firmed repeatedly; (ii) most of the data was considered compatible with transfer factor being an immunogen; and (iii) developments in vitro, particularly the activation of animal lymphocytes by dialyzable transfer factor of human origin, augur well for a rapid solution of the problem.

Bloom and Granger were the initiators for two separate discussion sessions devoted to the now recognized MIF and lymphotoxin as effector molecules of cellular immunity. Activated lymphocytes have now been shown to liberate factors with the following activities: MIF, LT, skin-reactivity, chemotaxis, mitogenicity, and interferon. Although the interaction of immune lymphocytes with specific antigen is required for the production of these effector molecules, the subsequent action of these effectors is nonspecific with respect to the target cells affected and, moreover, does not require the presence of antigen. With the exception of interferon, all of these agents have molecular weights around 80,000, and work is already under way to determine whether they are separate and discrete entities or reflect a single component.

The physiological role of these factors is not yet fully established. Chemotactic factor and MIF acting in concert could well account for the manifestations in vivo of delayed hypersensitivity, and the observed consequences of MIF injection can be interpreted in this light. Lymphotoxin, the cytotoxic factor, is suspected of playing a role in the homograft reaction, a concept which is supported by known instances of nonspecific spread of the reaction (for example, in the kidney) but contradicted by other instances of a highly selective reaction (such as in tumors and in the skin). Experiments with antiserums to the factors should rapidly resolve the problem.

In the final discussion, Uhr developed the evidence in support of immunoglobulin as the recognition unit in cellular immunity, and the thesis that the difference from humoral immunity probably hinged on a seemingly minor but essential aspect of immunoglobulin retention by thymic cells as compared to its secretion by plasma cells. The consensus was that our understanding of the effector side of the cellular immune response is now progressing rather rapidly, whereas there was less optimism concerning clarification of the induction side.

Publication (Academic Press) of the proceedings of the meeting is scheduled for October. The first volume of the new series was *Immunological Tolerance*, proceedings of a similar meeting in 1968.

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Sleep and Biorhythmicity

The relation of sleep research and biological rhythm research was examined in a symposium during the ninth annual meeting of the Association for the Psychophysiological Study of Sleep in Boston, 20–23 March 1969. The estrangement of these two related areas of work was ascribed to the preoccupation of sleep researchers with the psychophysiology of rapid eye movement (REM) sleep since its discovery 15 years ago. Since then a profusion of data, almost all of it involving measurements over time, has appeared.

Variable sleep dimensions in the time domain include latency to onset, total duration, duration of component phases (REM and non-REM), and period length of the cyclic alternation of component phases. Yet, in the post-REM era there has, until very recently, been no critical examination of the rhythmic aspects of sleep despite the fact that a highly sophisticated set of methods exists by which they may be studied. The student of sleep who was familiar with rhythm research could, at the least, define, measure, and control for periodic phenomena in his data.

Halberg showed how rhythms, especially circadian and ultradian ones, could be detected by the use of specialized computer programs whether or not they were apparent in sleep data plotted as a function of time. The parameters of such rhythms, namely, period (τ), amplitude (C), phase (ϕ), and phase difference (Φ), can likewise be estimated. For time series or sections thereof with constant phase angle, a least-squares spectrum and a cosinor display the amplitude and amplitude-weighted phase, respectively.

These measures have been determined for sleep data from diverse sources. Pöppel reviewed the evidence of the Aschoff school for the circadian character of the human sleep-waking cycle. The period (τ) of this rhythm in subjects isolated from time-givers was about 25 hours and such "free-running" individuals showed a change in phase difference (Φ) between the

sleep-waking rhythm and that of body temperature. Circadian rhythms of several sleep variables in monkeys were described by Crowley, Kripke, Pegram, and Schildkraut. Like man, the monkey was diurnal. Acrophase of temperature (or fitted peak) led that of the awake stage by only ½ hour and the fitted nadir of temperature was almost exactly in phase with stage non-REM sleep.

Such rhythms have been shown by Stroebel to undergo change in period and amplitude when monkeys are subjected to behavioral stress, changes which are reversed by phenothiazine medication. Periodic sleep attacks in man have been studied by Passouant with respect to their ultradian rhythmicity. Both the periodicity and manifestations of these narcoleptic attacks suggest that they represent loss of control of a clocklike REM generator which is normally damped in waking and released only in sleep. Treatment with amphetamines, imipramine, or monoamine oxidase inhibitors may help control this disorder. The evidence for the continuous operation of this 90-minute ultradian rhythm in man, the "basic rest-activity cycle," was reviewed by Kleitman.

The ubiquity of rhythms in plant and animal life suggests the operation of primitive, relatively simple, probably chemical mechanisms, operating even in single cells, of which sleep may be a complex but partially derivative manifestation. Thus the study of rhythms in single neurons provides a model for the study of sleep. The responsiveness of cat brain stem neurons was found by the Scheibels to undergo cyclic variation over a 3- to 6-hour period; a 2- to 4-hour period of sensitivity to exteroceptive inputs was followed by a 1- to 2-hour period of nonresponsiveness during which several presumed interoceptively generated patterns were observed. Strumwasser described a circadian rhythm of impulse activity emitted by a neurosecretory neuron in the isolated parietovisceral ganglion of the sea hare *Aplysia*. It thus seems possible that nerve cells contain endogenous programs of activity which operate by cytoplasmic mechanisms that couple to the excitable membrane; these cellular clocks may be related to the circadian rest-activity cycle demonstrated by time-lapse cinematography of the intact organism.

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