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THE VALUE OF CREOSOTE IN INSOMNIA.

THESIS presented for the degree of M.D. of the
University of Edinburgh

by

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The prevalence of periodicity throughout the material world is a striking fact. The individual cells, as well as the whole organism, pass their existence in alternating periods of rest and activity.

The period of physiological rest of the individual as a whole, and of his conscious relationship to the external world is termed "sleep."

It has been defined as "a suspension, a more or less complete interruption of conscious and voluntary activity."⁽¹⁾

Many theories as to its causation have been put forward. No one of them is entirely satisfactory.

I. That it is due to the action of special organs or tissues.

- (a) The Thyroid Gland⁽²⁾
- (b) The arachnoid plexus⁽³⁾
- (c) The Ganglia at the base of the brain.⁽⁴⁾

The idea that there is a stasis of blood in the thyroid which becomes swollen at night owing to this accumulation is contrary to fact and untenable as a cause of sleep, equally so is the theory that the arachnoid plexus fills the ventricles during sleep, and so prevents communication between the brain and the rest of the body.

The ganglia at the base of the brain were supposed

(1)

Physiology of the Nervous System. Morat.

(2)

Gazetta Sard. 1858. Formeris. Osborne. London Med. Gaz. 1849. vol.viii. p.977. (4)

Purkinje.

(1)



by Purkinje to become distended and compress the "corona radiata" thus interrupting communication.

II. That the effect is produced through the agency of vaso-motor mechanism.

(1) The theory of cerebral congestion in sleep was long and widely held. Certain conditions occurring in coma and narcosis by drugs helped to keep up the fallacy.

By actual observation and experiment it has been proved that a condition of cerebral anaemia obtains during sleep. (2) Blumenbach first actually noted this anaemia in a case of injury to the skull, and it has been amply confirmed by Durham and Hammond and more conclusively by Torchanoff's experiments on puppies. Along with this anaemia there is a fall of intra-cranial pressure.

These two conditions not only accompany but also precede sleep, as shown by the manometer experiments (3) of Hammond.

This has an important bearing in relation to insomnia and the methods of inducing sleep. The work done by Leonard Hill (4) on the cerebral circulation and the theories deduced are widely accepted. He argues that in all physiological conditions the volume of blood in the brain is but slightly variable, that any increase in the arteries means corresponding diminution in the veins, and that there is no general or local vaso-motor system at work

(1) Cappie, Theory of Sleep. 1872. Physiology - Carpenter.

(2) Blumenbach, Physiological Journal, 1795.

(3) Quarterly Journal of Psych. Med. 1869.

(4) Clifford Allbutt vii. Article "Experimental pathology of cerebral circulation," Leonard Hill.

in the brain, though fibres are histologically demonstrable. (1)

Insufficient allowance is, according to Ford Robertson, made for variations of cerebral-spinal fluid in the lymph-spaces of brain, and for the elasticity of tissues and the compressibility of the brain. The fact for our purpose is that the vaso-motor mechanism in the cerebral circulation has little action, and consequently, a general increase of blood pressure causes increased flow through brain. (2)

A rhythmic periodicity in loss and gain of tone of the vaso-motor centre is suggested by Howell (3) as the cause of sleep.

The centre becoming relaxed, after great fatigue, or a lesser amount of fatigue plus the withdrawal of all forms of external stimulation, general blood pressure falls, the cutaneous vessels dilate, cerebral anaemia occurs, and sleep ensues. It is to this end that we adopt our preparations for sleep; the exclusion of light and sound, the recumbent posture, and the many methods of producing monotony.

III. Chemical theories have been advanced.

(a) Want of Oxygen in the brain, the idea being that there is a reserve of Oxygen in the tissues, and when that is used up, sleep ensues.

(1) Encycl. Med. vol.V. p.313.

(2) Foxwell. B.M.J. 1905. Oct.21.

(3) Howell. Journal of Experimental Medicine, 1897.

(b) ⁽¹⁾ That there are certain fatigue products, leucomaines, the result of tissue Katabolism, which act as narcotics on the brain cells, reaching them by the blood. In this connection the action of the urethanes is interesting, as urea is largely formed by the expenditure of muscular energy, and the activity of nerve-cells produces in them lactic acid. ⁽²⁾

IV. Theories connected with the histology of the brain. Rable Rückhardt first enunciated the influence of amoeboid movements of cerebral cells on psychic processes and sleep. Lepine, Ramon y Cajal, Matthias Duval, and Lugaro have followed, and the more accurate knowledge of the nerve-cell which has grown from the work of Golgi, Ramon y Cajal, Waldeyer, &c., has led to many fresh ideas as to the conductivity of nervous impulses. Each cell, consisting of body and axis-cylinder process (in some cells more than one) and numerous short branching processes, is now considered to be a separate isolated unit, and neighbouring cells are in relation with each other only by the contiguity of their interlacing branching processes, there being no structural continuity between them. Every nervous path is formed of a chain of nerve-cells, and an impulse on reaching the ends of the processes of one cell, does not pass directly through to, but excites a fresh impulse in the neighbouring cell or cells.

(1) Lants. Amer. Med. Psych. Journal. Nov. 1895.

(2) Physiology. Schäfer II. 607.

