new crisis was commenced, completing a cycle of 13 days. Such cycle was not so well delineated for patient DA (which had also a doubtful diagnostic), but it was very clear for patient GRS, as shown in the Figure.

In the Figure we plotted the daily concentrations of pyruvate, assayed in blood samples collected from the fasting patient (empty marks), besides those drawn just after each crisis, regardless of fast (black marks). As it can be seen, during a first period of observation of 25 days the patient had six seizures (A, B, C, D, E, and F). The very high concentrations of blood pyruvate found in B and F were assumed to be due to the fact that the samples were drawn in the afternoon, after the heavy midday meal. During this period the patient was under INH-therapy.

The results shown in the Figure suggest the existence of a 'pyruvate cycle' in epileptic patient GRS, similar to that found for patient NAS (Table). Attention must be called to the fact that, according to the results obtained before crisis D, E, and F, the increase in blood pyruvate may procede the seizures. As before, convulsions seem to be started by the fall of blood pyruvate down to the levels found for normal patients (Table).

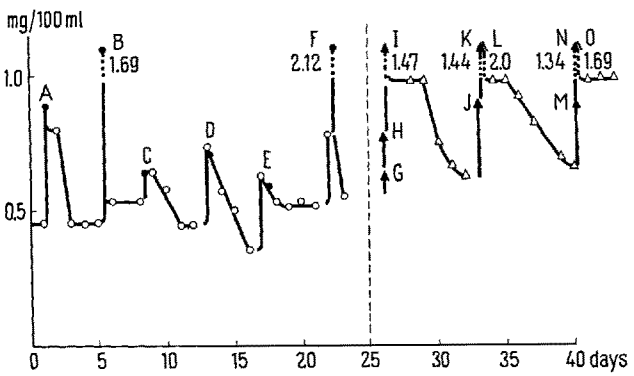

Fig. 1. Pyruvate cycle in the blood of an epileptic tuberculous patient (GRS) during INH-therapy (o–o) and after INH was suspended (Δ–Δ). The empty marks are for fasting values and the black ones for the values found after the crisis, regardless of fast.

The peculiar toxicity of isoniazid for epileptic tuberculous patients would be explained by the augmented consumption of blood pyruvate during the formation of the isonicotinyl-hydrazone of pyruvic acid[1] and consequent shortening of the 'pyruvate cycle'. This was confirmed by interrupting INH-therapy, as shown in the second part of the Figure. The 'pyruvate cycle', which was of 3 to 5 days during INH-therapy, was augmented to 7 days, with a correspondent spacing of the crisis.

Much higher levels were found for blood pyruvate after INH was suspended. Besides that, special attention must be paid to the fact that seizures, if more spaced, were now recurrent (GHI, JKL, and MNO), blood pyruvate increasing with each crisis. We tried to avoid that by keeping supposedly safe high levels of blood pyruvate. The number of crisis was reduced to a single one weekly when sodium pyruvate was orally administered in two daily 200 mg doses. However, this was the sole noticeable result, even when the daily dose was augmented to 600 mg[8].

Résumé. Les auteurs ont étudié la variation de la concentration de l'acide pyruvique dans le sang de 3 tuberculeux épileptiques. Ils ont vérifié l'existence d'un cycle dont le maximum coïncide avec la crise épileptique et dont le minimum la précède et semble la causer. L'effet nuisible de l'isoniazide pour les épileptiques serait dû à la consommation accélerée de l'acide pyruvique, utilisé pour la formation de l'hydrazone respective.

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On Driving and Synchronization of the Rate of Clonic Discharges of the Two Autonomous Hippocampal Epileptogenic Foci by Thalamic Stimulation

It has been demonstrated in a previous paper[1] that clonic discharges, evoked by a discrete, separate electrical stimulation of two bilateral, widely separated and mutually unrelated areas of the cerebral isocortex, could be controlled, synchronized and prolonged beyond their intrinsic durations by single shock stimuli applied to the intralaminar thalamic nuclei.

The present experiments have been designed to see if the activity of the two bilateral, autonomous, hippocampal epileptogenic foci, having various rates of discharge, could equally be controlled and synchronized by appropriate electrical stimulation of midline thalamic nuclei.

Cats were used for this investigation. Under Nembutal anaesthesia, having taken all the necessary aseptic precautions and by means of the standard stereotaxic technique, a minute amount of alumina cream was introduced, first into the hippocampus proper of one side and, several days later, into the homologous structure of the other side of the brain. A typical 'injury discharge' indicated the penetration of the combined needle-electrode shift into the desired depth of the brain. After the substance has been instilled, the needle was removed and the operative wound closed properly. Twenty days following the application of alumina cream, the animals were reoperated. Needle electrodes were introduced into the hippocampus of both sides and into the intralaminar thalamic nuclei. After complete recovery from anaesthesia, the electrical activity was recorded using an Alvar-Reega EEG apparatus. Grass stimulator, Model 4 S, with stimulus isolation unit, was employed for stimulating the thalamus. The single unidirectional, 0.2 msec pulses were delivered to the thalamus at the rate of 0.5–3/sec. After the experiments have been completed, the position of the electrodes was

[1] Lj. Mihailović, Exper. *15*, 119 (1959).

