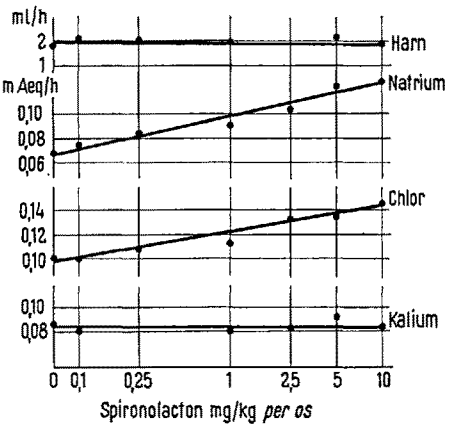
an Natrium und Kalium (flammenphotometrische Bestimmung) sowie Chlor (potentiometrische Titration) während 5 h erfasst.

Resultate. Im Gegensatz zu Hygroton führt Spironolacton im gleichen Dosierungsbereich an der Ratte zu keiner signifikanten Änderung der Elektrolytausscheidung im Urin (Tabelle), was auf Grund des Wirkungsmechanismus der Spirolactone bei normaler Mineralocorticoid-Bilanz auch nicht zu erwarten ist[4–7].

Durch gleichzeitige perorale Applikation von Hygroton 5 mg/kg und Spironolacton 0,1–10 mg/kg lässt sich eine Intensivierung des natriuretischen und chloruretischen Effektes von Hygroton in Abhängigkeit von der Spironolactondosis erzielen (Figur), wobei Natriurese und Chlorurese parallel verlaufen und die Elimination an Chlor die an Natrium übertrifft; die Kaliumausscheidung hingegen erfährt *keine* Steigerung.

Wenn es im vorliegenden Kombinationsversuch trotz normalem Mineralocorticoidspiegel der Versuchstiere zu einer natriuretischen Wirkung des Spironolacton kommt, so scheint uns folgende Interpretation am wahrscheinlichsten: am Normaltier ist die Natrium-Rückresorption in den proximalen Abschnitten des Nephrons bereits so stark, dass distal, also am Wirkungsort der Spirolactone, nicht mehr genügend Natrium zur Entfaltung eines messbaren Spirolacton-Effektes zur Verfügung steht. Wird dagegen durch gleichzeitige Verabreichung von Hygroton die proximale Natrium-Rückresorption teilweise blockiert, so gelangt genügend Natrium als Substrat für die Spironolacton-Wirkung in die distalen Abschnitte des Nephrons. Ähnliche Überlegungen stellten HILD et al.[8], VEYRAT et al.[9] für eine Kombinationstherapie Salureticum-Spirolacton bei therapieresistenten Ödemen an.



Elektrolytelimination im Urin nach Kombination von Hygroton® 5 mg/kg *per os* + Spironolacton, wasserbelastete Ratte (50 ml/kg *per os* Wasser).

Summary. When Hygroton® and spironolactone are given together to rats, the urinary excretion of sodium and chlorides induced by Hygroton increases with increasing doses of spironolactone, but that of potassium does not.

E. G. STENGER

Wissenschaftliche Laboratorien der J. R. Geigy A.G., Basel, 11. April 1961.

[7] G. W. LIDDLE, Science *126*, 1016 (1957).
[8] R. HILD und F. KRÜCK, Klin. Wschr. *39*, 178 (1961).
[9] R. VEYRAT, E. ENGEL, P. DUCOMMUN und A. F. MULLER, Helv. med. Acta *27*, 683 (1960).

EEG Synchronization Produced by Peripheral Nerve Stimulation[1]

The present experiments are concerned with the influence of peripheral nerve stimulation on the EEG synchronizing mechanisms.

Using barbiturate anesthesia, the following electrodes were chronically implanted in each of 20 cats: 1–3 nerve stimulating electrodes, 1–2 EMG electrodes placed in the neck extensor muscles, and 6–10 screwtype cortical electrodes. The superficial radial, sciatic, femoral, gastrocnemius, hamstring, and saphenous nerves were tested. No recordings were taken until 48 h after the operation. The testing procedure involved placing the unrestrained animals in a large box which permitted continuous observation of their reactions to the stimuli.

