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Robert R. Schopbach

Keith B. Akins

THE NEUROPHYSIOLOGY OF THE CENTRAL NERVOUS SYSTEM; A SIMPLIFIED REVIEW

ROBERT R. SCHOPBACH, M.D.* AND KEITH B. AKINS, M.D*.

Studies concerning the mode of action of the nervous system are daily producing new information. Because different animals may respond differently and because the response varies widely under only slightly different experimental conditions, the results may be quite contradictory. With present incomplete and imperfect knowledge more than one hypothesis can explain the action and who can say which is correct. With this in mind one viewpoint is presented here to clarify the rationale behind current neuropharmacology.[1]

Behavior was formerly considered to result from sensory stimuli going to discrete cortical sensory areas and thence evoking responses from other discrete motor areas with a few checks and balances furnished by associated areas. Today studies indicate that the brain is a most complex network of feedback, inhibitory, and amplifying circuits acting as a unit; each must function properly if the optimum response is to be made. With the aid of almost incredible technical devices such as pipettes and electrodes placed within single cells our dim understanding of these functions is rapidly increasing and altering former hypotheses. A functional balance peripherally between the sympathetic and the parasympathetic systems is still considered valid. A similar balance has been postulated for subcortical portions of the central nervous system; the components are called ergotrophic and trophotrophic.[2] The ergotrophic system is integrated with the sympathetic system to effect arousal and increased muscular and psychic activity while the trophotrophic system tends to return the body to a state of equilibrium, inactivity, decreased muscular tone, and even sleep. The ergotrophic system acting with the peripheral sympathetic system deals with fight or flight and similarly the trophotrophic with the maintenance of the specie through its own metabolism and through reproduction. The activity of each of these systems is effected by corresponding neurohumors; nor-epinephrine and acetyl choline[3] peripherally and nor-epinephrine[4] and serotonin[5] centrally respectively. Although some believe that serotonin merely modifies the actions of the nor-epinephrine rather than being a separate transmitter substance,[6] this is not the most common opinion. This paper will review primarily the activity of the central nervous system.

Coordinated cellular activity depends to a great degree upon synaptic transmission.[7,8] Such transmission is accomplished as follows: neurohumors are stored in the terminal axone buttons bound to a protein.[9] Upon the arrival of electrical impulses this bound form is split releasing the neurohumor which escapes through pores in the cell membrane into the intercellular fluid. (Diag. I) Under resting conditions this free form is released so slowly that the enzymes in the intercellular fluid and responsible for its degradation inactivate it before it has had an opportunity to affect the post-synaptic cell's membrane. When greater amounts are freed, the concentration immediately around the terminal button is so great that for a millisecond or so the enzyme is incapable of deactivating all of it and it is able to affect the post-synaptic membrane.

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*Department of Psychiatry.