(1)

The idea of contiguity without continuity, the inter-
lacement of the branches, is expressed by the word
"synapses," or claspings. The short processes are called
dendrons and their finer terminations dendrites, but the
whole terminology is at present undefined. Nervous im-
pulses are started, not in the cell-body, but in the
dendrites, the microscopic evidence that the fibrillae
of the axis cylinder do not end in the body but pass
through to the dendrons showing this. The dendrites end
in small knobs or points, and their terminal portion bears
small bud-like projections. (2)

Sir W. Gowers expresses
the view that in sleep there is retraction of the terminal
ends of the dendrites and a drawing in of the "buds,"
thus breaking off connection with neighbouring cells.

(3)
But Lugaro has shown on experimental evidence that
rapid movements of retraction and expansion occur in
functional activity, and that the position of rest is one
of expansion, retraction occurring only in response to
stimuli. During sleep he maintains that there is a
general expansion of the processes implying multiplication
of contacts and wide diffusion. The power of contractility
is greatly diminished with fatigue. (4)

Lugaro conceives
that in insomnia of mental origin the cortical neurons
are in an irritable condition in which their processes
are unable to assume the position of rest (general ex-

(1) Gowers. Lancet, 1906, July. (2) Ibid.

(3) Encycl. Med. vol.V. 309. (4) Ibid.

pansion) but continue to retract and expand on receipt of every stimulus. The whole enquiry relates rather to the conditions than the causation of sleep, which is still unexplained, and as Sir M. Foster ⁽¹⁾ has said, "the essence of the condition is to be sought in purely molecular changes."

Passing to the consideration of the actual phenomena during normal sleep. There is general relaxation of muscles, the eyelids droop, the pupils are retracted. The heart beats more slowly and with less force, the surface blood-vessels dilate, and actual increase in the size of the limbs can be demonstrated. ⁽²⁾ The amount of blood to the brain is diminished and intra-cranial pressure falls; according to Krause a drop of one millimetre occurs at the actual moment of going to sleep. Intra-cranial pressure and anaemia are not constant quantities during sleep, stimuli from without, insufficient to awaken the sleeper, raise the pressure and increase the flow of blood.

Respiration is slower, and in men more costal in type, and marked changes occur in the gaseous interchanges of the body, ⁽³⁾ the amount of Carbonic Oxide eliminated is diminished and the amount of Oxygen ^{absorbed} is increased.

Diet also has a direct bearing on this. With the dilatation of skin vessels, its eliminative function is increased. All the processes of digestion may be continued

(1) Physiology. Foster. p.1552. (2) Howell. Journ. Exp. Med. vol. II. 1897.
(3) Hyslop. Encycl. Med. vol. II. 195.

during sleep, and the kidneys and other glands continue their functions.

(1)

Certain processes of cell-metabolism are diminished and notably the formation of red blood corpuscles decreases. Actual processes connected with cell nutrition, development and growth would appear to advance more favourably during sleep, and this is probably the explanation of the necessity for longer sleep in children, rather than their relatively small powers of consciousness as is argued by de Menacéine.

The reflex arc is still active, and many movements of voluntary muscles are performed without waking in response to stimuli. The knee-jerks are diminished, but occurrence of noise or other external stimuli increase them without waking the sleeper. In the brain itself the centres in relation to the receipt of impressions from the special sense organs can still show functional activity. The brain-cells concerned in the most highly-evolved centres of consciousness, ideation, and volition are at rest.

The phenomena connected with dreaming, the somnambulistic and hypnagogic states do not concern the purpose of this thesis.

(2)

It is possible to estimate the depth of sleep at any time. In healthy sleep the greatest depth is gradually attained in the first two hours, maintained for about

(1)

Ibid.

(2)

Hyslop. Encyl.Med. vol.II. p.199.

three hours (after a slight rise at the end of the second hour), and then slowly and gradually lessened until awakening occurs at the end of seven or eight hours. Many conditions prevent the regular recurrence of such normal sleep. Inability to attain or maintain sleep constitutes "Insomnia."

Temperament is of enormous importance in the causation of insomnia. The neurotic, highly sensitive, and excitable, particularly those in whom vaso-motor action is easily disturbed are especially predisposed to it. Any condition that raises the blood pressure, or increases the excitability of the brain-cells, or prevents their dissociation, acts as an exciting cause.

(1)

Sir J.Sawyer has divided cases of insomnia into the following classes:-

- I. Symptomatic: caused by such conditions as cough, fever, pain, &c.
- II. Intrinsic, including -
(a) Psychic, (b) Toxic, (c) Senile.

If our knowledge of the causation and conditions of sleep were more accurate it would be wiser to class insomnias accordingly. Thus the "senile" of Sir J.Sawyer would go into a class including all circulatory disturbances producing insomnia; the cases resulting from atheromatous arteries, increased blood pressure from over-exertion, or the effects of dyspepsia would all be united. The conditions affecting the nerve-cells and preventing the

(1)

Insomnia, its cause and cure. Sawyer. p.21.

dendrites assuming the position of rest, e.g., worry, anxiety, and certain poisons, would form a second class, and all forms of external stimuli, a third.

