

LES
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DE
L'INSTITUT
DE LA VIE

1968 No 18

LES
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DE L'INSTITUT
DE LA VIE

Siège: 89, B^o Saint Michel, Paris V^e
Téléphone: 033-94-86
Périodicité: trimestrielle

Prix du numéro: France 5 F. Étranger 6 F
Abonnement: France 18 F. Étranger 22 F
Conditions spéciales aux membres de
l'Institut de la Vie.
Renseignements au Siège.

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CONFÉRENCE INTERNATIONALE
PHYSIQUE THÉORIQUE ET BIOLOGIE
Versailles 26-30 juin 1967

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DISCUSSIONS

B. B. LLOYD: You alluded, Dr. Halberg, to the periodicity of liver glycogen and you also talked about Claude Bernard's earlier statement of liver glycogen being sometimes very low (in fact, I think, sometimes zero) and sometimes very high. Has this periodicity anything to do with the nervous system and is it related to Bernard's work on *piqûre* diabetes.

F. HALBERG: Thank you kindly, Dr. Lloyd, for providing me with this opportunity to comment on Claude Bernard in relation to the study of rhythms. Let me refer you in this connection to comments made earlier [1]. To the thinker [2], not to mention Bernard the demonstrator of experimental procedure [3], the significance of physiologic timing should have been apparent. Yet if one scrutinizes his writing about the conditions of a "continuous life", one finds only somewhat ambiguous remarks such as the following:

"The phenomenon of nutrition is accomplished in two times (he probably means two stages), and these two times are always separated one from the other by a period of more or less long duration, which (duration) is a function of a variety of circumstances" (. . . dont la durée est fonction d'une foule de circonstances) [2].

At 52 years of age, the active investigator recognizes explicitly the "milieu intérieur variable" (sic); in 1856, the editors of the *Journal de l'Anatomie et de la Physiologie* announce [4] that Mr. Claude Bernard will soon publish an introduction to the study of experimental medicine. They do so in a footnote to an article by Claude Bernard himself, written under the title "Of the diversity of animals subjected to experimentation" and—what is more important in our context—"Of the *variability* (italics mine) of organic conditions in which they (the animals) present themselves to the experimenter":

"M. Claude Bernard doit publier prochainement une 'Introduction à l'étude de la médecine expérimentale', 1 vol. in-8 de 400 pages. Nous sommes heureux d'offrir à nos lecteurs un extrait de ce livre, qui est un exposé de doctrines présentant le tableau complet des faits et des idées que le professeur a développés dans son cours de médecine au Collège de France et dans son cours de physiologie générale à la Faculté des sciences, depuis ses dernières publications de 1859." [4].

This footnote states that they (the editors) are happy to offer to their readers an "extract" of the book prepared by its author. The material in the article then reflects what the active (rather than senescent) Bernard himself regarded as his most important experience. Of primary interest in the same context remains

Bernard's emphasis that "one must keep in mind not only the variations of the cosmic external milieu, *but also the variation of the organic milieu* (italics mine), i.e., that of the actual state of the organism".

Claude Bernard writes further that one might be in great error in assuming that it suffices to experiment on two animals of the same species in order to obtain identical experimental conditions and suggests that *the physiologic conditions of the internal milieu manifest an extreme variability* (italics mine); that, at a given moment, such variability introduces considerable differences into the results from experimentation on animals of the same species that appear to be identical.

He states further that "more than anybody else," he has insisted on the need to study these different physiologic conditions and to have demonstrated that they are the essential basis of experimental physiology. He points out that one must admit in fact that, in a given animal, the vital phenomena vary (sic) only according to precise and determined conditions of the internal milieu.

Students who evaluate rhythms as the elements of an organism's time structure will hasten to agree with such statements much more readily than students of "constancy". From appropriate statistical work one can indeed specify circadian system phases "dans lesquelles il y a *toujours* du sucre et d'autres conditions dans lesquelles il n'y en a *jamais*"—as will become apparent from fig. 1 for the case of glycogen, if not sugar, in mouse liver. Liver glycogen contents of, say, intact ad libitum fed animals continue to be presented by prominent biochemists without a qualification of the sampling time in terms of rhythms. However, the best chemical procedure will yield results that in such instances are physiologically difficult to interpret or actually misleading (fig. 1). One can cite Claude Bernard further in this connection:

"... Pour le moment, je veux uniquement appeler l'attention des expérimentateurs sur l'importance qu'il y a à *préciser les conditions organiques* (sic), parce qu'elles sont, ainsi que je l'ai déjà dit, la seule base de la physiologie et de la médecine expérimentale. Il me suffira, dans ce qui va suivre, de me borner à des indications, car c'est à propos de chaque expérience en particulier qu'il s'agira ensuite d'examiner ces conditions, aux trois points de vue physiologique, pathologique et thérapeutique." [4].

Furthermore, in his *Phenomena*, on page 114, [2] Bernard indicates that constancy presupposes the "self-perfecting" of an organism in such a fashion that the external variations are at each moment *compensated and balanced*; the "higher animal", rather than being indifferent to the external world, is in a *close and wise relationship* with it, in such a fashion that animal equilibrium results from a continuous and delicate compensation established by the most sensitive of balances.

The temptation is great to read "rhythm" into "equilibrium", and to attribute to the aged Bernard a hint of the close and wise interactions ("... étroite et

