine unmyelinated nerve endings in the dental pulp, HARRIS & GRIFFIN (1968).

BARKER (1961) summed up the various features of pain carrying fibres. He noted that pain from periodontal structures was distinguishable in part from pulpitic pain because of the difference in nerve fibre size and therefore in the rapidity of impulse transmission. DARIAN-SMITH (1973) observes that the peripheral mechanism of toothache will remain a mystery until the functional properties of small myelinated and unmyelinated fibres in pulpal and periodontal tissue are analysed. While different fibre sizes may contribute to change in the quality of pain, the structure of the pulpal fibres is the same as that of fine myelinated cutaneous nerve endings. Thus, the conduction of noxious impulses in either set of fibres appears to be identical.

PAIN MECHANISMS

THEORETICAL CONCEPTS

The variance of opinion concerning the way in which information about pain is carried from the receptor mechanism to the CNS constitutes a debate which tends to parallel the receptor controversy.