For the purpose of this thesis it is convenient to classify insomnia according to its type as follows:-

1. Sleep easily attained but disturbed by slight causes;
2. Sleep easily attained but of short duration;
3. Sleep difficult to attain, but when reached yielding good period of sound sleep.
4. Sleep difficult to attain and easily disturbed.

It is with cases of type 3 that this thesis is mainly concerned, and the conditions most likely to produce it are over-exertion, either mental or physical, and digestive disturbances. Slight exertion in those weakened by illness - particularly influenza and the infective fevers - or suffering from the effects of over-indulgence in tobacco, or other heart or nerve poisons, has the same effect as over-exertion in the healthy.

The difficulty of getting to sleep manifests itself in two different ways. In the first sleepiness soon supervenes, the early stages are quickly and normally passed through, and sound sleep is all but reached before interference occurs. In the second there is no tendency to sleepiness, and varying periods of restlessness and increasing wakefulness occur, which may prevent sleep altogether, or only delay it.

As far as I have been able to discover, the exhibition of creosote with the direct object of affecting either of these conditions has not been recommended by any authority.

(1)

Creosote is a mixture of cresols and other homologous compounds obtained by the destructive distillation of coal-tar. The name is derived from **κρέας**, flesh, and the root of **σώζειν**, to save, and indicates the first use of the drug as a meat preservative.

It occurs in commerce in two forms obtained from pinewood and beechwood respectively. The former, anhydrous, consisting mainly of creosol; the latter (the official preparation) is more soluble in water and contains on an average -

40% creosol,

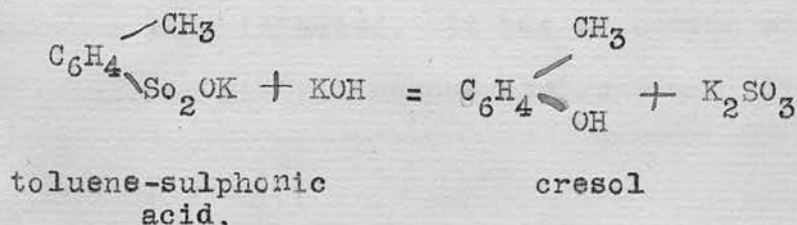
40% monatomic phenol (15% cresylols), and

20% guaiacol.

(3)

Creosol $C_6H_3 \cdot CH_3 \cdot (OH) (O \cdot CH_3)$ is the mono-methyl ether of Homo-pyrocatechin, while Guaiacol $C_6H_4(OH) (O \cdot CH_3)$ is the mono-methyl ether of pyrocatechin.

The cresols are toluene-phenols and may be obtained from the amido-compounds.



(1)

Organic Chemistry. Wade. p.311.

(2) The Extra Pharmacopoeia. Martindale & Westcott. p.204.

(3) Organic Chemistry. Bernthsen. p.425.

(1) The methyl group is protected by the hydroxyl group, and is not easily oxidised into carboxyl.

(2) P.cresol is produced by the decay of albumen.

The cresols very closely resemble phenol.

In the preparation of phenol from benzene-sulphonic acid, the toluene-sulphonic acids are hydrolysed to the cresols.

(3) Creosote is a colourless or straw-coloured fluid with a strong odour and acrid burning taste. It is soluble in ether and alcohol, but only slightly in water. When mixed with an equal volume of collodion it does not gelatinise. It volatilises at 100°C and leaves no stain on white filter paper. A 1% solution with a drop of dilute neutral solution of Ferric Chloride yields a green coloration changing to brown.

Creosote is antiseptic, disinfectant, deodorant, and germicide. A solution of three parts in one thousand kills tubercle bacilli in two hours.

(4) It acts, in small doses, as a gastric sedative, and has a corresponding sedative action on the respiratory mucous membranes when inhaled, and on urethral mucous membrane when injected. It has an action similar to that of garlic on gastric mucous membrane and stimulates appetite. (5)

(1) Wade. p.311.

(2) Bernthsen, Organ.Chem. p.423.

(3) Materia Med. Garrod. p.175.

(4) Ibid.

(5) Price. Edin.Med.Journal. 1905.

(1)

It slows respiratory rhythm, checks cell-metabolism, and is a dynamogenic agent. Dr Savage allows it no sedative action on mucous membrane but says: ⁽²⁾ "It is antiseptic and deodorant and when absorbed has a well-marked physiological action, causing great embarrassment of respiration, and weakness of the heart's action."

In another paragraph he says: "In its general physiological action guaiacol is like creosote, an irritant to the mucous membrane and a cardiac depressant." He gives no grounds for these statements. Creosote has a local anaesthetic action on nerve-endings less powerful than that of phenol.

(3)

In toxic doses it acts as an irritant, and causes excessive perspiration, coma, meningitis, and inflammation of stomach and kidneys. Its constituent guaiacol was thought to be its active principle, but was found in ⁽⁴⁾ practice to have no advantage.

Creosote was first introduced into therapeutics by Bouchard in 1877. It has been used most largely in cases of Phthisis and in gastric disorders. It has no specific action in the tissues on the tubercle bacilli.

The official dose is M to Mv, but very much larger doses have been taken, a dose of 340 minims ⁽⁵⁾ per diem for months consecutively has been given with no toxic effects.