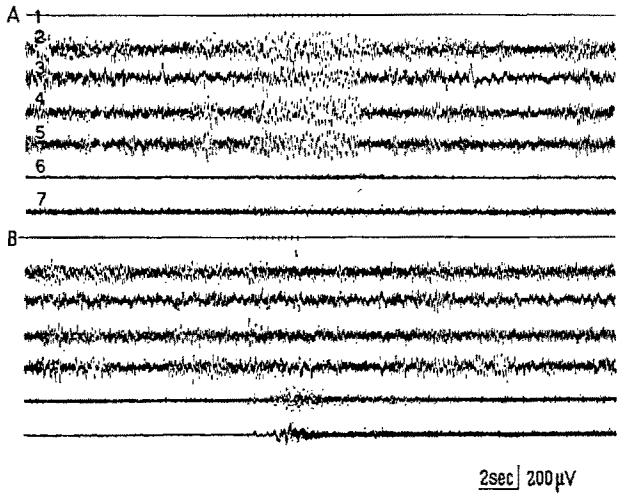
Providing that cortical activity had a natural tendency to be synchronized, carefully controlled peripheral nerve stimuli at 3–8/sec (0.1–0.5 msec pulse duration) could repeatedly induce a clear-cut generalyzed EEG synchronization. Stimulus trains, 2–4 sec in duration, were given approximately every 20 sec. The induced pattern of EEG synchronization exhibited waxing and waning characteristics and was sometimes accompanied by closure of the eyes at the onset of the stimulus. Also the tonic EMG activity of the skeletal musculature decreased providing that the EMG activity was already at a low level. The optimum stimulus values for obtaining EEG synchronization were unable to produce this effect during an EEG background of low voltage fast activity seen in either full alertness or deep sleep[2].

The problem of eliciting EEG synchronization is complicated by some habituation to the stimulus at the beginning of every recording period. The first stimulus of low intensity causes strong EEG arousal and an increase of EMG activity, but after a few repetitions this reaction completely disappears. If the stimulus intensity is increased in stages, this phenomenon repeats itself until a stimulus value is reached which always gives a weak arousal reaction. This is defined as the threshold for arousal and it is always determined for the particular type of EEG background best for inducing EEG synchronization. It is only at this point, when the animal's reactions to the stimuli have become stabilized, that EEG synchronization can be obtained at mean stimulus intensities 0.4–0.9 times the threshold for arousal. The Figure illustrates the effect of low frequency stimulation of a cutaneous nerve at slightly different stimulus strengths.

The superficial radial nerve was best for producing EEG synchronization since there were no arousing effects due to muscular movements as had been found when stimulating mixed or pure muscular nerves. However, it was also possible to obtain synchronization with these latter nerve types at stimulus values capable of producing muscular contraction.

Altering the frequency of impulses in the stimulus train which produced EEG synchronization caused two opposing effects on the same EEG background. At frequencies below 3/sec each shock could regularly trip brief spindle

[1] This investigation was supported by PHS research grant B-2990 from the National Institute of Neurological Diseases and Blindness, N.I.H., Public Health Services, U.S.A.
[2] M. JOUVET, J. DECHAUME et F. MICHEL, Lyon méd. *38*, 1 (1960).