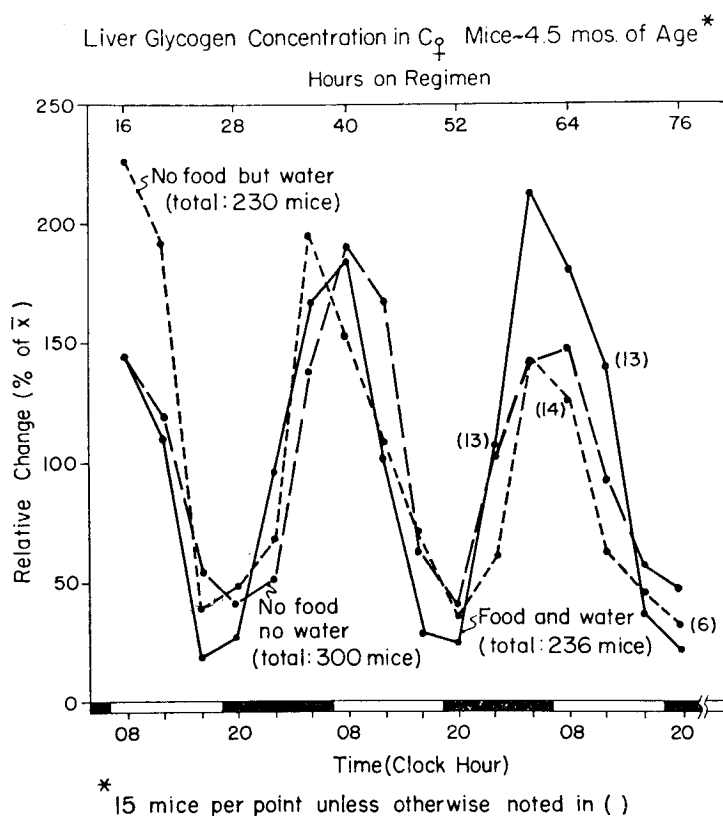


Fig. 1

savante relation . . .”) in which the cycles of a terrestrial environment are “anticipated” by rhythmic organisms evolved on earth. This would probably be no more than wishful thinking—as far as can be judged from Bernard’s writings. It is difficult further to reconcile the remarks on a “close and wise interaction” with the concept of a *shielding* of the organism from the environment by an internal milieu that is constant. Indeed, it is important at this symposium to emphasize that shielding by a basic constancy currently credited to Bernard must not be confused with the view of basic rhythmic physiologic interactions underlying a superficial constancy or, rather, a limited variability. In the former view, rhythms remain secondary or even trivial considerations as to both interpretation of body function and experimental method. In the latter view, rhythms become primary basic features of temporal integration and adaptation in organisms.

It is probably because Claude Bernard gave precedence to shielding over rhythms that throughout his work on diabetes and glycogenesis there is not a single reference indicating precautions taken to control the rhythm in liver glycogen.

To turn to Dr. Lloyd's question as to whether Bernard's work on the "piqûre diabétique" relates to periodicity, one might suggest that Bernard failed to recognize such a relation. In his *Leçons sur Le Diabète et La Glycogénèse Animale* (Baillière, Paris 1877), Bernard recalls how he arrived at the piqûre after describing its effects; he writes that he had the preconceived idea to augment hepatic secretion and sugar production "en excitant les origines du pneumogastrique, comme j'avais, dans d'autres circonstances, augmenté la sécrétion salivaire en excitant les origines de la cinquième paire." (p. 370). The most prominent periodicity of this variable remains ignored until the explicit statement by Erik Forsgren in 1927 that liver glycogen undergoes about 24-hour periodic changes that are partly independent of nutrition. For a discussion of historical features to Bernard's piqûre and to subsequent work, interested individuals can be referred to a book by Jakob Möllerstrom, *Das Diabetesproblem: Die rhythmischen Stoffwechselforgänge*, (Thieme, 1943).

- [1] F. Halberg, Claude Bernard, referring to an "extreme variability of the internal milieu" in *Claude Bernard and Experimental Medicine*, (Shenkman, Cambridge, Mass., 1967) 193-210.
- [2] C. Bernard, *Leçons sur les phénomènes de la vie communs aux animaux et aux végétaux* (Baillière, Paris, 1885).
- [3] L. Binet, (editor), *Claude Bernard, Introduction à l'étude de la médecine expérimentale* (Paris, Les Chefs-d'Œuvre Classiques et Modernes, 1963).
- [4] C. Bernard, De la diversité des animaux soumis à l'expérimentation. De la variabilité des conditions organiques dans lesquelles ils s'offrent à l'expérimentateur. *J. Anat. Physiol. Homme Animaux* 2 (1865) 497-506.

P. DEJOURS: Deux questions à M. Halberg: Pouvez-vous expliquer pourquoi il est plus difficile d'aller d'Ouest en Est que dans la direction opposée? En ce qui concerne les oiseaux migrateurs entre l'hémisphère Nord et l'hémisphère Sud, que devient leur cycle circadien? Existe-t-il un déphasage de 180 degrés lorsqu'ils passent l'équateur?

F. HALBERG: We are searching for the answer to Dr. Dejour's question, which gains greatly in importance in this day and age of global travel not only for passengers but also for the aviator and finally for all of those concerned with work hygiene. Short reflection will lead one to recognize that to adapt following rapid eastward travel, one must advance a rhythm, whereas after a westward flight, one adapts by a delay of rhythm. These two adaptations are distinctly different. It appears that the circadian system has some "polarity", as demonstrated for the rat in my text-fig. 4. The same point is also made by fig. 2 for man. This figure summarizes studies done in cooperation with Dr. Walter Nelson and Dr. Erhard Haus of our laboratory at the University of Minnesota. It shows for the variables and subjects studied a much more rapid delay of rhythm as compared to an

advance. Another question concerning the relative ease of adaptations after transmeridian travel relates to the extent of transient frequency and phase desynchronization during such adaptations. From fig. 2 it also appears that while the adaptation following a flight from east to west is faster, the transient desynchronization among certain urinary variables during this relatively short shift time is greater than that occurring in connection with an advance of rhythms.

Such problems of chronophysiology relate perhaps to accident prevention. Certainly the avoidance of performance decrements by manipulating the adaptation of rhythms in the physiologically most favorable fashion compatible with logistic needs can be expected to lower the accident rate following changes in routine.

PHASE-SHIFTS OF THE HUMAN CIRCADIAN SYSTEM AS A RESULT OF 2 INTERCONTINENTAL FLIGHTS, GAUGED BY URINARY EXCRETION RATES*

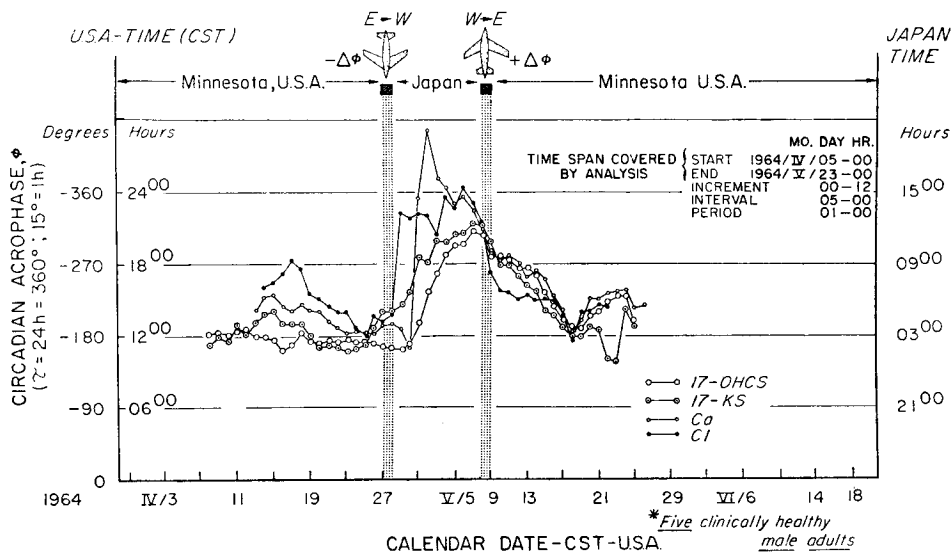


Fig. 2

With such problems in mind, Dr. Fessard, Dr. Reinberg and a number of us in other parts of the world intend to assign to the facilitation of rhythm shifts required by transmeridian flight or by odd work routines a prominent place in a chronobiologic project now planned within the framework of the International Biologic Program.

