of the data. For compounds formed from differing rows of the periodic table the only apparent relationship is $P < E/2\Delta V$. InAs is an exception which would be corrected by using the 70 kb transition pressure of Paquin and Gregory (*7*). As usual in these empirical relationships carbon fails to fit. A reasonably obvious explanation for this is that its electronic configuration is basically different from that of the other group IV elements. Carbon has only its 1*s* shell under its valence electrons, while the others all have a substantial core of complete *p*-shells and *d*-shells and so on. Hence any rule based essentially on interatomic distance is very apt to fail for carbon.

There is a very simple interpretation of the equality shown by the first five entries in Table 2. From the simplest model of a semiconductor, $\Delta E/2$ is easily shown to be the position of the Fermi level (*10*). Hence at a pressure of 1 atm the Fermi level of the (unstable) metallic modification lies at the same height as the bottom of the conduction band of the semiconducting elements and compounds obeying the rule $P\Delta V = \Delta E/2$. Considering the known complexity of the band structure of these materials, this is too good to be true, but the numbers speak for themselves.

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Botulinus Toxin: Effect on the Central Nervous System of Man

Abstract. *Electrical stimulation of multiple peripheral nerves, elicited "H" reflexes in a patient, 61 years old, with botulism. These reflexes are extremely suggestive of some central release or failure of inhibitory control of a monosynaptic or polysynaptic spinal reflex arc. This "central" action of botulinus toxin is similar to that suggested for tetanus toxin.*

Botulism is an extremely rare, yet deadly, form of food poisoning. The poisoning results from an exotoxin released from *Clostridium botulinum*. The toxin is one of the most lethal poisons known.

Previous knowledge of the physiological action of botulinus toxin is based primarily on laboratory experimentation in cold- and warm-blooded animals. The marked differences among species in response to toxin suggested the importance of investigating the effects of the toxin in man. It has generally been assumed that the toxin has its primary action at the nerve ending blocking the nerve impulse before it reaches the muscle, or glandular end organ. This toxic action has been attributed to an inhibition of the release of acetylcholine (*1, 2*), probably at the tips of the nerve endings (*2*), or to a block of the transmission of nerve impulses into final presynaptic arborization (*3*).

The concept of botulinus toxin as a pure peripheral neuromuscular toxin has been questioned by some Russian experimenters in the last decade. Mikhailov (*4*) has shown a defect in brain stem cardiac reflexes in botulinized animals. Erzina (*5*) and Matveev (*6*) note that botulinus toxin can attack non-neural tissue.

Recent studies in humans affected with severe botulinus poisoning have confirmed the severe peripheral neuromuscular effect of the toxin (*7*). Some evidence to support a simultaneous central effect of the toxin is described in this report.

The findings are based on studies of a 61-year-old man with severe botulinus poisoning and a severe progressive weakness, who was admitted to the hospital 48 hours after the ingestion of home-canned mushrooms. A son-in-law had milder symptoms.

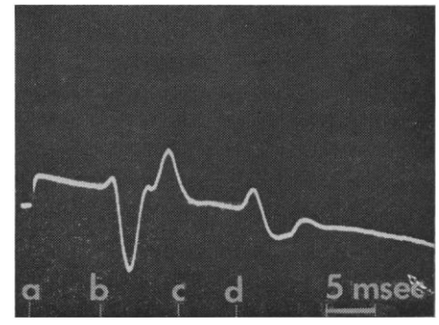

Fig. 1. "H" reflex from stimulation of ulnar nerve of a patient (at elbow). The nerve was stimulated for 0.1 msec at 150 v.

Figure 1 shows the result of stimulation of the ulnar nerve at the elbow with current pulses of 0.1 msec duration, with a voltage difference of 150 between the skin over the ulnar nerve at the elbow and an anode 1 cm away. The recording was taken from a surface electrode over the abductor digiti quinti (a partially affected muscle) in the hand. The indifferent electrode was 0.5 cm away.

The distance from the shock artifact *a* to the onset of the muscle response at *b* represents the time of conduction down the ulnar nerve, across the neuromuscular junction until the first muscle-fibers discharge. The period *b* to *c* represents the muscle discharge. At *d*, one sees a delayed response. This response was initiated at a lower threshold than the motor response *bc*. It was well developed by the time stimulation reached 80 volts and the muscle response first became apparent. It was only partially suppressed as the strength of stimulation increased up to 150 volts. The time the response appeared varied appropriately when the nerve was stimulated distally or proximally. This delayed response was recorded earlier, over the abductor digiti quinti muscle, when the nerve was stimulated at the elbow as compared to the wrist. This is the so-called "H" reflex, which was present and prominent in multiple recordings from different areas after stimulation of the peripheral nerve.