DIAGRAM I

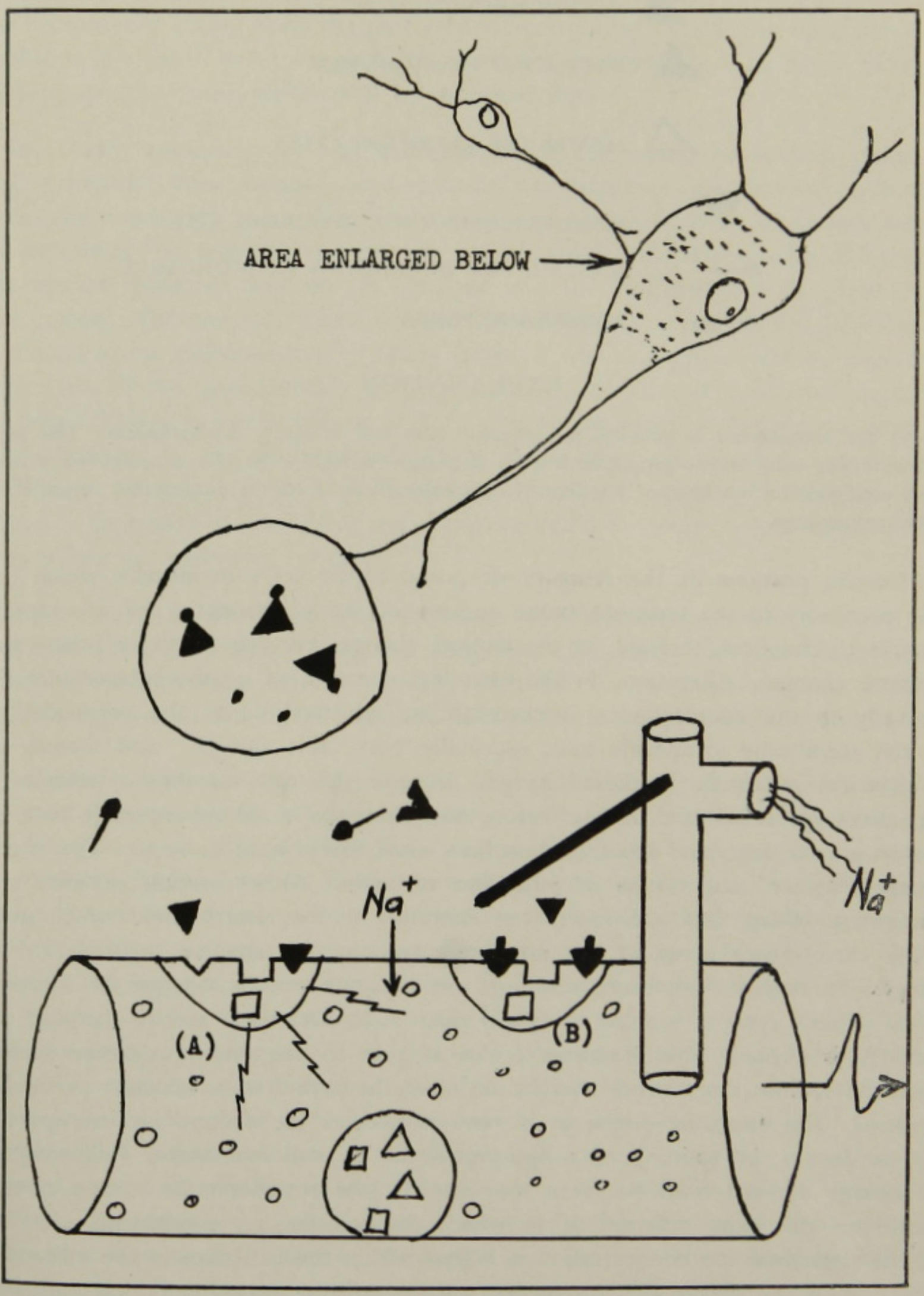
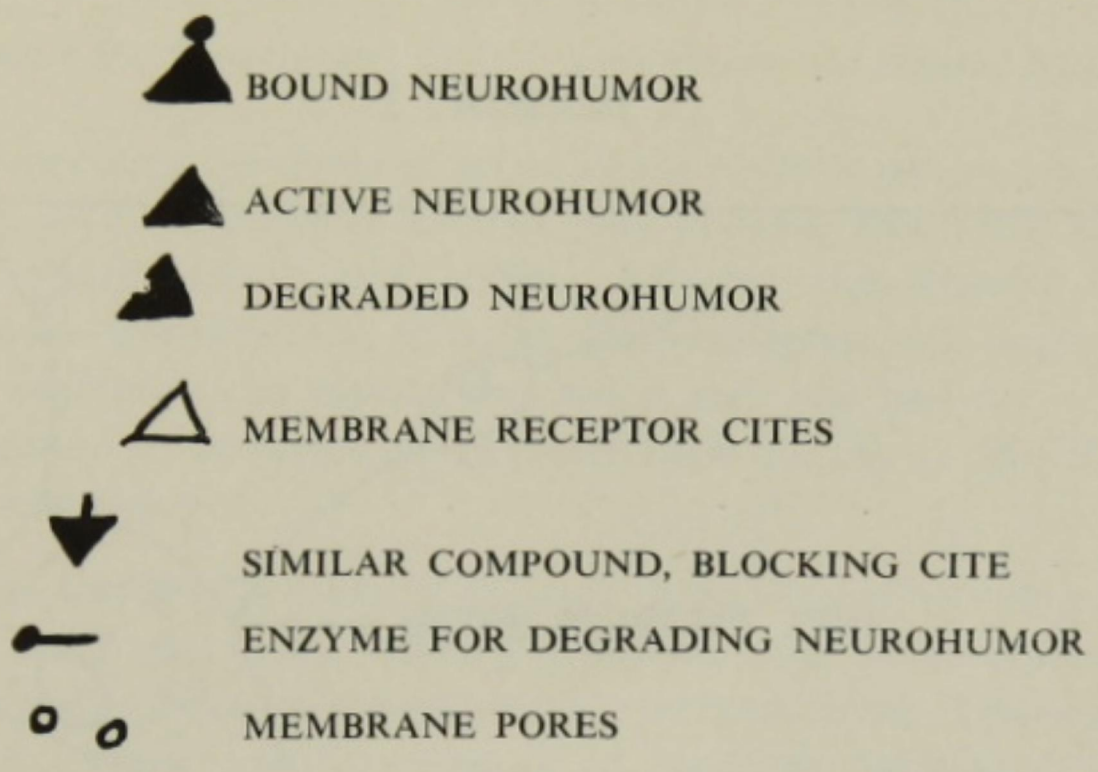


DIAGRAM I

SYMBOLS



EXPLANATION

At (A) the neurohumor is entering the receptor cites and initiating depolarization. This permits Na+ to rapidly enter and to propagate a spike discharge (at right). At (B) a compound of similar spatial configuration has blocked the cites. In the intercellular fluid the enzyme has degraded some of the neurohumor.