(1)

Bravat and Sallet.

(2) Pharmacology. Hale White. p.466.

(3) Chaumier. Lancet, 1898.

(4) Ibid.

(5) Brit.Med.Journal, 1898, p.144.

When used for the purpose indicated in this thesis, I have always used doses of Mi or Mii and have found pills or palatinoids to be the best form of administration.

We now turn to the study of those drugs which have recognised hypnotic action. They may be classed as follows:-

1. Organic Substances.

- (a) Various compounds containing one of the Halogen elements in combination, e.g., Chloral.
- (b) The alcohols and close allies, e.g., paraldehyde.
- (c) Compounds containing Sulphur united with alcohol radicles, e.g., sulphonal.
- (d) Compounds of urea with alcohol radicles, e.g., Urethane.

2. Drugs derived from vegetable kingdom and the alkaloids obtained from them, e.g., Opium and Morphine.

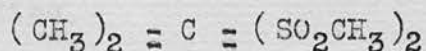
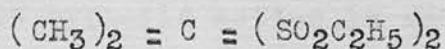
In studying organic substances in relation to their pharmacological action we note that the structure of the molecule - the nature of the grouping of the elements - more than the influence of individual elements, is the important factor.

All the members of Schmiedeberg's "alcohol group" - alcohols, ethers, aldehydes, and ketones - have the action of first exciting and then depressing the cells of the cerebral cortex and bulb. All the primary monatomic alcohols of the fatty series show a like pharmacological action, i.e., an intoxication followed by narcosis and in fatal doses paralysis of the respiratory centre, and their toxicity is in direct proportion to their molecular

weight. In many compounds the substitution of "ethyl" for "methyl" radicles seems to be productive of, or to increase, hypnotic effect, e.g., tri-methyl carbinol - $(\text{CH}_3)_3 \text{COH}$ - is almost inactive, while dimethyl-ethyl carbinol - $(\text{CH}_3)_2 \text{C}_2\text{H}_5 \text{COH}$ - is an active hypnotic; and in many bodies besides the alcohol group we notice some causal relation between the introduction of intact alkyl radicles of the fatty series and an action which from the first, or in its later stages, tends to be narcotic or depressant.

In many organic substances a very slight difference in chemical structure may mean a great difference in physiological action. For instance, out of eight isomeric amyl-alcohols which exist, only one (introduced by von Mering under the name of amylene hydrate) is markedly hypnotic.

Again take the three bodies:-



The first is sulphonal and has marked hypnotic action, the second has exactly similar action, while the third is practically inactive. We note then the importance of alkyl radicles, particularly "ethyl" on hypnotic action.

The presence of the Halogen elements in substances of various types is attended with anaesthetic, hypnotic or narcotic properties. All the chlorine derivatives of methane -

— CH_3Cl , CH_2Cl_2 , CHCl_3 , CCl_4 —exert powerful anaesthetic effect, increasing with the number of atoms of Chlorine. The Bromine and Iodine substitution products exhibit similar tendencies, e.g., ethyl bromide and ethyl Iodide are both anaesthetic. According to Binz these compounds owe their action to the actual liberation of the halogen in the body, but this does not seem to be the case; further it does not seem that the introduction of the halogen atom is the cause of the hypnotic effect, as we find the properties of Chloral to be already present in paraldehyde - which is the polymerised form of its halogen-free precursor, and yet a body oxalethylene has mainly convulsant action while its chlorine derivative is a strong narcotic. The actual essential in these Halogen compounds has not been satisfactorily explained.

The bodies in group(c) all contain alkyl radicles, and that it is not solely the introduction of the SO_2 group that causes hypnotic action is shown by the example given above to illustrate the difference of action in closely allied bodies.

The bodies in group (d), the urethanes, are also seen to contain alkyl radicles.

Turning to aromatic substances we find that the Hydrocarbons of the benzene series are more active than the paraffins and still more so on the entry of hydroxyl into the molecule, while the entry of carboxyl seems to diminish activity.

The main action of the monohydroxy-derivatives of the aromatic hydrocarbons is to exhibit toxicity to the lower organisms, and they thus form the great class of antiseptics and this action is particularly prominent in substances containing the OH group, e.g., C_6H_5 OH carbolic acid or phenol to which the cresols are closely related, both in constitution and physiological action.

Dujardin-Beaumez formulated the law that among the derivatives of Benzene, those which contain Hydroxyl are antiseptic, those which contain an amido-group are antipyretic, and those which contain a hydrocarbon residue, chiefly analgesic.

This is very inexact, the only point for our purpose being that in the great group of Antipyretics and analgesics we still find the introduction of the ethyl radicle bringing with it hypnotic action, e.g., phenacetin. We may further state here that certain substances have the power of acting as local anaesthetics, i.e., they abolish the functions of the sensory nerves with the endings of which they come in contact, e.g., carbolic acid, creosote, cocaine.⁽¹⁾

Previous to 1869, there were no synthetically-produced chemical substances available as hypnotics. In that year Oscar Liebreich introduced Chloral into therapeutics. His supposition was that it became transformed into Chloroform and a formate of its base in the human body,

(1) Pharmacology. Hale White. p.87.

as it did in alkaline solutions outside. This is not the case, but it is still the most valuable hypnotic of its class. Chloral, CCl_3CHO , is the aldehyde of trichloroacetic acid and is a pungent liquid, boiling at 97° . Its Hydrate is a crystalline substance melting at 57° and contains two hydroxyl groups linked to the same Carbon atom.

