wandveränderungen kann mit einer Senkung des Cholesterinspiegels allein das Problem niemals gelöst werden. Es scheint uns aber unter Berücksichtigung der bereits vorliegenden Literatur und unserer eigenen Befunde unbestreitbar, dass die Erforschung des Verhaltens von ungesättigten Fettsäuren in ihren gegenseitigen qualitativen und quantitativen Beziehungen und in ihrer Verteilung auf die verschiedenen Lipoidfraktionen unter den Bedingungen des Tierexperiments sowie beim Menschen sinnvoll und notwendig ist, käme doch der Aufklärung der Rolle der ungesättigten Fettsäuren für Biochemie, Physiologie und Pathologie des Gesamtstoffwechsels grösste Bedeutung zu.

Summary. The influence of chronic overfeeding of rats with saturated (lard, cream) and unsaturated (linseed oil) fats was studied by estimating total lipids and polyunsaturated fatty acids in the serum. Preliminary assays had shown that the determination of β-ketoacids, pyruvic acid and blood sugar gave no useful information on the regulation of the intermediate fat metabolism. Using an additional acute loading with corn oil, and comparing the blood fat values before and after this procedure, the following results were obtained:

Normal rats showed no changes of the values for total lipids after chronic overfeeding with saturated fat in comparison with the untreated controls. After linseed oil the lipid level is significantly lower and the rise after acute corn oil-feeding becomes smaller, most probably as a sign of an acceleration of the fat metabolism. Characteristic changes were seen by examining the 2 and 4 times unsaturated linoleic and arachidonic acids. Whilst linoleic acid shows a rise after feeding both saturated and unsaturated fat, still increasing after corn oil, arachidonic acid remains nearly unchanged by chronic fat-feeding but falls regularly after acute corn oil loading. Here we have a typical alteration of the saturation degree of polyunsaturated fatty acids after longer periods of overfeeding with fats.

If we produced a sclerosis of the media of the aortic wall in rats by treating them with calciferol-parathormone, we observed a strong hyperlipemia which became still more pronounced after corn oil. The values for linoleic acid were also high but did not rise after corn il; the behaviour of arachidonic acid was not uniform. 20 days later the untreated controls, as well as the lard-fed animals, showed normal data. By pretreating the rats with a diet rich in cholesterol and protein (diet I), or rich in cholesterol and carbohydrate but poor in protein (diet II), atherosclerosis-like changes developed. In the serum of these animals, the lipids were still more accumulated and were highest after acute corn oil loading. The values for linoleic acid were scarcely altered by corn oil; the arachidonic acid was low after diet I and II and increased after 20 days to an unusually high level. Total lipid values and the reaction to lard feeding were normalized after 20 days.

Our findings are discussed and compared with some facts to be found in the literature. Even if the importance of polyunsaturated fatty acids for human atherosclerosis is not yet to be judged, further investigation in this field seems highly justified, considering the complete lack of exact knowledge of the functional significance of these substances for basic metabolic processes under physiological and pathological conditions.

S. MARKEES

Medizinische Poliklinik Basel, 27. März 1961.

STUDIORUM PROGRESSUS

The Adrenal Cycle in Men on Different Schedules of Motor and Mental Activity[1]

The circadian[2–5] cycle of the mammalian adrenal cortex, an endocrine entity intimately related to over-all motor and mental activity[6,7], is not a direct or immediate 'response' to the activities of everyday life. First, the rhythm of blood eosinophils, admittedly an indirect index, persists in men active more or less continuously for two consecutive days in the absence of overt sleep, on a demanding schedule of sampling and laboratory work, carried out with rest periods of only short duration for eating and other essential needs[8]. Second, the onsets of the circadian periodic decrease in blood eosinophils[8] and of the rise in the corticosterone content of mouse serum[9,10], which are preparatory to activity[7], usually lead-in-phase the major daily bursts in gross motor behavior. Apart from the direct and well-known adrenal cortical 'reactions' to environmental stimuli eliciting activity, the spontaneous physiologic activation of this gland seems to occur during sleep or rest[9]. Other aspects of the relation between circadian periodic body activity and the adrenal cortical cycle, such as phase-shifts and phase-drifts, also have been explored, at least in the mouse[9,11,12], by eosinophil counts, and, more recently and more directly, by hormone determinations in the blood[9,10] and the adrenal gland itself[13] of the same species.