Certain portions of the receptor or post-synaptic cell's membrane which lie in close proximity to the terminal axone endings of the pre-synaptic cell are especially sensitive to chemical, thermal, or mechanical changes but are relatively insensitive to electrical changes. Alterations in the chemical constitution of the intercellular fluid, especially in the neurohumoral concentrations, selectively alter the permeability of the cell membrane to specific ions, especially Na^+, K^+, and Cl^- and thereby alter its electrical potential. If these changes increase the cell membrane potential, no spike discharge is initiated, in fact before any discharge could subsequently be elicited an even greater degree of depolarization than usual would have to occur. This is called hyperpolarization and results in inhibition of action. Other stimuli produce a depolarization (Diag. IA) and initiate an alteration in the electric field which spreads to the surrounding areas of the membrane which are sensitive to such electrical changes. Through the continued action of one receptor area or through the summation of the actions from a number of such areas a characteristic electro-chemical spike discharge is elicited. This discharge is due in part to the almost explosive speed by which the sodium ion reaches equilibrium once the membrane's selective permeability is altered. The electrical discharge however antedates the sodium ion transport and may be due to the splitting of a lipo-protein in the cell membrane. Following such a discharge the cell must be given time for its inherent metabolic sodium pump to re-establish the ionic differentials in which the sodium ion concentration is lower and the potassium ion concentration is higher within the cell than in the extracellular fluid. Should the chemically responsive portion of the post-synaptic cell membrane be constantly stimulated, it would constantly produce depolarizing currents which would prevent the re-establishment of these differentials and the cell would be unable to generate the potential to fire again. This is known as depolarizing blockade.

From this it can be seen that the response is dependent upon the concentration of the neurohumor. If there is too little, the cell will not be stimulated into action and the opposing system will assume functional predominance. If the correct amount is present, a normal balance will obtain. If the amount is increased moderately, the cell will fire more often and that system will predominate. Finally if there is too much of the neurohumor acting upon the post-synaptic membrane, it will fire once but then be unable to fire again and the opposing system will predominate. The many methods of altering synaptic transimission will be discussed later.

The energy necessary for the maintenance of the metabolic sodium pump is derived primarily from pyruvic acid-adenosine triphosphate metabolism[10] although under special conditions it can also be obtained from the metabolism of certain amino acid compounds.[11] If these energy systems are impaired, the proper ionic differential and membrane potential will not be attained and the cell will not be capable of normal activity. The enzymes which control these metabolic processes are believed to be contained in the mitochondria.[12,13] Many drugs as well as asphyxia act by impairing the functions of the mitochondria thereby reducing the overall functional capacity of the cells. GABA (γ-amino butyric acid) is closely concerned with neuronal activity and transmission. It has been considered to be another neurohumor but current neurochemical studies suggest a predominantly metabolic function.[14] That its concentration is decreased in convulsive states and increased by some anticonvulsive drugs suggests it has an inhibitory function.

In those cases in which the spike discharge must traverse a sheathed axone, any alteration in the lipids which form the sheath will interfere with the transmission especially at the internodal regions.[15] Finally with the arrival of an adequate impulse or series of impulses at the axonal dendritic buttons the entire process is recommenced.

The activity of this transmitting system can be altered at any level. The amount of the neurohumors cannot readily be increased by their administration orally or even intravenously as they do not readily cross the blood-brain barrier. However their precursors in the form of DOPA (dihydroxy phenyl al*a*nine) for NE[16] and 5 hydroxy tryptoph*a*ne for serotonin do cross this barrier and cause increased activity of their respective systems.[17] This effect becomes even more marked if an MAO inhibitor (v.i.) has been previously given. The storage of bound-form is altered greatly by trace metals and even altered Ca^{++}. The storage of bound neurohumors may be prevented by reserpine. This releases both serotonin and nor-epinephrine.[18] Initially these may cause a transitory period of increased activity. Subsequently the serotonin is reformed about fifty times as rapidly as the nor-epinephrine[19] so that the trophotrophic system is stimulated much more than the ergotrophic. The results in decreased motor and psychic activity to the point of somnolence and sometimes depression. Other cholinergic actions such as increased nasal secretion or bowel activity may provide annoying side effects. Reserpine also prevents the storage of NE in peripheral sympathetic nerves to further decrease the motor activity and, with the bradycardia, to produce hypotension. By choosing others of the reserpine analogues it is possible to obtain either the central or peripheral effects separately.[20,21] Certain other benzoquinolizine and reserpine derivatives are also capable to affecting separately

NE or serotonin. Under slightly different experimental conditions completely opposite results have been obtained in an attempt to determine which neurohumor is responsible for the sedative effects.[22,23] So the answer is as yet far from clear.

