Table II.—Variations in Weight, Lipid, and Pyridoxalphosphate Contents in the Heart of Rats (Mean value ± S. E.)

Diet Type	Fat Administered (Diet 'C')	Heart Weight (mg/100 g body weight)	Total Lipids (g%)	Pyridoxalphosphate (μg/100 g)
A	—	324·8 ± 29·5	1·667 ± 0·104	108·6 ± 8·1
B	—	418·5 ± 38·1	2·194 ± 0·178	41·7 ± 3·5
C	Coconut Oil	513·2 ± 42·7	2·838 ± 0·261	16·0 ± 1.3
C	Cocoa Butter	497·5 ± 41·4	2·751 ± 0·246	14·8 ± 1·1
C	Olive Oil	490·8 ± 44.3	2·696 ± 0·225	12·1 ± 0·7
C	Peanut Oil	479·3 ± 38.6	2·655 ± 0·218	14·6 ± 1·2
C	Cottonseed Oil	450·7 ± 36·2	2·618 ± 0·234	24·2 ± 2·2
C	Sesame Oil	461·4 ± 40·7	2·573 ± 0·226	21·5 ± 1·8
C	Corn Oil	454·9 ± 41·5	2·546 ± 0·198	22·9 ± 2·1
C	Wheat Germ Oil	441·6 ± 39.2	2·470 ± 0·183	27·4 ± 2·5
C	Soybean Oil	433·6 ± 41·4	2·484 ± 0·232	29·5 ± 2·7
C	Linseed Oil	428·5 ± 37·4	2·469 ± 0·177	32·2 ± 1·9

Diet 'A' – Devitaminized casein, 16% – Corn Oil, 15% – Vitaminized lactose, 4%* – Salt mixture IV, 4% – sucrose to make 100.

Diet 'B' – Same as 'A' but minus vitamin B_6 in vitaminic supplement.

Diet 'C' – Same as 'B' plus 25% vegetable fat.

* 100 g vitaminized lactose contain: thiamine mononitrate, riboflavine, and pyridoxine hydrochloride, each 12·5 mg – calcium pantothenate, p-aminobenzoic acid, each 50 mg – nicotinamide, 62·5 mg – biothin, folic acid, each 2·5 mg – vitamin A acetate (cryst.), 25000 U. – vitamin D 2, 7500 U. – choline chloride, 5 g – inositol, 2·5 g.

decreases with no evident, direct relationship to the iodine values of the oils used.

To sum up, while heart hypertrophy and lipid contents appear to be evidently related to the non-saturated fatty acid contents of the oils added to the diet, no similar relation exists in respect of pyridoxalphosphate concentration. Consequently, if the effect exerted by alimentary fats upon heart size and lipid contents may be attributed to non-saturated fatty acids being more easily metabolized than saturated ones, the same reasoning does not apply to the action exerted by the very same fats on the coenzyme, whose variations seem to be explainable otherwise.

One of the possible interpretations of the latter phenomenon is related to the oleic acid contents of the fat used, as this acid is known to aggravate the effects of a lack of vitamin B_6[9]. This would account for the severer depletion of pyridoxalphosphate in the heart tissue of such rats as were administered olive oil, wherein oleic acid amounts to 85% of the aggregate fatty acid contents. In addition to this, oleic acid promotes the absorption of alimentary cholesterol by the intestine to a substantial extent[10], thereby further increasing such already heavy cholesterol concentrations as are determined in the blood by lipid diets.

Such a view appears to be supported by the fact that the decrease in pyridoxalphosphate concentrations determined by peanut oil (wherein oleic acid amounts to 57·2% of total fatty acids) is only slightly less than the one determined by olive oil, as well as by the fact that a greater effect is developed by cocoa butter than by coconut oil, the former featuring a higher iodine value but also a greater amount of oleic acid. The same remark applies to cottonseed oil in respect of both sesame and corn oils.

Finally, a considerably important factor appears to be the linoleic contents of the fats used, for the fact should be stressed that linseed oil (highest iodine value among all fats tested) appears to lower the pyridoxalphosphate contents to a greater extent than do cottonseed, wheat germ or soybean oils – all of which have a higher linoleic-acid contents although their iodine values are lower.

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Farmavigor S. p. A. Milano, Research Department, October 9, 1958.

Riassunto

L'effetto di diete contenenti un eccesso di grassi vegetali e carenti di vitamina B_6 è stato studiato dal punto di vista del contenuto di lipidi e di piridossalfosfato nel tessuto cardiaco. Dei dieci grassi vegetali presi in esame il massimo aumento dei lipidi cardiaci si verifica per il burro di cacao e per l'olio di cocco, i più saturi di tutti i grassi usati.

Per quanto riguarda le concentrazioni cardiache di piridossalfosfato la massima diminuzione si registra per l'olio d'oliva, mentre la diminuzione minima si registra per l'olio di germe di grano e per l'olio di soia. Vengono brevemente discusse, dal punto di vista del grado di insaturazione e del contenuto di acidi grassi, le possibili cause di questi risultati.