Stimulation of the left superficial radial nerve at 3/sec, 0.5 msec and 395 μA produced synchronization (A). The eyes promptly closed at the onset of the stimulus and remained so. The stimulus intensity used was just below arousal threshold, as shown by the slight increase of EMG activity near the end of the stimulus train. Slight increase of the stimulus intensity to 430 μA caused arousal (B). The animal's eyes reopened and EMG activity increased markedly. 1: stimulus artefact; 2: right parietal-temporal; 3: right temporo-occipital; 4: left parietal-temporal; 5: left temporo-occipital; 6: EMG left neck extensor; 7: EMG right neck extensor.

bursts. Between 3–8/sec the EEG synchronization was usually uninterrupted and often tended to follow the frequency of the stimulus providing the stimulus intensity was sufficiently high. Increasing the frequency above 8/sec brought about a gradual reduction of the amplitude of the synchronized EEG pattern until all evidence of an induced synchronization disappeared altogether. The appearance of the true arousal occurred at frequencies higher than 12–16/sec. In such cases the effect was stronger when stimulus intensity was high enough to excite a small number of fibers of higher threshold capable of producing arousal in addition to those driving synchronizing mechanisms.

The conclusion is drawn that, under appropriate conditions, peripheral nerve stimulation may activate mechanisms responsible for EEG synchronization.

Riassunto. La stimolazione a 3–8/sec di nervi cutanei e muscolari, eseguita in gatti integri non anestetizzati, produce una sincronizzazione dell'attività elettrica cerebrale. La soglia per questa risposta corrisponde in media a 0,4–0,9 volte l'intensità minima di corrente che applicata allo stesso nervo e in analoghe condizioni sperimentali produce la reazione di risveglio.

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The Effect of Litter Rank on the Secondary Sex Ratio

The secondary sex ratio (the number of males per 100 females at birth) has been reported to decrease in succeeding litters of rats[1] and with increasing birth order in humans[2]. In mice PARKES[3] found a decrease in later litters while HOWARD et al.[4] failed to observe any change. Recently, during the course of investigations employing mice from a variety of inbred strains data were obtained pertaining to the secondary sex ratio in succeeding litters. Even though the sample size was small, it was felt that

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[2] E. NOVITSKI and L. SANDER, Ann. Human Genet. *21*, 123 (1956–57).
[3] A. S. PARKES, Biol. Rev. *2*, 1 (1926–27).
[4] A. HOWARD, A. MCLAREN, D. MICHIE, and G. SANDER, J. Genet. *53*, 200 (1955).

The secondary sex ratio of mice of successive litters

Strain	Litter rank	Litters	Total mice	Males	Males per litter	Females	Females per litter	Ratio
C3H/Sp	1	17	82	55	3.2 (0.4)[a]	27	1.6 (0.3)[a]	204
	2	17	101	55	3.2 (0.4)	46	2.7 (0.3)	120
	3	12	75	37	3.1 (0.3)	38	3.2 (0.5)	97
C3Hf/Sp	1	13	64	40	3.1 (0.5)	24	1.8 (0.3)	167
	2	17	91	56	3.3 (0.3)	35	2.1 (0.2)	160
	3	10	52	22	2.2 (0.4)	30	3.0 (0.5)	73
PL/Sp	1	18	77	57	3.2 (0.5)	20	1.1 (0.3)	285
	2	18	83	48	2.7 (0.4)	35	1.9 (0.4)	137
	3	9	42	25	2.8 (0.7)	17	1.9 (0.3)	147
AKR/Sp	1	16	90	62	3.9 (0.5)	28	1.7 (0.4)	221
	2	14	76	42	3.0 (0.4)	34	2.4 (0.4)	124
	3	6	34	22	3.7 (0.6)	12	2.0 (0.5)	183
MA/Sp	1	10	59	39	3.9 (0.8)	20	2.0 (0.4)	195
	2	9	57	31	3.4 (0.5)	26	2.9 (0.3)	119
	3	8	53	38	4.7 (1.1)	15	1.9 (0.4)	253
C57BL/Sp	1	10	42	23	2.3 (0.4)	19	1.9 (0.3)	121
	2	9	44	21	2.3 (0.6)	23	2.6 (0.3)	91
	3	7	36	18	2.6 (0.7)	18	2.6 (0.7)	100
Pooled F_1 hybrids C57BL × PL/Sp	1	13	82	46	3.5 (0.4)	36	2.8 (0.4)	128

[a] Figures are averages and standard errors.