In the mouse, hormone rhythms, among others, can be studied by serially independent sampling[14] in the absence of effects from sampling as such, which in itself is a powerful environmental stimulus. Through the use, at consecutive time points, of separate groups of animals that are comparable in terms of strain, sex, age, and history, highly significant sampling effects[15] can be controlled in this species.

[1] Supported by grants from the Teagle Foundation, through Dr. M. COHEN, the U.S. Public Health Service (No. C-4359(C1), No. 1A-1573(C3), No. H-1983(C3), the American Cancer Society (No. E-155B), and the Minnesota State Department of Public Welfare.

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The question of sampling effects, however, is more difficult to handle in human beings studied by conventional venipuncture although the rhythm of cortical adrenal hormones in human urine[16] and blood[17–19] is well-established. Data on the plasma 17-hydroxycorticosteroid rhythm of men not awakened by venipuncture then are of interest, particularly if sleep can be verified by electroencephalograms recorded during blood withdrawal. In results thus obtained, sampling effects probably are minimized. One might thus explore the question whether, as has been postulated[7], the major endogenous adrenal cortical activation occurs during actual sleep. The possibility that awakening, as such, may result in the circadian rise of plasma 17-hydroxycorticosteroid could thus be ruled out.

Data pertinent to these problems recently became available from work on the relation of the adrenal cycle to circadian changes in the electroencephalogram, recorded with concomitant frequency analysis (to be reported elsewhere[20]). Two groups of subjects were involved. One of these, Group I, was composed of 13 normal mature males, 22 to 35 years of age. These individuals rested during the night. By day, they followed their habitual activities as medical school staff. From some of the Group I subjects the sample of blood was withdrawn through an indwelling venous catheter without disturbance of sleep and this was verified electroencephalographically as well as behaviorally. In other Group I subjects, despite the catheter, sampling was associated with drowsiness or awakening.

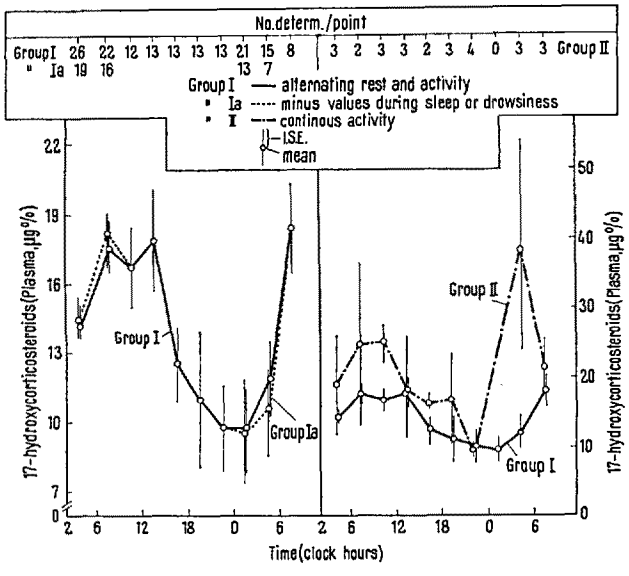
Group II consisted of three of the experimenters, who also carried venous catheters. These subjects had followed their regular hospital staff activities during the day preceding the start of sampling and they did not go to bed during the entire period of the study. Group II subjects were engaged, moreover, in almost continuous mental, if not gross motor, activity. They sat down only for short periods, that did not exceed 30 min and were spread irregularly over the day and the night. The activities of Group II subjects included the withdrawal of samples, around the clock, from the Group I subjects and from each other, the operation of the electroencephalograph, of the frequency analyzer and other aspects of experimental work (e.g. preparation of test tubes, labeling of samples, recording of data).

The Figure, left, shows the significant circadian periodic change in plasma 17-hydroxycorticosteroids of Group I subjects, active by day but resting by night. For the hours of rest two curves are shown, one including the values obtained during sleep or drowsiness (Group I curve), the other excluding the latter values (Group Ia curve). The curves are similar.