Chloral acts rapidly as a hypnotic. It slows the pulse, lowers the blood pressure and depresses cardiac action. It causes dilatation of cutaneous arterioles, and slackens respiratory movements and diminishes body-heat and the reflex excitability of the spinal cord. It causes flaccidity of muscles and lessens the functional activity of nerve cells. Its effects thus approximate very closely to the conditions we have seen to obtain in normal sleep.

Many compounds and closely allied bodies to Chloral have been introduced, all having similar action, e.g., Chloralamide produced by addition of formamide to Chloral Hydrate; Chloralose, made from anhydrous chloral and glucose; Hypnal, a compound of Antipyrin and Chloral; Chlorobrom, a mixture of Chloramid and Bromide of Potassium.

(1)
The Bromides were first used to cause absorption of inflammatory products but were found to cause drowsiness and to have marked antaphrodisiac action. They all have direct action on nervous tissue rendering the cortex of

(1)
Mat.Med. Garrod. p.24.

the brain less excitable; according to Gowers the action is on the dendrites of the nerve cells, and Wright claims to have shown that in excessive doses Potassium Bromide produces degeneration of the cortical cells which begins in the periphery of the dendrons. ⁽¹⁾ Under their influence the reflexes are rapidly reduced, the sensory tracts of cord being depressed before the motor. The bromides have a slight depressant action on the heart and circulation.

The action of alcohol is said to be stimulating to the cortical cells and then depressant, but it acts from the higher centres downwards, and is probably depressant from the start, the well known excitement and volubility attending its absorption being due to the depressant action on the very highest centres of inhibition and control. It also dilates the cutaneous vessels, but is stimulant to the heart. It lowers temperature. Paraldehyde has similar effects but the preliminary intoxicant stage is not so common.

The group containing Sulphur in combination was introduced owing to the researches of Bauman and Kast. The Sulphones are bodies containing in their molecules the oxidised Sulphur group SO_2 to which alkyl radicles are linked, with direct association between the Carbon and Sulphur atoms. All Sulphones which contain no alkyl group directly linked to central Carbon atom are excreted unchanged and have no action. Of those that become de-

(1) Pharmacology. Hale White.

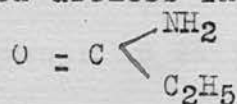
composed in the body, only such as contain at least one ethyl radicle have hypnotic action, those containing only methyl radicles having none.

Sulphonal is obtained by oxidation from acetone-mercaptan and is di-methyl-methan-di-ethyl sulphone and by substituting ethyl for methyl radicles two other bodies trional, methyl-ethyl-methane diethyl-sulphone and tetronal-diethyl-methane-diethyl sulphone were obtained having increasingly active hypnotic action.

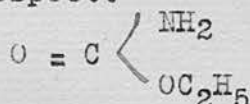
This was found to be true in dogs on which Bauman and Kast conducted their experiments, but in man trional seems to be the most active. The reason is unknown.

Sulphonal acts - slowly because of its insolubility - on higher nervous centres, but may also cause transient raising of blood pressure. ⁽¹⁾ Trional is of greatest value in sleeplessness from over-work and in neurasthenic conditions.

Urethane was the first successful attempt to produce a substance uniting the hypnotic action of an alkyl-radicle-containing body with the antidepressant influence of an Ammonia derivative. The basic amines and acid-amides had proved useless in this respect.



Propionamide



ethyl urethane.

Urea itself, the diamide of Carbonic Acid $Co (NH_2)_2$ has no hypnotic action, but the compound of it with ethyl

(1) Savage. Pharmacology. Hale White. 305.

alcohol - urethane - is markedly hypnotic. It was introduced by Schmiedeberg, and has been followed by two other bodies, methyl-propyl-carbinol urethane, or Hedonal; and diethyl-malonyl-urea, or veronal - both of which have powerful hypnotic action.

These three drugs seem to have little action on circulation, but exert their influence on the nerve-cells, causing the cell-processes to remain in the condition of rest. It is very probable that bodies resembling them are produced normally in the body by fatigue.

Of the alkaloids obtained from opium, hyoscyamus, &c., we need only point out that the complex molecule of morphine contains two hydroxyl groups, and that in Codeine, which excites the cord more and depresses the cortex less, one of the H atoms of an OH group has been replaced by the methyl radicle. And with our present knowledge of their constitution they seem to follow the same lines as other less complex organic bodies.

The study of the chemical constitution and affinities of "Creosote" thus leaves it apparent that it possesses none of those peculiarities of structure found in any of the groups of well-known "hypnotics." Neither has it any action on cerebral tissue, nor on the circulatory system suggestive of hypnotic influence. On the other hand it is very closely allied to the phenols in chemical structure and is possessed of those antiseptic, germicidal,

and local anaesthetic properties we should have deduced
(1)
from such a relationship.

We are thus driven to the conclusion that its action
in insomnia is only indirect.