Concerning Dr. Dejour's second question, it would be desirable indeed to telemeter the rhythms of an arctic tern while this animal flies from one Pole to the other. I wish I knew how long this flight takes on the average, and I plead guilty to not having studied classical papers such as those of Bertil Kullenberg

(Über Verbreitung und Wanderungen von vier Sterna-Arten, *Arkiv. Zool.* **38 A** (1946) no. 17 and Finn Salomonsen (Migratory movements of the arctic tern (*Sterna Paradisaea* Pontoppidan) in the Southern Ocean; Danske Videnskabernes Selskab, *Biol. Meddelelser* **24** (1967) 1.

If the flight from Pole to Pole takes weeks rather than a few days, there may be a slow adjustment to the local setting, as has been reported for the case of sea travel by man. In 1905, Gibson reported an apparent adjustment of the timing of the body temperature rhythm—day by day and coincident with the shifting of the routine—during sea travel from the United States to the Philippine Islands and back. This author, who studied two individuals, describes for both of them a “somewhat limited daily range of variations” in body temperature after arrival in Manila, the Philippines (R. B. Gibson: The effects of transposition of the daily routine on the rhythm of temperature variation; *Amer. J. Med. Sci.* **129** (1905) 1408). During a sea voyage from Melbourne, Australia, Osborne in 1908 found that throughout the journey the evening maxima of the body temperature rhythm followed local time (C. Osborne: Body temperature and periodicity; *J. Physiol.* **36** (1908) 34–41). Conceivably, the arctic terns adjust their circadian rhythms in the case of slow travel across latitudes and longitudes as do human beings. Finn Salomonsen’s fig. 2 on page 7 of the above mentioned publication indicates that some terns, at least, follow a transmeridian path during part of their inter-polar journey as champion long-distance migrants, a circumstance kindly indicated to me by Mr. David Cline of the Museum of Natural History of the University of Minnesota.

For information on rhythmicity in arctic birds, two reviews by Donald S. Farner are quite pertinent: Role of extreme changes in photoperiod in the annual cycles of birds and insects, *Federation Proc.* **23** (1964) 1215–1220; and Circadian systems in the photoperiodic responses of vertebrates in *Circadian Clocks*, Proceedings of the Feldafing Summer School, Ed. J. Aschoff (North-Holland, 1965) p. 357–369. Further research may well be aimed at evaluating the time course of any circannual rhythm adaptation during 5 or 6 inter-polar round-trips made by an arctic tern in consecutive years.

H. MARGENAU: I have a question or two, Sir. The first one is this. Is anything known about the physiological or chemical mechanism which carries these rhythms? I am particularly interested in those rhythms which one might call active, which originate within the organism itself and are not tied to the surroundings.

The second question which I might voice at the same time concerns the interesting paper by Dr. Lindauer. I would like very much to know whether there is any knowledge or whether there are any conjectures as to how bees become aware of a magnetic field?

M. LINDAUER: In a few years, so we hope, this question can be answered by experimental data. Theoretically a magnetic field can affect the organism (the sensory cells or the neurons):

- 1) by generation of electromotive force in moving conductors (a honey bee performing the waggle dance is a fairly fast moving conductor);
- 2) by the force exerted upon moving charge carriers (Hall-effect);
- 3) by force or torque exerted on para- and diamagnetic particles.

The voltages resulting from the effects can be very small only (in case 1 $\approx 0,1 \mu\text{V}/\text{cm}$); however Lissmann and Machin have shown that "electric" fish can sense voltage gradients as low as $0,03 \mu\text{V}/\text{cm}$.

F. HALBERG: In the mammal, adrenocortical steroids represent the mechanism of certain circadian rhythms but not of others. Corticosteroids are, of course, entities that are chemically well defined, recognized physiologically as well and amenable to anatomical localization as to their site of production. Removal of the adrenal gland in man and mouse or Addison's disease—a condition associated with adrenocortical insufficiency—resulted in the obliteration of a circadian rhythm in blood eosinophil cells, at Michigan [1] in Utah [2] as well as at Minnesota [3]. Dr. Azerad, Dr. Reinberg and Dr. Ghata in France, over a decade ago, demonstrated that circadian rhythms in the urinary excretion of certain electrolytes also are obliterated as group phenomena in human adrenocortical insufficiency [4].

Aussi pour le cas de l'incorporation du radiophosphore dans les phospholipides hépatiques le cortex adrénalien semble être un mécanisme critique [5]. Nous avons été un peu troublés lorsque nous avons étudié les rythmes du marquage de l'ADN, il y a dix ans. Nous avons trouvé que les rythmes dans le métabolisme de l'acide désoxynucléique persistent après une adrénalectomie bilatérale. Alors il y a des différents mécanismes endocriniens et cellulaires pour différents rythmes circadiens. En passant du mammifère au microorganisme, on signale un travail intéressant qui a été fait par Sweeney et Haxo sur l'acetabularia [6]. Dans ce cas on peut couper les "rhizopodes" de base et enlever ainsi le noyau. Dans ce travail de Sweeney et Haxo et autres, vous avez la continuation d'un rythme circadien photosynthétique, en l'absence des acides nucléiques formes et connus [7, 8]. Finalement, on peut démontrer avec les méthodes modernes de rythmométrie des rythmes mêmes pour *E. coli* [9].

- [1] Mechanisms of diurnal eosinophil rhythm in man, *J. Lab. Clin. Med.* **45** (1955) 247.
- [2] The diurnal variation of blood leucocytes in normal and adrenalectomized mice, *Endocrinology* **58** (1956) 365.
- [3] Diurnal rhythmic changes in blood eosinophil levels in health and in certain diseases, *J. Lancet* **71** (1951) 312; Eosinophil rhythm in mice: Range of occurrence; effects of illumination, feeding and adrenalectomy. *Am. J. Physiol.* **174** (1953) 313–315.
- [4] Disparition du rythme nyctéméral de la diurèse et de la kaliurie dans 8 cas d'insuffisance

- surrénale, *Ann. Endocrinol. Paris* **18** (1957) 484-491; See also Rythmes des fonctions cortico-surrénales et systèmes circadiens, in: *Symp. int. sur la Neuro-endocrinologie*, (L'Expansion Scientifique Française, Paris, 1966) 75.
- [5] F. Halberg, H. Vermund, E. Halberg and C. P. Barnum, Adrenal hormones and phospholipid metabolism in livercytoplasm of adrenalectomized mice, *Endocrinology* **59** (1956) 364.
- [6] B. M. Sweeney and F. T. Haxo, *Science* **134** (1961) 1361.
- [7] E. Schweiger, H. G. Wallraff and H. G. Schweiger, Endogenous circadian rhythm in cytoplasm of acetabularia: Influence of the nucleus, *Science* **146** (1964) 658.
- [8] E. Schweiger, H. G. Wallraff and H. G. Schweiger, Über tagesperiodische Schwankungen der Sauerstoffbilanz kernhaltiger und kernloser *Acetabularia mediterranea*. *Z. Naturforsch.* **19** (1964) 499.
- [9] F. Halberg, and R. L. Conner, Circadian organization and microbiology: variance spectra and a periodogram on behavior of *Escherichia coli* growing in fluid culture, *Proc. Minn. Acad. Sci.* **29** (1961) 227.