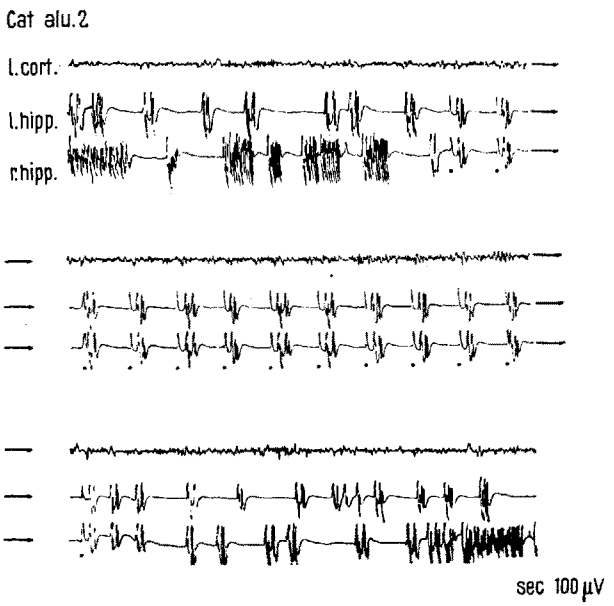
checked in histological preparations. Details concerning electrode construction and implantation, stimulus measuring and monitoring and electrode position identifying techniques have been published elsewhere[2–4].

As could be expected, on the grounds of previous experience[5], 28–30 days after the application of alumina cream, the spontaneous seizure activity appeared, originating first in one and several days later in the other hippocampus as well. The first stage of global, recurring, tonic-clonic hippocampal seizures which, transmitted from the site of origin, involved as a rule the homologous area of the opposite hemisphere, was followed by a long-lasting clonic activity, becoming increasingly more restricted to the corresponding side of origin. Finally, autonomous and persistant focal epileptiform activity could be recorded on both sides of the brain. At this stage of development, the single shock stimuli of an adequate rate (roughly corresponding to the predominating rhythm of the hippocampal discharges) if applied to the thalamic nuclei (N. anterior, N. medialis dorsalis) were invariably found to be effective in driving and synchronizing the rate of otherwise quite independantly and asynchronously discharging hippocampal foci. As illustrated in the Figure, the two foci continued to fire synchronously following the cessation of the driving thalamic stimulation, but resumed their own autonomous rates of discharge shortly afterwards.

The general conditions, indispensable in order to control the activity of a primary discharging focus by stimuli applied to a given distant structure, and the possible mechanisms underlying this phenomenon have been extensively discussed elsewhere[4,6]. In this respect, results of the present work fully support the earlier investigations.

The experiments reported here, clearly demonstrate the important role which the structures constituting the diffuse non-specific thalamo-cortical system[7] could play in synchronization of activity of the two bilateral and autonomous hippocampal, epileptogenic foci. In addition, if one bears in mind results of the previously published investigations[1], these experiments indicate how multiple, mutually unrelated isocortical and allocortical cerebral areas could be effectively coupled and synchronously subordinated to the thalamic rhythm, when, in the course of convulsive activity, the intralaminar nuclei of the thalamus reach the dominant level of background excitation. Experiments have already been undertaken to check this assumption[8].

Zusammenfassung. Bei Katzen wurde auf beiden Seiten im Hippocampus je ein epileptischer Fokus (Aluminapaste) geschaffen. In einer zweiten Sitzung wurden Elektroden in jeden Hippocampus und in die intralaminären Thalamuskerne implantiert. Durch Reizung in den letzteren Strukturen konnten die sonst voneinander unabhängigen epileptischen Entladungen der beiden Hippocampi synchronisiert werden.



Synchronisation of the clonic activity of the two autonomously discharging hippocampal epileptogenic foci, by single shock stimuli delivered to the thalamus (N. anterior) at the rate of 1/sec. Black dots indicate the stimulus artifacts. L. cort. = left cortex; l. hipp. = left hippocampus; r. hipp. = right hippocampus.

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The Postnatal Development of Homoiothermy and Cold Resistance in Mice

Earlier studies have indicated that the capacity for the regulation of body temperature is relatively poorly developed in newborn mice[1] and rats[2]. On the other hand, the ability to resist low body temperatures is better in newborn rats than in the adult ones[3]. In order to find out the causal mechanisms of these phenomena, a more detailed study of the time-course of the postnatal development of the homoiothermy and cold resistance is necessary. With this the present study is concerned. The simultaneous

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