Typical curves of upper channel activity versus date are shown in Fig. 1 for Bismarck, N.D., and for New Orleans, La. The constancy of the potassium-40 assay is indicated by the reproducibility of the results for the first 6 weeks.

The peak concentrations given in Table 1 can be compared with the International Commission on Radiological Protection's maximum permissible concentration for barium-140/lanthanum-140 in drinking water of 300 mμc/lit (*3*). The latter value is for continuous exposure for an indefinite period of time, while the exposure resulting from weapons testing is of short duration. Unlike strontium-90, barium-140 cannot present a cumulative hazard because of its very short half-life. Barium-140 has not been observed in any human subjects, although a search has been made for it.

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28 October 1957

Action of Blood-Borne Gamma-Aminobutyric Acid on Central Synapses

When substances are identified in the brain, it is natural at the same time to inquire into their function. Thus they become candidates for various roles, including that of potential neurohumoral transmitters. Such, indeed, has been the case with serotonin (*1*), and such is now the case with gamma-aminobutyric acid (GABA). Bazemore, Elliott, and Florey (*2*) have identified the latter as an active principle of factor I, which Florey and McLennan (*3*) had extracted from mammalian brain and had shown to have inhibitory actions.

One of the readiest methods of acquiring preliminary information of this sort is to paint a solution of the material upon the exposed cerebral cortex. The high doses thus applied and the unusually high concentration gradients that result serve to uncover any possible actions. Effects achieved in this highly abnormal way are undeniable but difficult to interpret in terms of physiological function, even when specificity can be asssured. Although the usefulness of this method, as in the topical application of strychnine (*4*) to fire brain areas, in order to map them, has gained it considerable respectability, this should not be extended to other uses. Thus, Kato (*5*), in studying conduction in nerve, found it convenient to make use of mechanical stimulation by a miniature mallet, but there was no suggestion that this was a normal way to activate or that this mechanical stimulus played a part in propagation of the nerve impulse. Nevertheless, the actions of GABA have been studied almost exclusively by topical application.

We have, therefore, wished to study the effects of blood-borne GABA and have resorted to the method we have previously used to help establish the roles of acetylcholine, adrenaline and nor-adrenaline (*6*), and serotonin (*1*) as neurohumoral transmitters in mammalian brain. This has been the relatively close arterial injection in the common carotid artery serving effectively to bring across the blood-brain barrier relatively small doses which, therefore, on dilution in the systemic blood stream become subthreshold for peripheral actions and consequently exhibit the cerebral actions in isolation or in relatively pure form—that is, not complicated by the peripheral actions and the resulting barrage of afferent impulses which bombard the brain. In this manner, by activating cortical synapses through the transcallosal pathway and recording the response as evoked cortical potentials in the lightly anesthetized cat, we have demonstrated that GABA, when delivered through the natural route (that is, when it is blood-borne), can, like adrenaline, nor-adrenaline, and serotonin, inhibit synaptic transmission. It does this in doses of 50 to 500 μg/kg (Fig. 1); thus it has a potency of about 1/50 that of serotonin, intermediate between that of nor-adrenaline and adrenaline, the series being nor-adrenaline, 1; GABA, 7×; adrenaline, 15×; serotonin, 300×. Unlike the effects of topical application reported by Purpura and Grundfest (*7*) the surface negative evoked response is usually reduced without affecting the positive wave or inverting the negative wave into a positive one.

Comparison with serotonin brings out further significant differences. The time course of the GABA action is faster in all respects. As the continuous plot of the surface negative evoked responses shows, the time of onset and the duration of action are remarkably short. The latter suggests an enzymatic destruction of GABA as was supposed by Florey and McLennan (*3*) or a binding into an inactive state by adsorption as believed by Elliott (*8*). Successful interference with this enzymatic or this binding process would result in abnormal accumulation of GABA, which would be evi-

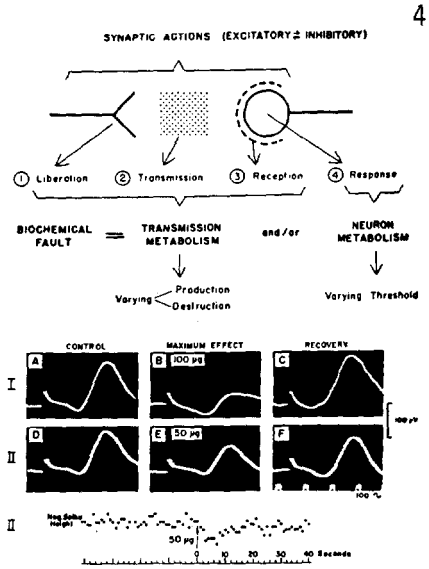

Fig. 1. Cerebral synaptic action of gamma-aminobutyric acid in a two-neurone intercortical (transcallosal) system. (Top) Potential factors in disturbed synaptic equilibrium. (Bottom) Potentials evoked in the cerebral cortex of the cat by electrical stimulation of the contralateral cortex every second. Gamma-aminobutyric acid was injected into the ipsilateral common carotid artery.

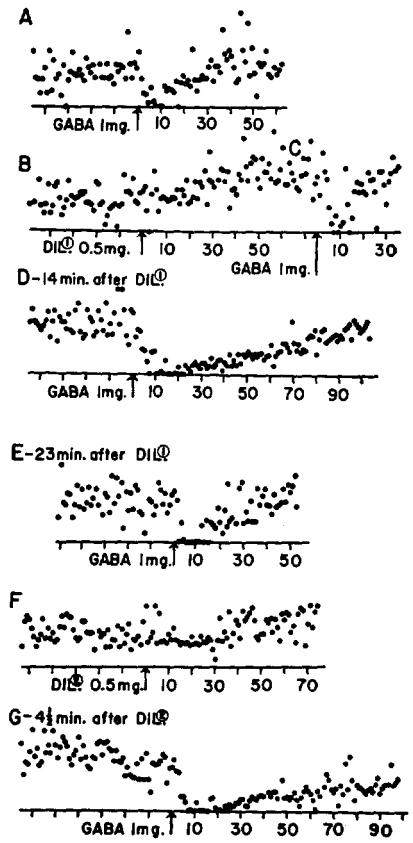

Fig. 2. Augmentation of GABA cerebral synaptic inhibition by dilantin. Negative cortical spike heights from transcallosal system potentials evoked by contralateral cortical stimulation (one per second). Injections were made into the ipsilateral common carotid artery.