K. MENDELSSOHN: There is of course a rotation of the polarization axis and the thing that is observed is a polarization. It would be a small effect, but biological indicators are sensitive.

H. C. LONGUET-HIGGINS: I have two observations to make. First, an observation on the proposal of Dr. Mendelsohn. He must be thinking of the Faraday effect, because he referred to the rotation of the plane of polarization of light by a magnetic field. This is all very well for radio waves passing through the ionosphere, where you have free electrons with a large mean free path. But for light the effect is quite negligible, and very difficult even to detect. One must then suppose that the earth's magnetic field produces a variation, in the plane of polarization of the light from the sky, of several degrees, because the error that the animals seem to make is of the order of 5 or 10 degrees. This is what your hypothesis seems to imply; but quite possibly I have misunderstood your original suggestion. That is my first point.

The second point is quite different; it concerns the speculations raised by the question which you brought up, Mr. Halberg. I have been trying to think of a reason why it is, apparently, easier to slow down a biological rhythm than to speed it up. These rhythms must arise from metabolic processes, and one may imagine that some of these processes take place with the maximum possible speed, if one thinks of the processes which have been described to us by Dr. Thomas of Denmark. If they do indeed go at maximum speed, it will be very difficult to hurry the rhythm of the overall cycle. One may take as an analogy a person playing a scale on the piano as fast as he can; it will be easy for him to slow down, but quite impossible to go faster.

F. HALBERG: There are examples of a different "polarity" of the circadian system. For instance, Dr. Aschoff found in certain birds that an advance of circadian

rhythms occurred faster than a delay [1]. He obtained similar results even in a human being studied in his bunker for possible differences in shift time following advances and delays of schedule [2]. Nonetheless, in our hands a number of human subjects studied after intercontinental flights, and rats, undergo much faster delays of their circadian rhythms investigated thus far, as compared to advances. All I am trying to say is that too broad a generalization may be premature. Furthermore, a number of rhythms have been found to be accelerated in disease. Thus, in human cancer we encounter what might be interpreted as a clear acceleration revealed by variance spectra [3].

This "speeding up" comes to the fore if one takes serial biopsies every two hours from human cancers and analyzes these data thereafter by variance spectra, as was done for the research by Dr. Tähti and Dr. Voutilainen of Finland. From such analyses it becomes apparent that in a number of human cancers a circadian component may no longer be demonstrable. The so-called "ultradian" component predominates, indicating that indeed one can "accelerate" the rate of one cycle in 24 hours; one may do so of course by "napping" as well. Nonetheless, from studies carried out in the isolation of caves on mature healthy men, one might be tempted to agree with the suggestion that we are indeed running with maximal frequency, if we keep in mind that under such conditions sleep-wakefulness at least on occasion changes from a primarily circadian phenomenon to a prominently infradian one. Some such isolated subjects sleep once in 48 hours rather than once in 24 hours, but many more individuals will have to be studied for more variables and under additional conditions before the most interesting polarity commented upon by Dr. Longuet-Higgins can properly be discussed.

Nous sommes de tels poltrons que nous n'osons pas mettre de côté les données sûres que nous avons pour nous lancer un peu dans l'inconnu, mais je suis d'accord avec vous: il est très probable que les opinions de M. Longuet-Higgins sont une bonne hypothèse à l'état actuel des informations.

Par les travaux français de M. Michel Siffre avec Alain Reinberg et Jean Ghata et aussi par les études de John Mills en Grande-Bretagne, on peut démontrer, au moins pour l'état de veille et de sommeil—ce qui n'est pas un bon index pour le métabolisme que dans ces conditions on trouve dans quelques sujets une transposition, au moins partielle, de la variance de la région spectrale circadienne avec des cycles d'environ 24 heures (± 4 h) à la région spectrale infradienne (notamment, des fréquences d'environ un cycle en 48 heures).

Ceci s'aligne très bien sur votre proposition: que la veille/sommeil sinon le métabolisme représente un oscillateur qui fonctionne à l'état maximum. Mais comme nous l'avons discuté en haut, pour le cas des cancers humains, on peut trouver un déplacement de fréquence dans la direction opposée, notamment une accélération très claire, révélée par des spectres de variance [3]. Donc, en jugeant sur le cancer, nous constatons que nous pouvons "accélérer", dans une notable proportion, par rapport au rythme d'un cycle en 24 heures.

Ceci nous ramène à des questions de base, qui ont à faire avec l'activité cellulaire comme aussi avec l'organisme global. On trouve donc à tous les niveaux de l'organisme une structure temporelle dont les composantes pourraient être dans une relation des harmoniques—dans le sens physique plutôt que musical. Ainsi on peut élaborer sur les idées originales de M. Fessard en ce qui concerne la spontanéité des rythmes.

- [1] J. Aschoff, R. Wever, Resynchronisation der Tagesperiodik von Vögeln nach Phasensprung des Zeitgebers, *Z. Vergleich. Physiol.* **46** (1963) 321.
- [2] J. Aschoff, Adaptive cycles: their significance for defining environmental hazards, *Int. J. Biometeorology* **11** (1967) 255.
- [3] M. Garcia Sainz and F. Halberg, Mitotic rhythms in human cancer, reevaluated by electronic computer programs—evidence for temporal pathology, *J. Nat. Cancer Inst.* **37** (1966) 279.

L. TISZA: I would like to ask Dr. Lindauer how long does it take for bees transferred from the Northern hemisphere to the Southern hemisphere to readjust their north sense orientation? Do you know something about it?

M. LINDAUER: After the translocation experiment we have tested the bees every second week. Only after the 40th day they had readjusted their orientation to the new situation. The result is different however if we let hatch bees in an incubator and then raise them without sun (the bee colony is put in a cellarroom by artificial illumination). After 4 weeks I took the bees out of the cellar into the field. They were unable to use the sun as compass, they used it on the first 3 days just as it would be a fixed light point on the sky. After the 5th day however (the bees had absolved 500 collecting flights for a goal in 200 m distance) all collectors had *learned*, how fast and in what direction the sun moves across the sky. They had changed from the simple "angle orientation" to the true "compass orientation".