In the true sense of the word to a man who is kept
from sleep by anxiety over an unpaid bill, a £5 note is
the best hypnotic obtainable. It acts not by dulling or
paralysing his nervous centres excited by anxious thought,
nor by directly causing any circulatory changes, but by
removing the cause of his insomnia.

In like manner the patient who is prevented from
sleeping by some subjective sensation is being treated
in the most rational way by the exhibition of a drug which
simply removes that sensation without other action; and
it is the purpose of this thesis to show that such a cause

(1)x

Phenol, C_6H_5OH , termed phenyl-alcohol by Laurent in
1841, exhibits many of the characters of the alcohols,
it is intermediate in character between the tertiary al-
cohols and acids, and is the hydroxy-compound correspond-
ing to bromo-benzene. The phenyl radicle, C_6H_5 , enters
into combination with metals, &c., in the same way as the
tertiary alkyl radicles. One of the tertiary alcohols
has been seen to be hypnotic in action, and ^xBradbury found
that phenyl-urethane was active, but he states that the
simple radicles of the series (e.g. phenyl) cannot be used
to introduce hypnotic effect into compounds. The reduced
phenols and quinones possess the characters of the second-
ary alcohols and ketones and form the connecting link
between the aliphatic and aromatic bodies.^x The methyl
group is present in creosol, cresol and guaiacol and it
is instructive to note that paracresol is formed in the
breaking down of albumen, but there are no definite facts
to logically account for hypnotic action.

x
Org. Chem.
Wade. 251.

Brit. Med. Journ.
1899. vol. II
p. 75

x
Wade.
p. 299.

of insomnia exists, and that it is removable by the action of creosote - and further, that many patients suffering in this way and unable to obtain sleep with ordinary doses of hypnotics, are quickly relieved by the exhibition of creosote.

What is this subjective phenomenon, and how does creosote remove it?

In many people, after unusual exertion (whether physical or mental), sudden anxiety, or long continued worry, or convalescing from acute illness, inability to sleep presents itself in the following manner:-

At the moment corresponding to the end of the first stage of Chloroform anaesthesia, just as consciousness has been lost, and after the preliminary stages of "going to sleep" have been normally passed through, a sudden "flip," instantly rousing the patient to full consciousness, is experienced. The sensation is very short, and is exactly that of a "flip" of the finger from within the chest cavity against the anterior wall, and is situated in the region of the heart's apex. This "sensation," "jump," or "flip" is absolutely single and is followed by no palpitation, no pain, and no praecordial or epigastric sensation whatever. In many cases it is accompanied by a grave feeling of dread or alarm, but this is no essential part of the phenomenon; the actual "flip" is sufficient to render the patient wide-awake in an instant. If there be the feeling of dread it soon passes off, and

the patient settles down again to sleep and is very likely aroused again in the same way just as he loses consciousness. This may be repeated many times on the same night, or only occur once, but whenever the second stage of sleep is entered, the "flip" not occurring, normal sleep lasting seven or eight hours ensues. In some this symptom occurs without causing much annoyance, merely delaying sleep, but in others its persistent recurrence is provocative of real insomnia, and attended with grave distress. The symptom shows itself most frequently after unusual fatigue or strain.

It is important to note that it is one sudden and single individual sensation occurring at one particular and exact moment, and unassociated with any consciousness of flatulence or digestive disturbance, and unattended with palpitation. It is also absolutely unaffected by dread of its occurrence, or forgetfulness of its existence, being just as likely to be absent when the patient lies down fearing that it will occur, as to be present when it has not suggested itself to his mind, and it may be entirely absent for months or years. The associated feeling of dread is most marked in women near the menopause, and in young neurotic males.

It is in this condition that I have found creosote to act as a specific.

From the description given above it seems probable that the subjective sensation is caused by some temporary

abnormality of the heart's action.

(1)

The condition of jumping or starting on going to sleep, which is mentioned by de Menaceine and which is experienced by most people from time to time, is an entirely different condition. It is felt to emanate from the spinal cord, causes muscular contraction, and is caused by convulsive or irregular action of lower centres relieved from cerebral control.

(2)

A case is narrated by Dr Balfour of an old gentleman whose only complaint was an occasional "dunt" - throb - in his chest. Dr Balfour found that it was due to the augmentor impulse following an inhibition. This is, doubtless, the phenomenon we are studying with the important distinction that it occurred at any time, and when the patient was wide awake.

(3)

When seen by Dr Balfour the heart had been dilated for some time, but there was medical evidence to show that the symptom had occurred long before any sign of heart disease could be discovered. Intermission is a reflex inhibition of the heart through the vagus, and may result from emotional or physical causes. Shock, overwork, or worry often produce it. Gastric irritation from flatulence or undigested food is the commonest reflex cause of intermissions; while the abuse of tea, or tobacco,

(1)

Sleep. de Menaceine. p.186.

(2)

The Senile Heart. Balfour. p.42.

(3)

do.

do.

p.43.

acute illness, and any form of myocardial weakness, or impoverished blood supply render the heart liable to its occurrence. Intermittence from gastric causes is more prone to occur in the recumbent posture, and Dr Pye Smith (1) attributes this to the presence of solid lumps of undigested food in the stomach being pressed against the cardia in this position of the body.