Figure 2 is a similar recording taken from a normal subject. Two successive stimuli are superimposed. The experiments were performed under identical conditions to those in Fig. 1. The markings in the background denote 5 msec. No "H" response is seen. The curve is characteristic of the simpler

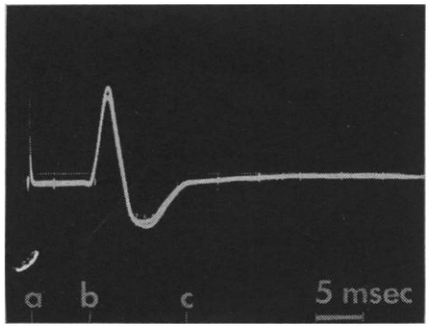

Fig. 2. Tracing obtained when ulnar nerve was stimulated for 0.1 msec at 150 v in a normal patient.

form that is recorded in normal patients.

The "H" reflexes were first described by Magladery and McDougall (*8*). They represent the response in muscle recordings when the afferent fibers from muscle are stimulated by low-threshold nerve stimulation. They usually follow the direct motor efferent response of nerve stimulation and have a latent period of the order of 30 to 40 msec. The afferent impulse is presumed to travel to the spinal cord and then both monosynaptic and polysynaptic connections cause a discharge over the lower motor neuron which is then recorded at the periphery as an "H" response. In a series of extensive and thorough investigations, Magladery and his coworkers (*8, 9*) demonstrated that these responses are not usually seen in normal persons but are seen predominantly in patients who have cerebral, brain stem, and spinal lesions. They postulated that to observe these reflexes, some release of inhibitory influences on the final lower motor neuron was necessary. The closer the lesion was to the segmental reflex studies, the clearer was the phenomena. The "H" reflexes have also been demonstrated in tetanus intoxication (*10*), where there is a depression of certain inhibitory actions of interneurons upon the motor neuron (*11*).

The prominence of the "H" reflexes in almost all the records of nerve conduction strongly suggests some effect of the botulinus toxin at the spinal level. Since both tetanus and botulinus toxin are clostridial toxins, it is possible that botulinus toxin may have an effect on inhibitory actions of some interneurons similar to that reported for tetanus. A direct action upon the cholinergically innervated inhibitory neurons in the cord (Renshaw cells) is also possible. A central action of the toxin could explain phenomena such as tonic spasm of the hand (*12*) and occasional respiratory or cardiac irregularities seen in these patients. These phenomena are difficult to understand if the action of botulinus toxin is solely limited to the periphery (*13*).

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Rhodopsin: An Enzyme

Electron histochemical evidence indicates that a nucleoside triphosphatase is present in the membranes of the outer segments of frog retinal receptors (*1*). On the possibility that this enzyme is actually rhodopsin, we examined the adenosine triphosphatase activity of digitonin extracts of frog rhodopsin.

These extracts exhibit substantial adenosine triphosphatase activity, and the activity is twofold greater in bright tungsten light than it is in the dark. The activity of the enzyme is virtually eliminated by hydroxylamine, which presumably traps retinene away from the opsin. Furthermore, when the light is passed through different colored filters which transmit equal absolute energies (as measured by a thermopile), a filter with maximum transmission in the neighborhood of frog rhodopsin's maximum absorption —502 mμ—is the most effective in accelerating enzyme activity.

Finally, when solutions of either frog or cattle opsin, obtained by extraction of bleached retinas with digitonin, are incubated with a solution of all-trans retinene$_1$ which has been partially converted to the cis-isomer by irradiation with tungsten light, the activity of the enzyme increases in the same manner in which rhodopsin recovers its absorption peak.

We infer that rhodopsin is an adenosine triphosphatase which requires the attachment of its retinene chromophore for activity either in the light or dark. The retinene may act both as a light trap and as a cofactor for the enzyme.

George Wald recently wrote that all the best discoveries should have been anticipated (*2*). That rhodopsin is in fact an enzyme was anticipated no later than a dozen years ago—by George Wald.

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