K. MENDELSSOHN: Since we now seem to have a little time left, allow me to reply shortly to Dr. Longuet-Higgins. I have no wish to be dogmatic about my suggestion that the magnetic rotation of the axis of polarization is the operative mechanism occurring in the bee. It only occurred to me that it may be a possible explanation. Of course, the effect is a small one but the relationship involved is not necessarily a linear one. There are cases where a small external field can, in a suitable substance, affect the direction of a very much larger internal field. This means that the field registered in the sensing mechanism could be of the order of a kilogauss rather than one gauss.

F. HALBERG: Si j'ai bien compris votre question, M. Lindauer (nous en avons parlé en aparté): vous avez un renforcement temporel de la mise en condition. Donc, le comportement dépend de la structure temps comme étant un certain

nombre des programmes et engrammes de M. Fessard. Pendant très longtemps, la structure temps a été considérée comme étant imprimée par l'extérieur et persistant de l'intérieur. Les études et les données dont on dispose maintenant, au niveau cellulaire, à celui des processus inter-cellulaires, ou même au niveau du comportement de l'organisme global, nous permettraient de supposer que certaines "fréquences" existent dans l'organisme dès la naissance.

Tout comme l'enfant humain, sur auto-demande, aura un déplacement ultradien vers circadien en fonction de son âge pour l'alternance veille-sommeil, les abeilles ont peut-être également un rythme circadien. Il sera bien important d'étudier les abeilles en libre cours. Peut-être est-il possible de mesurer le bruit dans une ruche comme une fonction de temps? Cette mesure paraît simple, mais peut-être est elle compliquée par la possibilité qu'un nombre indéterminé d'abeilles n'est pas synchronisé avec la population entière étudiée. Naturellement il serait bien préférable d'étudier une fonction de l'abeille elle-même, laquelle peut être évaluée par une analyse longitudinale, individuelle. Ceci permettrait de savoir si une mise en condition quelconque—pour la menthe, dont vous avez parlé—est un réflexe conditionné, qui est superposé à une formation temporelle circadienne de base de l'abeille.

Tout ceci se rapproche de la théorie de M. Fessard: il y a un programme, le programme s'écoule. A tel ou tel moment, l'organisme est exposé à une stimulation; il commence à apprendre et ce qu'il va apprendre dépend aussi de sa phase au moment de la stimulation. Puis, ce qu'on a appris doit être reproduit; il faut consulter cette information avant d'agir—comme déterminant d'une action orientée de l'organisme. Les tâches de tenir en réserve ("storage") et de reproduire ("retrieval") l'information sont probablement, au moins en partie, une fonction du système circadien.

The interesting studies described by Dr. Lindauer reemphasize a discussion of long standing as to the extent to which rhythms relate to learning and vice versa (the extent to which learning depends upon an organism's time structure). Some features of a rhythm's synchronization have indeed been compared to conditioned reflexes. Thus Maizelis [1] described as a "cause" of spontaneous changes in motor activity the formation of positive condition reflexes to the time and environment in which muscular work was performed. Few will question the suggestion that conditioning contributes to our time structure, consisting of a number of programs and engrams as discussed by Dr. Fessard. Our "memory traces" when they are being registered also may well be timecoded. This circumstance should not lead one to presume that conditioning usually brings about the rhythm at the outset; instead, the rhythm may well be innate and a determinant of conditioning. Several lines of evidence demonstrate indeed that conditioning can be determined by the stage of a circadian rhythm in which the conditioning procedure is applied—the work of Charles Stroebel at the Institute of Living in New Haven, Connecticut being a case in point [2]. Dr. E. Bünning in Tübingen

had once reported that a disturbance at a certain stage of the rhythm, I believe in leaf movement, might reappear in a fashion similar to a "memory trace" on subsequent days with a predictable timing.

To turn back to Dr. Lindauer's most interesting observation, the time may be ripe to study a relatively easily measured yet pertinent variable, the noise of a bee hive or, to avoid confounding from at least a partial lack of inter-bee synchronization, preferably some function that can be measured longitudinally on individual bees, under as constant conditions as possible. If, then, from such work a period desynchronized from both a 24-h solar and a 24.8-h lunar day could be found and the experiment with peppermint and honey described by Dr. Lindauer could then be repeated, one might have at least some tentative information toward the question whether the conditioning described by him represents simply a conditioned reflex or some kind of reinforcement of training, or whether there is indeed a "program" preexisting for the timed conditioning of such stimuli within the organism as suggested at this meeting by Dr. Fessard.

- [1] M. R. Maizellis, Time and Conditions of Performance of Muscular Work as Factors of Organization of Diurnal Periodicity, *Bull. Exp. Biol. Med.* **45** (1958) 526.
- [2] C. Stroebel, Behavioral aspects of circadian rhythms, *Comp. Psychopathology* (1967) 158.

P. O. LÖWDIN: There is one rhythmic phenomenon which I think is very intriguing. It's the phenomenon of sleep. Do you care to comment?

F. HALBERG: One of the interesting features of sleep is its multiple frequency structure. At the moment a good deal of work revolves around what is called „fast" sleep or REM (rapid eye movement) sleep. The seven or eight hours of behavioral sleep (diagnosed on the basis of relative quiescence with our eyes closed) are modulated by rhythms of say ~ 1.7 hours in a number of functions and perhaps in association with dreaming. It seems pertinent that in this day and age, molecular biology has already aimed at elucidating relations between dreams and molecules, at a symposium held recently at the Massachusetts Institute of Technology. Ultradian frequencies of human sleep become behaviorally overt by day as well as by night in patients with narcolepsy, a problem so rigorously studied by Pierre Passouant of Montpellier.

At the other extreme of the frequency components of spontaneous sleep one finds in some cases of human isolation the infradian component with one cycle in about 48 hours. What seems to be most important with respect to Dr. Löwdin's question may well be the recognition that whereas in human isolation sleep may change from a circadian to an infradian frequency, the adrenal cortical cycle may maintain a primary circadian rhythm. Thus the contention by many classical physiologists that most, if not all, bodily changes along the 24-hour scale are determined by sleep can be ruled out by results from studies by Michel Siffre

et al. covering several months and allowing the "self-selection" of a different frequency for sleep than for the adrenal cortical cycle [1].

This is not to say, however, that the time relations between these two functions are random. Temporal integration indeed can be achieved on more than one frequency, and such integration is particularly favored by the circumstance that the frequency of sleep-wakefulness "demultiplies" to one-half that of the adrenal cycle—as noted by us in the study on a human subject isolated for several months.

Pendant le sommeil l'enregistrement des mouvements de l'œil, l'électromyogramme, le pouls et la respiration complètent les études électroencéphalographique du sommeil rapide et il y a déjà des méthodes puissantes pour analyser de telles données si on fait l'enregistrement directement sur bande magnétique [2, 3]. Il sera très intéressant d'enregistrer chez les sujets ambulatoires et sains quelques unes de ces variables pour voir les équivalents d'un composant ultradien pendant la veille aussi bien que pendant le sommeil.