In diastole the heart follows the pull of gravity, while in systole the direction of the spring of the apex depends on the fulcrum, i.e., that part of the heart which is supported by other structures.

(2) It is the difference in the angle of the thrust and slight pressure on the fulcrum that renders the heart more liable to intermit in the recumbent posture, rather than actual solid masses in the stomach.

The condition known as "tremor cordis" is closely related to the subject of intermission. It is a curious phenomenon, the very opposite of palpitation. (3) Emotion has never anything to do with its causation. The suddenness of onset as well as the nature of the sensation, "Fluttering" of the heart, render it most alarming to the patient. The attacks occur absolutely without warning, and pass off in a few seconds, ending suddenly (4) "like an intermission, with an unusual^{ly} forcible beat, and from a similar cause." The shorter the period of tremor, the

(1) System of Medicine. Fagge & Pye Smith. Vol.I. p.900.
(2) Physiology. Schäfer. Vol.II.p.4.
(3) The Senile Heart. p.64.
(4) p.66.

less forcible is the impulse with which the heart returns to work. The heart resumes its natural rhythm without any palpitation or feeling of faintness. (In palpitation there is exaggerated and violent action of heart not producing proportionate results in the pulse wave; the strong ventricular systole from augmented action sends a powerful wave through all the vessels.)

(1) Sir Walter Scott suffered from tremor cordis in his youth, and it used to throw him into "an involuntary passion of causeless tears." (2) Tremor cordis is evidently connected with reflex vagus inhibition, and can generally be associated with some gastric disturbance, but is difficult of explanation.

The sensation described above as a "flip" is the slightly increased ventricular systole following a short "tremor cordis" with or without an actual intermission. I have been unable to obtain a sphygmographic tracing to elucidate this point. The occurrence of the phenomenon is to be explained somewhat as follows. In all forms of neurasthenia, whether induced by shock, or mental or physical overstrain, the heart is rendered more liable to arrhythmia, and the stomach to flatulence and dyspepsia; "the over-tired cannot digest efficiently." Indeed, according to Dr MacCallum (3) all forms of functional disease of the stomach may be neurasthenic. In conditions of over-fatigue the nerve-centres are hypersensitive to

(1)

The Journal of Sir W. Scott. p.153.

(2) Balfour. The Senile Heart. p.69.

(3) "Gastric Neurasthenia." Brit.Med.Journ. 1906. p.1031.

stimuli, (witness the intolerance to light and sound in acute neurasthenia.) During sleep the cortex cerebri⁽¹⁾ loses its function of inhibition over reflex action.

A sudden fall of blood pressure, amounting to one millimetre, occurs at the moment of losing consciousness.

The recumbent posture allows any gastric condition to have its greatest effect in interfering with the heart's action.

Thus, an amount of gastric disturbance insufficient to cause any subjective discomfort is capable, in the recumbent posture, as the vaso-motor centre goes to rest, of initiating a reflex inhibition of a heart unduly irritable; and this inhibition is followed by a ventricular systole of sufficient power to excite sensation and bring the hypersensitive brain-cells in the centres of consciousness into action.

Creosote prevents the initiation of this reflex act by its sedative action on the nerve-endings of the mucous membrane of the stomach, aided by its power of arresting fermentation and preventing flatulence by virtue of its antiseptic and bactericidal properties, and I have always found it efficient.

Of the fact, which I have proved by many experiments, that Carbolic acid, Bismuth, and Soda, Calomel, or Rhubarb and Gentian, have no power to avert the occurrence of the phenomenon, I have no elucidation to offer.

I have administered creosote in many other forms of insomnia, and have found it of value only in cases due to

(1) Physiology. Schäfer. p.711.

marked flatulence and dyspepsia, and in the cough of phthisis. In insomnia of mental origin and in those types in which sleep is disturbed after being once reached, I have not found it to have any hypnotic effect.

The following are notes of cases that have been attended in my own practice, illustrative of the points discussed in this thesis.

Case I.

In May, 1896, I myself, first experienced the symptom described in this thesis, and it proved in my case the source of most distressing insomnia, recurring nearly every night repeatedly during the whole of that summer. I have used the word "flip" in the body of the thesis to express the sensation. In my case the use of the short vowel "i" is essential to indicate the suddenness and shortness of the little jerk, or jump. In some people a deeper and longer vowel sound would better indicate their sensation. The first time the "flip" occurred to me, it was attended with quite unreasonable dread, but with constant repetition this accompaniment became less and less marked. Antecedent dread was absent to a surprising degree; I nearly always felt confident of going straight off to sleep. I had never

fainted in my life, nor had palpitation, and my pulse was perfectly steady and regular, and I had a singularly easy digestion. I had always been accustomed to violent exercise, but I noted that the attacks were more constant and recurrent after long bicycle rides, or hard rowing, and looked on over-fatigue as the cause of the trouble. At that time I did not attribute it in any way to the heart, but considered it a muscular spasm, probably of part of the diaphragm - a kind of local hiccough. I took no drugs of any kind, and became run down, worried, and depressed; after a holiday I became perfectly well and was no more troubled for some years. In 1902, after an anxious winter's work, the condition recurred. One night, having some capsules of creosote in my bedroom and bearing in mind that a phthisical patient had seemed to sleep much better under their influence, I swallowed one and promptly fell asleep not waking for more than eight hours.