Appetite Stimulating Effect of Barbiturate-Induced Therapeutic Sleep

In our previous papers[1,2] we gave evidence of an increased food intake as one of the characteristic metabolic peculiarities of therapeutic sleep (T. S.). An attempt at a more detailed analysis of this phenomenon was made in subsequent work by comparing caloric balances in a total of 50 patients (43 with peptic ulceration, 7 with various neurotic states), treated by T. S., induced by barbiturates

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[1] E. Kuhn and J. Mašek, Dtsch. Ges.-Wes. *11*, 577 (1956).

[2] E. Kuhn and J. Mašek, Acta Inst. Aliment. hum. Pragae *1*, 275 (1955).

(Amytal, Amobarbital, Dormiphen; 38 patients; average dose 0·26 g/day), chlorpromazine (50–200 mg/day; 7 patients), and by conditioned sleep (5 patients). The standard procedure and results were published in detail elsewhere[3].

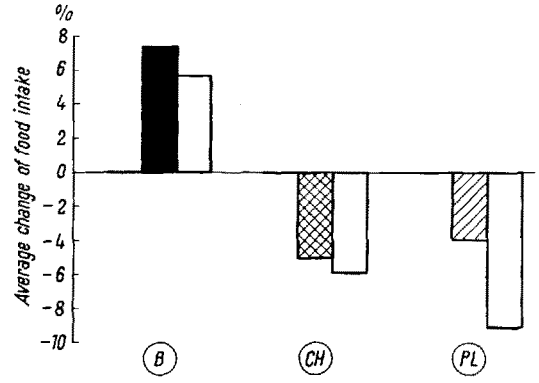

Fig. 1.—Changes of average food intake during period of sleep (black or shaded columns) and during 2nd control period (white columns) are expressed as percentages of the initial caloric intake during 1st control period (—)
B: barbiturate-induced sleep, CH: Chlorpromazine-induced sleep, Pl: conditioned sleep

Results: Changes in the food intake (Fig. 1) indicate clearly the difference between the group of patients where sleep was induced by barbiturate (average increase by 7·85%), chlorpromazine (average decrease by 4·99%), and conditioned sleep (average decrease by 3·75%). The analysis of dispersal made by means of the non-parameter test (Table) indicates that the differences of the average daily caloric intake during the investigation periods in all groups are statistically highly significant. The graphic presentation of the changes of food intake during barbiturate-induced sleep shows an even more significant difference (Fig. 2) if the average maximal caloric increase recorded during 3–5 days (on end) of the sleep period is used for comparison. We were, however, unable to reveal any relation between the caloric increment and the size of the administered dose of barbiturate.

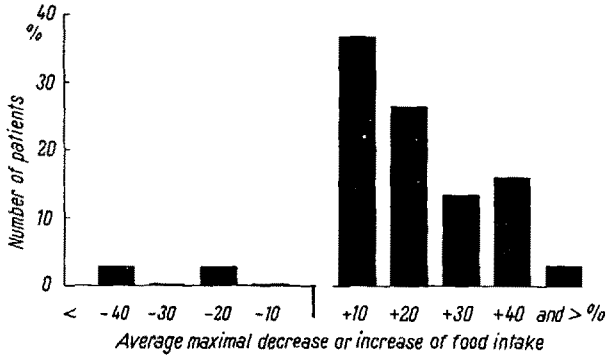

Fig. 2

Discussion: Among various papers dealing with the neurogenic regulation of appetite, the work of BROBECK *et al.*[4] appears important in explaining the mechanism of the changes observed. These authors, while investigating changes of electrical activity in various parts of the hypothalamus under the influence of amphetamine and its derivatives, noted a secondary finding during light anesthesia: barbiturate spindles from the hypothalamus with the exception of the ventromedial nuclei and from the neighbouring parts of the diencephalon and mesencephalon, i.e. from areas the electrical activity of which is not influenced by amphetamine preparations. This finding supplements their previous empirical observation of an increased food intake in rats with lesions of the ventromedial nucleus when recovering from barbiturate anesthesia[5]. As far as clinical work is concerned, we should like to draw attention to BAUMANN's trial to apply T. S. treatment in certain types of diabetes[6], the experience of HUNTER and GREENBERG[7] who observed deviations of carbohydrate metabolism associated with the habitual use of barbiturates, as well as to our own findings concerning the influence of barbiturates on the behaviour of glycemia of experimental subjects during 5 h periods on fasting, etc. As appears from MARK's communication[8], who observed that acetylation was inhibited to a different degree according to the type of barbiturate used, we may assume that the carbohydrate metabolism may be influenced in a different manner by different types of barbiturate used.