Sampling was not frequent enough to examine short-term changes, e.g. possible 90-min cycles in plasma 17-hydroxycorticosteroid behavior of sleeping men[21]. But despite the considerable scatter of individual values, in the presence as well as absence of electroencephalographically ascertained sleep, the nocturnal rise of plasma 17-hydroxycorticosteroids stands out clearly in these subjects habitually active by day and resting by night while they adhered to the same rest and activity schedule during the experimental period—some of them without interruption of sleep. Some of the individual sleep values were much higher than the group mean for the corresponding period.

Group II behavior is compared to that of Group I in the right half of the Figure. First of all, the adrenal hormone rhythm in plasma persists in the experimenters, Group II, who were more or less continuously active for two 24 h periods. The cyclic changes in Group II (as compared to Group I) are apparently characterized by (1) a higher over-all level, by (2) a greater peak-to-trough difference and by (3) a shortening of the interval between consecutive peaks, suggesting an acceleration of the adrenal cycle.

The Group II curve is based upon a limited number (26) of determinations (see right top of Figure). The curve serving (as the standard of reference) for comparison with Group II, however, comprises 156 determinations (for number of determinations see Group I, left top of Figure). The total of 172 determinations may suffice to support the foregoing interpretation; the latter must be qualified, however, as being applicable only to the type of 'continuous' activity involved in this study and to the particular stage of adrenal cycle in which novel activities were begun, i.e. the early ascending stage of the circadian plasma 17-hydroxycorticosteroid rhythm. Seasonal effects and other intercurrent (e.g. metereologic) sources of variation are unevaluated herein. Moreover, the transverse profiles[22] of this study involve determinations on several subjects for relatively short periods, yet they should approximate the behavior of such a group over many cycle lengths. The significance of such transverse profiles depends upon replications on other occasions. From this viewpoint the current study may, perhaps, be regarded as



Time-course of adrenal cycle in normal mature human males. Group I subjects, on a schedule of diurnal activity and nocturnal rest and sleep (N = 13). Group II subjects active by day and by night, without sleep (N = 3). Group I curve is the same in both halves of Figure; ordinates show different scales for the plasma 17-hydroxycorticoid value.

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a replication of the blood eosinophil profiles of normal men on different schedules of activity, studied earlier[6] with similar results.

Conclusions. The adrenal cortical cycle evaluated by plasma 17-hydroxycorticosteroid levels persists in healthy mature men sleeping undisturbed, while their blood is withdrawn through indwelling venous catheters. This cycle persists also in subjects continuously active for two days, mentally as well as physically. Moreover and at least for two days, continuous 'overall' activity in man actually enhances, rather than obliterates, the adrenal cortical cycle. More specifically, motor or mental activity continued for 48 h raises the peak-to-trough difference of the plasma 17-hydroxycorticosteroid rhythm, with an associated increase in overall hormone level, while the cycle's length shortens during the 24 h period following a first wakeful night.

These findings are viewed in the context of earlier work, showing (1) the persistence of the adrenal cycle evaluated by serially independent sampling on the mouse, in the absence of intentional stimulation[14], even in constant darkness[11], and (2) the persistence of a predominating circadian period (rather than primary 12 h period) in the eosinophil rhythm of human beings subjected to a drastic 12 h stressor schedule[9,22,23] until 'regressed' and disoriented in time.

In mice and man, the adrenal cycle thus constitutes an endocrine entity in its own right and it is not simply 'persisting from within while impressed from without'; its circadian periodic behavior, an aspect of functional integration[5,22], underlies our adaptation to changes in schedules[24]. Information on the adrenal cycle is of practical interest in dealing with many facets of temporal coordination in human physiology, ranging from the scheduling of activities on earth to the planning of routines for life in aerospace[25].

Zusammenfassung. Der venöse Plasmaspiegel von 17-Hydroxycorticosteroiden, als Mass der Nebennierenrindenaktivität verwendet, wurde bei gesunden jungen Männern mit Hilfe von Verweilkathetern in regelmässigen Abständen bestimmt. Die Corticoidsekretion steigt und fällt circadisch-periodisch. Auch bei (durch EEG) kontrolliertem ungestörtem Schlaf oder bei über 48 h anhaltender körperlicher und geistiger Arbeit wird der Sekretionsrhythmus nicht gestört, durch die Daueraktivität sogar verstärkt. Der circade Sekretionsrhythmus ist also weitgehend unabhängig vom Aktivitätsgrad des Organismus.

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