Except on occasions when I have experimented with other drugs I have never since been troubled on two consecutive nights with this symptom, and seldom allow it to happen more than once on any night, as I invariably keep capsules of creosote by my bedside, and always find them to act efficiently. I have suffered considerably from dyspepsia and the restless insomnia resulting from it during the

last few years. Any carminatives will help to relieve this, but with the single possible exception of "resorcin," I have found no drug having the slightest effect on the particular symptom that creosote removes so effectually. I have never experienced the "flip" during waking hours, and as far as I am aware my heart exhibits no sign of intermission or disease. The condition has always been most troublesome in hot weather.

Case II.

A dispensary patient, aged 22, had been attended by Dr. N. for some weeks for sleeplessness, and treated with bromide of Potassium, Hydrocyanic acid and Gentian, followed by iron and strychnine, but with no improvement. On enquiry sudden throb at the moment of losing consciousness, attended with fright, was admitted, which had occurred first after an unusually long bicycle ride; creosote was ordered and produced a good night's sleep, and there was no further trouble.

Case III.

Mrs A. - widow, aged 41 - had nursed husband through long illness - complained of sleeplessness started by a sudden "thump" in the chest which frightened her. In this case capsules containing Mii of creosote in addition to tonic treatment were

administered on alternate nights, and good and bad nights resulted accordingly.

Case IV.

Mrs D. - widow, aged 53, had received severe shock from sudden death of her husband - haemorrhage and detachment of retina resulting - experienced typical jump at the moment of losing consciousness with great sense of dread, this was repeated every time sleep was coming. Had been given Sulphonal, Bromides, and Trional.

On nights of January 18th & 19th powders containing gr.xv of Sulphonal and Ammon Bromide were given with no result. On January 20th Mii of creosote caused the "best night for weeks."

Case V.

Dr McF., a student contemporary of my own twelve years previously in Edinburgh, working ⁱⁿ Brighton for Diploma in Public Health, complained of inability to get off to sleep with consequent insomnia from a sudden "thump in his chest." He stated that he had suffered in the same way as a student when going in for cross-country running. He was small, well-knit, with healthy organs, and not a trace of indigestion. I told him my own experience and suggested creosote, and in his own words, "it acted like a charm."

Case VI.

Rev. J.N., aged 45, a religious enthusiast, overdone with building a new church - exhibited ^{typical} symptoms. He was anaemic and had poor digestion, and in the day sometimes troubled with palpitation - in combination with other treatment creosote at night gave great relief.

Case VII.

A.T., strong athletic youth, aged 20, with perfectly sound organs, was quite upset by a bad night from this cause during a tennis tournament week - thought his heart had burst. He was relieved at once by administration of creosote.

Case VIII.

Mrs S., wife of artist in grave pecuniary difficulties, came to me in great distress because of terrible fainting attacks and fright at night which proved on inquiry to be the typical symptom. This patient was a highly cultured, neurotic and anaemic woman, who had been told her heart was weak. Creosote, aided by the moral effect of explaining the symptom, gave great relief and quiet sleep returned.

Case IX.

Mrs. S., aged 31, hysterical - liable to severe neuralgias and dysmenorrhoea - six months pregnant -

suffered from fainting and sleepless nights - no sleep for three nights before January 22nd, when creosote was administered and sound sleep resulted. In this case there was no typical throb, but hysterical flatulence and neurasthenia, and the cure was not permanent.

Case X.

A.M., very muscular and athletic, aged 20, played much Rugby football - had always slept well previously and had excellent health and never suffered from indigestion - complained of bad nights with typical symptom - was relieved by creosote. In this case there was occasional intermittence for a time, but no sign of dilatation.

Case XI.

Mrs. W. - a case of flatulent dyspepsia with sleeplessness and sense of dread and genuine palpitation at times - only partially relieved by creosote. This patient has subsequently developed melancholia.

Case XII.

Mrs. P., neurotic married woman of 36 with chronic metritis, very despondent from time to time and subject to chronic insomnia - creosote produced no effect whatever.

Case XIII. (This case is typical of many patients.)

Mrs G. - attack of influenza followed with great weakness and insomnia - the typical symptom being well pronounced and completely relieved by creosote. This patient was seen in 1904 staying in Brighton, and a year later I received a letter asking for my prescription "for the little capsules." There had been another attack of influenza and nothing else "seems to stop the 'jumps,' and feeling of dread."

Case XIV.

Miss B. - seen this morning, April 26th, 1907, not previously seen for eighteen months. Another inmate of the house had developed mental symptoms and caused anxiety. Had return of sleeplessness and bad nights. She remarked: "I suddenly remembered those little pellets you sent me, and found one left which I took last night. I had a good night and feel quite well this morning."

These cases are sufficient to indicate the widespread occurrence of this particular symptom, and its ready relief by the administration of small doses of creosote the last thing at night. Careful enquiry is usually needed to elicit the actual symptom, and I doubt if it would have presented itself to my mind as a distinct and definite entity had I not experienced it myself. I have used creosote widely both in Hospital and private practice

during the last few years to remove this not uncommon
cause of insomnia.