- [1] M. Siffre, A. Reinberg, F. Halberg, J. Ghata, G. Perdriel and R. Slind, L'isolement souterrain prolongé, Etude de deux sujets adultes sains avant, pendant et après cet isolement, *Presse Med.* 74 (1966) 915.
- [2] D. F. Kripke, C. Clark and J. A. Merrit, A system for automated sleep analyses and physiological data reduction, Document ARL-TR-68-12, August, 1968.
- [3] N. Cartwright, D. F. Kripke and P. Cook, Statistical reduction of handstaged sleep analysis. Document ARL-TR-68-5, June, 1968.

G. CARERI: If there exists a periodicity in sleep, then suppose an organism take a sleep out the periodicity. Is there any phenomenon you could detect in this siesta which is different from the phenomenon observing in sleep, because you break the periodicity?

F. HALBERG: Rather than necessarily "breaking" a circadian periodicity by taking a "siesta" one may simply accentuate and/or prolong a physiologic phase of a presumably innate ultradian rhythm (with a frequency much higher than circadian). The ultradian rhythm can be gauged by the telemetered intraperitoneal temperature, among other functions.

Si vous chronométrez la température intra-péritonéale par un détecteur physiologique placé dans l'abdomen d'un rat, et même si l'animal se trouve dans une ambiance sous contrôle aussi absolu que possible (parce que la température d'ambiance est contrôlée ($\pm .5^\circ\text{C}$) et les bruits, dans la mesure du possible—on ne peut pas toujours faire les choses parfaitement!) vous trouvez des changements en température corporelle qui couvrent en quelques heures une différence aussi grande que 2°C que nous ne pouvons absolument pas expliquer dans le sens d'une "réponse" à des facteurs connus. Ce sont des changements ultradiens.

Voici donc un rythme circadien avec une modulation par l'élément ultradien. Et vous arrivez à ceci: la sieste est peut être simplement l'expression du rythme

ultradien "approfondi". On trouve des rythmes, ou pararythmes, ultradiens avec des fréquences peu définies qu'on peut démontrer par des spectres de variances aussi dans la concentration du sang en hormones corticostéroïdes, même dans l'effluent de la surrénale cannulée [1]! Je ne sais donc pas ce que la sieste fait à notre physiologie, mais nous faisons beaucoup plus de siestes que vous ne le pensez.

Concerning uncertainties in experimentation, one would have to do so from both theoretical and practical viewpoints. Dr. Fessard's thoughts on the role played by a transducer between stimulus and response included reference to an observer-effect upon the phenomenon being observed, i.e., reference to the equivalent of a biologic uncertainty relation to be considered in the context of Heisenberg's thoughts [2]. In rhythmometry there are in addition many practical points to be considered, including the effect of the interval between consecutive samples upon data analysis on the one hand and upon the subject himself on the other hand. In this connection it is indeed a considerable step forward to dispose of electronic computer programs allowing the analysis of data obtained at unequal intervals whereby certain kinds of interval artifacts are prevented and, what is no less important, the human subject is allowed undisturbed sleep [3]. The only condition for such analyses at unequal intervals is that the density of the data during most of the span be not too drastically different. Of course, for certain tasks other than performance tests, continuous physiologic monitoring—eventually from birth to death—may well be feasible by transducers that, thanks to NASA, already are within the "state of the art".

By achieving such goals, we could obtain for any physical examination at any time of our choice information on the preceding 60 or 80 (or more) circadian cycles in a given monitored variable of interest—body temperature, heart rate or other. Such a desideratum is no more than what we require for the evaluation of high frequency rhythms in current medical practice. More specifically we evaluate heart rates on the basis of 60 or more cardiac cycles. Thus, it seems only fair to require more than a single sample spotcheck and, in some cases, data covering more than a single cardiac cycle, for an assessment of a circadian modulation of the heart rate. However because such monitoring of heart rates and of other pertinent functions such as blood pressure is currently still expensive the student of rhythms will have to demonstrate that such information on certain rhythms with medial or low frequency is worth collecting.

- [1] J. H. Galicich, E. Haus, F. Halberg and L. A. French, Variance spectra of corticosteroid in adrenal venous effluent of anesthetized dogs, *Ann. N.Y. Acad. Sci.* **117** (1964) 281.
- [2] F. Halberg, Chapter on "Medizin" in *Jahrbuch der Internationalen Hochschulwochen des Oesterreichischen College*, (Igonta Verlag, Salzburg, 1946) 336–351.
- [3] F. Halberg, M. Engeli, C. Hamburger and D. Hillman, Spectral resolution of low-frequency, small-amplitude rhythms in excreted ketosteroid; probable androgen-induced circaseptan desynchronization, *Acta Endocrinologica Suppl.* **103** (1965).

B. B. LLOYD: I have a friend who does experiments on himself from time to time. He was measuring his body temperature day and night about twenty years ago. In the course of one day he was sitting by the gas fire, a primitive sort of heating still used in England, at 6 o'clock in the evening until he sweated profusely. The next evening at 6 o'clock, not sitting by the gas fire, he found that his body temperature went down. I would regard this as an example of a memory and of an anticipation in a homeostasis.

One more point. I think you do see Cheyne-Stokes breathing in a dog if you lengthen the path between the lungs and the carotid body, and fiddle the gaseous atmosphere—a feedback loop showing oscillation rather than being critically damped.

F. HALBERG: Dr. Lloyd considers a feed-back loop in relation to Cheyne-Stokes breathing—indeed in one of the several interesting rhythms of the respiratory system. In discussing such feed-back models for high frequency rhythms, one does not as a rule encounter the dangers and limitations so characteristic of feed-back considerations in the domain of rhythms with medial and low frequencies. The following remarks will be restricted to physiologic phenomena in the latter domain—adrenal physiology, cortical as well as medullary, being a case in point. Much work is being done, in the adrenocortical field in particular, without identifying the stage in which a given “feed-back study” is carried out—despite the demonstration of, for instance, a reproducible circadian rhythm with a large amplitude in adrenocortical reactivity to ACTH, *in vitro* as well as *in vivo*. Also ignored is the added feature that *in vivo*, in the C-mouse, adrenal reactivity to relatively unspecific stimuli such as saline also is circadian rhythmic and that furthermore such rhythms in the reactivity of the adrenal cortex to saline solution on the one hand and to ACTH on the other hand are out of phase with each other. Equally pertinent rhythms in pituitary ACTH content and in the corticotropin releasing factor, CRF, of the hypothalamus also are usually ignored, with the mistaken tacit assumption that whatever one does in terms of a “feed-back study” at one time will be reproduced at any other time. Today, successes in electronics have attracted biologists to an often uncritical transfer of comments out of context, i.e., to an application of control system theory to “biologicals”, just as if they were fully inert materials. Thus we repeat the mistakes of a few centuries ago. For instance, so great were Newton's successes and his consequent influence that so distinguished a physiologist as Borelli was prompted to a mechanistic thinking that apparently led him to explain all of digestion by mechanical friction.