The neurohumors must pass from the axone to the receptor membrane in a great enough concentration to propagate an electrical pulse. During this passage they are being metabolized by specific enzymes especially mono-amine oxidases but also methyl transferases. The amounts of these enzymes available to act on the neuro-humors may be decreased by the presence of other compounds of similar structure which "compete" for the enzymes.[24] If the $-NH_2$ is not in the terminal position, the enzyme is removed from further action. These compounds may also have some stimulatory action of their own to further increase their effectiveness. This is felt to explain the actions of amphetamines. Many CNS depressants decrease the rate of release of bound serotonin[25] but this is not felt to be the cause of the depression (sedation); their depression of cellular metabolism is considered the more important action.

If the enzyme's activity is blocked, the neurohumors will not be destroyed but will accumulate. Mono-amine oxidase is the enzyme which normally degrades both NE and serotonin; its inhibition leads to accumulations of both of these. However nor-epinephrine is additionally much more susceptible to degradation through a secondary pathway by methyl transferase than is serotonin.[26,27] This results is marked increases in serotonin and lesser increases in NE. One possible explanation is that the serotonin level rises to such a point as to "flood" the synapses and to create a depolarized blockade of the trophotrophic system. In our exprience there has been a transient period of psychic impairment a few hours after taking the MAO-inhibitor which might indicate a point where the serotonin was stimulating the trophotrophic system into temporary predominance. Although the psyche is subsequently stimulated suggesting ergotrophic domination centrally, peripherally there are signs of para-sympathetic dominance especially in the genitourinary tracts.[30] Clinically MAO in-hibitors were being tried to inhibit the metabolism of tubercle bacilli when it was noted that an euphoria often occurred.[28] This antidepressant action is now their chief indication although it is not certain that the improved mood is the result of either serotonin or NE; there are many other enzymes and amines which might possibly be involved.[29]

The combination of reserpine with MAO inhibitors produces opposite effects de-pending upon which is given first. Should the reserpine be given first, the MAO-in-hibitor has no effect and sedation persists. However, should the MAO inhibitor be given first, the neurohumors released by the reserpine are not destroyed but reach such high concentrations that hyperactivity and even convulsions may occurr.[31] This could be due to stimulation by NE or flooding by serotonin. The former may be true as phenothiazines which interfere with NE block this reaction.

The receptor areas of the post synaptic cells' membrane offer intriguing possibili-ties for chemical activity. It can be pictured as a layer of cylindrical macromolecules with varying size pores.[31] Many drugs are of such small molecular size that they can slip through these pores and enter into the cell where they interfere with some of

the mitochondrial metabolic processes to have a very general sedative effect. This is the action of most sedatives[10] and one of the actions of phenothiazines.[33] If the drug molecules are larger, they must be of the correct spatial configuration to fit into the pore; such drugs have much more specific effects as they fit relatively few pores. Yohimbine, harman, lysergic acid, adrenochrome, and adrenolutin are all structurally related to serotonin and nor-epinephrine and might occupy their receptor sites but, being different, would produce an altered response (Diag. IB). For normal mentation the total sensory input must lie within a certain range. This varies from individual to individual. But, if it is increased too much, even the "strong" have their breaking point as was observed under prolonged stressful conditions as in World War II.[34] The opposite extreme, isolation with as complete sensory deprivation as possible, also gives rise to abnormal mental processes.[35] Thus it is not suprising that the alteration in responsivity produced by these related compounds produces disturbances in mental processes. Perhaps by understanding these "model psychoses" we can gradually understand the naturally occuring psychoses. One current postulate suggests a disturbance in epinephrine metabolism with the production of adrenochrome to be one of the causes of schizophrenia[36,37] but this is the subject of much argument. The research to prove or disprove this point adds to our general knowledge bit by bit. Such increases in neurophysiologic knowledge have permitted great advances in neuropharmacology in recent years. Future research may replace all of the above hypotheses but momentarily they serve as a convenient frame of reference. It is hoped that the interested reader will study critically forthcoming reports and add his own observations.

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