Kind of Therapeutic Sleep	Experimental Period	
	1st Control: Sleep	1st Control: 2nd Control
B	95·50**	155·36**
CH	9·18**	10·70**
Conditioned	17·39**	21·65**

** Values are statistically significant at the 1% level.

In our original explanation of the increased food intake under the influence of barbiturate-induced sleep[1,2] we concentrated our attention on the regulatory action of the central factor, where a predominance of inhibition changes the mutual relationship between cortex and subcortical regions, particularly by eliminating its inhibitory action on hypothalamic nuclei which are an important part of the functional structure of the alimentary centre as conceived by PAVLOV[9]. The finding of BROBECK *et al.*, recorded but not analysed in greater detail, of a certain relation of anesthesia to the regulation of food intake does not rule out a possible more specific connection of a certain type of barbiturates and the controlling function of the lateral or medial mechanism. This can manifest itself as activation of the lateral or inhibition of the ventromedial nucleus. We are, however, aware of the fact that apart from producing purely nervous phenomena by the pharmacological action of hypnotics, these substances may directly influence the metabolic activity on an enzymatic level and interfere with the carbohydrate metabolism. These mechanisms may regulate the biochemical homeostasis and act at the same time on neurogenic factors. The structural similarity of the barbituric acid molecule and alloxan as well as the hypoglycaemic effect of some barbiturates we referred to, does not rule out the possible participation of insulin in the development of hyper-

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[5] J. R. BROBECK, J. TEPPERMAN, and C. N. H. LONG, Yale J. Biol. Med. *15*, 831 (1943).

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[8] B. H. MARKS, Science *123*, 332 (1956).

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phagia. A differentiation of these individual mechanisms of the action of barbiturates – the nervous and humoral component of the regulation of food intake, based hitherto assembled clinical results, is not yet possible.

E. KUHN

Institute of Human Nutrition, Prague (Czechoslovakia), September 16, 1958.

Zusammenfassung

Im Gegensatz zum Chlorpromazin- und bedingt reflektorischen Heilschlaf löst die Medikation von kleinen Dosen kurzwirkender Barbiturate während der 14tägigen Schlafperiode bei Geschwürkranken und Neurotikern eine zeitweilige Hyperphagie verschiedenen Grades aus. Der relative Anteil von einzelnen mitbeteiligten Mechanismen wird diskutiert.

PRO EXPERIMENTIS

Ein Nomogramm zur Kombination mehrerer Ergebniswahrscheinlichkeiten

Für die zusammenfassende Beurteilung der gemeinsamen Wahrscheinlichkeit mehrerer voneinander unabhängiger Versuchsergebnisse gibt es verschiedene methodische Möglichkeiten[1,2], von denen die Kombination mittels der χ^2-Werte nach FISHER[3] wohl die unter den gewöhnlichen Umständen vorteilhafteste[1] und deshalb auch die verbreitetste[4] sein dürfte. Sie beruht darauf, dass die Grösse $-2 \sum_1^k \log_e P_i$ wie χ^2 mit $2k$ Freiheitsgraden verteilt und daher exakt testbar ist.

Das angeführte Nomogramm gestattet nun die schnelle und hinreichend genaue graphische Bestimmung der kombinierten Totalwahrscheinlichkeit P_t bei der Zusammenfassung von 2, 3 oder 4 Versuchen. Der Ablesungsvorgang ergibt sich aus der Rechentafel selbst, bzw. ist aus den beigefügten Schemen zu erkennen.

Im Falle zweier Versuche genügt die linke Bildhälfte: man geht mit P_1 und P_2 in die linke Netztafel ein und erhält das gesuchte P_t mittels deren Schnittpunktes, bzw. genauer durch dessen Verschiebung parallel zu den gestrichelten Leitlinien bis auf die *Resultatleiter II*.

Im Falle dreier Versuche wird die Leiter II zur Dreh- oder Zapfenlinie[5]: von ihr aus wird eine Ablesegerade durch den Wert für P_3 auf Leiter $P3a$ (nicht P_3!) gelegt, deren Schnittpunkt mit der *Resultatleiter III* das gesuchte P_t ergibt.

Im Falle von vier Versuchen geht man wie bei II, aber beiderseits symmetrisch von P_1 und P_2 links, bzw. P_3 und P_4 rechts aus vor, wobei zu beachten ist, dass nunmehr auch Leiter $P3a$ zur Zapfenlinie wird. (Ihre Skala entspricht nur dem P eines einzigen Versuches, nämlich dem des dritten von dreien, und ist daher als solche zur Ablesung des kombinierten Wertes von P_3 und P_4 allein nicht verwendbar.) Die gesuchte Totalwahrscheinlichkeit P_t wird in diesem Falle mittels einer durch die entsprechenden Punkte auf II und $3a$ gelegten Ablesegeraden auf der *Resultatleiter IV* ermittelt.

Abschliessend wird noch darauf hingewiesen, dass zwecks Vermeidung überflüssiger Dezimalstellen alle P-Werte *in Prozenten* angegeben sind und daher zum Beispiel der Ausdruck «0,1» einem Zehntelprozent, das heisst einer Wahrscheinlichkeit von 0,001 entspricht.

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[3] R. A. FISHER, *Statistical Methods for Research Workers* (Edinburgh 1934).
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[5] P. LUCKEY, *Nomographie* (Leipzig 1953).