The foregoing comments are directed not against a consideration of control mechanisms in physiologic work but rather against the prevailing custom of ignoring rhythms while one does so, whereby mistaken conclusions may be drawn concerning controls. Feed-back considerations then are a useful “scaffold”

for physiologists and should prompt him to evaluate rhythms more rigorously and quantitatively and to search for the underlying factors, rather than misusing them as legitimate excuses for studying rhythmic variables without any consideration for time structure.

L. ROSENFELD: I am not sure that I understand your standpoint. It seems to me that scaffolding, as you call it, is not an obstacle to building a house, but on the contrary helps to do it.

F. HALBERG: We need a scaffolding. However, we must not mistake the scaffolding for the house and move into or onto it. For instance, homeostasis has been a scaffolding for some, and unqualified feedbacks or "stress reactions" were a scaffolding for others. I have used feedback models [1] myself but only as a transition to the specification of physiologic phenomena as they relate to chemical compounds in anatomical locations. A simple black box approach ignoring all anatomical, physiological and biochemical rhythms has unfortunately led to the practice of assessing presumed stress reactions or feedbacks at some single time point convenient only to the experimenter. This approach ignores results such as those indicating a rhythmic change as drastic as the difference between death and survival occurring in response to the identical agent and as a function solely of timing [2]. Such results on the hours of changing resistance dramatize the need to, first and foremost, control the stage of a rhythm in work on an organism's frequency structure and, second, use endpoints from rhythmometry as gauges of physiologic "responses".

Pertinent in this connection are not only studies on rodents [2, 3] but also the important French studies of Alain Reinberg on men [4].

- [1] F. Halberg, E. Halberg, C. P. Barnum and J. J. Bittner, Physiologic 24-hour periodicity in human beings and mice, the lighting regimen and daily routine, in *Photoperiodism and Related Phenomena in Plants and Animals*, Ed. Robert B. Withrow, Ed. Publ. No. 55 of Amer. Assoc. Adv. Sci. Washington (1959) 803-878.
- [2] F. Halberg, Organisms as circadian systems; temporal analysis of their physiologic and pathologic responses, including injury and death, in: Walter Reed Army Institute of Research Symposium, Medical Aspects of Stress in the Military Climate, April, 1964, 1-36.
- [3] L. E. Scheving, Circadian rhythms in susceptibility of rodents to nicotine and amphetamine, AAAS, Washington, Resume in *J. Amer. Med. Assn.* **199** (1967) 33.
- [4] A. Reinberg, The hours of changing responsiveness and susceptibility. *Pers. Biol. Med.* **11** (1967) 111.

H. C. LONGUET-HIGGINS: I cannot see, speaking as an outsider, that there is anything inconsistent between thinking that it is good to investigate the cyclic phenomena in the cell, or in the body, or in the organism, and thinking that it is also good to investigate the non-cyclic processes. Living things are very complicated; one must pay attention to many different things. To stress the value of

your own studies is not necessarily to imply that other sorts of studies are not also valuable.

F. HALBERG: Dr. Longuet-Higgins emphasizes of course that there are many approaches to any one biologic problem. Let me hasten to agree and apologize if I gave the impression that rhythmometry is a panacea for any and all problems. Nonetheless, it is difficult to accept "homeostatic" work on rhythmic variables when, as is customary, the identification of the stage of a rhythm in the variable used for sampling is altogether ignored. Knowledge of the stage of the circadian rhythm may be as desirable for a variable such as corticosteroid as is the statement on whether a blood pressure measurement is systolic or diastolic. Our interpretation of a blood pressure determination of, say, 100 mm Hg will be drastically different as a function of whether it is diastolic or systolic; accordingly one may distinguish a hypertensive patient from a hypotensive subject. Quite clearly the Reverend Stephen Hale must have been aware of the difference between diastole and systole when he measured blood pressure directly by attaching a glass tube to the artery of a horse and observing how a column of blood rose and fell with the heartbeat. According to Dr. Leonard Wilson, Borelli had already discussed the change in pressure occurring with each contraction of the heart and had reported that with the systole the aorta stretched and subsequently relaxed. Circadian changes in serum corticosteroid or liver glycogen are no less drastic. Furthermore, the research work on yeast by Kendall Pye and Britton Chance, who regretfully could not be present, shows "ultra-ultradian" trains of oscillations with relatively very little damping once trehalose, a carbohydrate, is added to the medium. [1]

Thus, many aspects of metabolism are rhythmic and yet biochemical journals continue to publish papers by molecular biologists, endocrinologists and others, who ignore any and all periodicity in variables previously shown to undergo large amplitude rhythms amenable to rigorous standardization (e.g., murine liver glycogen). However to remedy this situation is hardly the major task for students of rhythm. Many of us are lead to study a given rhythm because we encounter it as a source of variation that must be controlled, yet in my opinion the primary tasks of the chronobiologist *in statu nascendi* lie on an entirely different plane.

We can raise new questions as to body function in health and disease—whether our interest relates to 1) transmeridian dyschronism after an intercontinental flight, to 2) the hygiene of shift workers, to 3) the failure of rhythmic integration in a psychotic patient, or to 4) the rhythm alteration found in a cancer patient. Such rhythm alterations could constitute determinants of a performance decrement, a resistance deficit or of an actual disease process. If indeed rhythms should prove to play an important role in such processes, sound biophysical theory for the ubiquitous and nontrivial spectral structure of organisms will become yet more desirable. Meetings such as the present one may contribute

to better human performance and health by fostering such theoretical developments—that can be anticipated from the interaction between physicists and biologists and that can hardly fail to have eventual applied value.

[1] K. Pye and B. Chance: Sustained sinusoidal oscillations of reduced pyridine nucleotide in a cell-free extract of *Saccharomyces carlsbergensis*, *Proc. Nat. Acad. Sci.* **55** (1966) 888.

A. REINBERG: Dans son analyse, portant sur les phénomènes rythmiques des nerfs et des muscles, M. Fessard a dit que l'activité rythmique apparaît comme une des propriétés fondamentales de la matière vivante. Nos connaissances actuelles permettent de généraliser cette notion à tous les systèmes vivants. Il apparaît en effet que des processus rythmiques peuvent être mis en évidence à tous les niveaux d'organisation:

- 1) des organismes uni-cellulaires jusqu'à l'homme y compris,
- 2) à tous les niveaux d'organisation chez un être vivant, l'homme par exemple ou les mammifères supérieurs. Qu'il s'agisse de fonctions globales physiologiques ou biologiques, de groupe d'organes, de tissus, de cellules et même de fonctions sub-cellulaires, l'existence de rythmes a été prouvée objectivement. Par exemple: rythmes de l'incorporation du P^{32} dans le D.N.A. et le R.N.A. des cellules de divers tissus.

- 3) l'analyse objective de ces rythmes, réalisée suivant des processus de calculs électroniques mis au point par M. Halberg et ses collaborateurs de l'Université du Minnesota, permet de donner une estimation des différents paramètres et de caractériser ces variations périodiques. Il s'agit en particulier de la période ou de la fréquence des phénomènes, de leur amplitude et de leur relation de phase. C'est ainsi que, pour une même fonction physiologique (le rythme cardiaque, l'excrétion urinaire des 17 cétostéroïdes, la température par exemple), des analyses spectrales ont pu être réalisées permettant d'estimer les différentes périodes suivant lesquelles chacune de ces fonctions peut se manifester. L'étude des rythmes biologiques introduit donc une nouvelle dimension dans l'analyse des phénomènes vivants: le temps. Les résultats acquis permettent déjà de discuter les phénomènes sous leur aspect chrono-biologique et chrono-physiologique. Ces recherches ouvrent de nouveaux chapitres qui sont: la chronopharmacologie, la chronopathologie et la chronothérapie.

Journée du 30 juin 1967

DISCUSSIONS GENERALES ET CONCLUSIONS

3ème séance

PRÉSIDENT A. LICHNEROWICZ

A. LICHNEROWICZ: Nous sommes au commencement d'une séance importante, parce qu'elle est la dernière. Je voudrais vous proposer de la partager en deux parties. Nous avons fait le cycle, la boucle si je puis dire. Des considérations théoriques générales nous ont amenés, à travers des phénomènes biologiques extrêmement intéressants pour nous tous, à de belles séances, comme celle de ce matin.

Un certain nombre de nos collègues, physiciens ou théoriciens, soit par les hasards de la discussion, soit par une trop grande discrétion naturelle, n'ont pas pris suffisamment la parole. J'aimerais donc que, dans une première partie, nous bouclions la boucle avec une espèce de retour théorique, en donnant la parole à un certain nombre d'entre vous, de manière aussi libre qu'ils le veulent.

Je souhaite entendre tous nos collègues, plus particulièrement le Pr. Onsager, que nous avons l'honneur d'avoir parmi nous.

GENERAL DISCUSSIONS AND CONCLUSIONS

L. ONSAGER: At a conference like this, few if any questions are answered. Rather, when biologists and physicists with varied experience in different fields come together, each can learn the lore and the problems of the others.

The clarification of pertinent theories and principles will help the biologists to organize and interpret their physical observations. Conversely, while we have cause to believe that biological systems obey the general laws of physics, they do present such unique situations that the proper adaptation of physical theories becomes a formidable task. This week the biologists have alone much to help us define the problems involved, and we shall need more such help in the future.

K. MENDELSSOHN: Listening to the biologists at this conference I was, like Dr. Onsager, most impressed by the progress which has been made in their field, particularly when we look at the almost fantastic success of the molecular biologists. One therefore wonders, as a physicist, whether and where we can make a useful contribution. We must remember that, unlike physics, biology is operating with concepts which are purposely designed to fit the study of the properties of life.

Probably what the physicists need is the formulation of one or more new concepts to deal with a subject which is so new to them. This will be a major task for the completion of which one cannot hope in the framework of a conference but perhaps — and this may be similar to what Dr. Onsager hopes — we may learn to ask the right sort of question. This in itself is extremely difficult.

What, for instance, is in the terms used by the physicist the salient feature of life? In private discussion with one of the eminent biologists at this conference I was told that: "Life has neither purpose nor meaning". This seems fair enough, except that physicists occasionally have the habit of referring to "meaningful" explanations and while they are unlikely to talk about the purpose of a physical system, they are forever interested in its future state. In early thermodynamics a forecast of the future state of the system was often arrived at by noting its "tendency" at the time of observation. Say, you have two containers connected by a tap, and one should be empty while the other is filled with air. As the tap is opened, the air flows into the empty container until the pressure in both containers is equal. This "tendency" was noted and led to the second law of thermodynamics well before the kinetic explanation of the phenomenon was provided.

As a physicist one may equally ask: "What is the tendency of life?" One of the answers is clearly that it tends to survive. It does so at very considerable odds against the random statistics usually employed by physicists or, as Thornton Wilder says in the title of his play, we live "by the skin of our teeth". How life

manages to survive is an intriguing question about which the biologists know a lot but, I suspect, that this is not one of the primary questions on tendencies.

Another clear tendency which we observe is that life develops. The biologists have amassed a great deal of information about the fact that life develops under the environmental constraint, part of which is, of course, provided by life itself. However, in the process of development the structures of life become increasingly complex. It is by no means clear whether this tendency towards complexity is a feature which is forced on life or whether it must be treated as a separate basic phenomenon. Possibly, in order to survive against each other, the various forms of life have to become more complex and then this tendency towards complexity would be a necessary corollary of survival, requiring no separate explanation.

Physicists, dealing with a world of random processes connect complexity by statistical treatment to improbability. According to this, life is extremely improbable. Thermodynamically speaking, a state of low probability is one of low entropy. However, this statement by itself is not very helpful since it seems unlikely to lead to a meaningful description of life. The statement of complexity may be insufficient if it turns out that only a certain type of complexity is capable of showing the phenomena of life. Earlier in this conference Dr. Bergmann used the term of "specificity" when discussing living structure and we must ask ourselves whether there exists a specificity principle without which life cannot be described.

Possibly, here the right question to ask might run as follows: "Can we arrive by random processes at many stable structures which each are as complex as the simplest structures of life?" If this were possible — and we don't know whether it is — then more is required than the high degree of complexity which we can possibly postulate without further basic assumptions beyond the tendency to survive. In this case we would have to specify a certain type of complexity which is distinguished from other equally complex structures by the fact that it confers the property of life on only one of them. This is a question which, even at this stage, can perhaps be decided.

The great complexity of life in itself should not deter us — irrespective of whether or not a specificity principle is required. One somehow would suspect that complexity, too, and even specific complexity might be described and handled by simple methods. As Plato already suspected, God is a mathematician, a fact that has now been borne out by two millenia of observation. However, one can probably go further and suspect that God is a simple mathematician in his grand design and that it should be capable of simple solution. Somehow it seems that he tends to leave the complex solutions to his research students, the archangels, but that these complex solutions are not needed for comprehending the basic principles of the creation.

Physics is full of examples of this kind. Going back to the behaviour of a gas, the motion of its individual molecules, changing direction and speed after each collision, presents an aspect of formidable complexity. The solution of the New-

tonian equations of motion for even only 10 or 20 molecules becomes quite hopeless. Nevertheless, a simple solution exists which has become the stock in trade of any first year student. All that was required, was to look at averages rather than at individual events and borrowing the mathematical methods developed for the problems of state craft.

We therefore have no reason to assume that because of their complexity the phenomena of life must resist solution by simple methods. That so far we have failed to find the right method is no argument to the contrary. In fact, we have hardly tried. Admittedly the assumption that the basic features of the physical world are revealed to our mind in a form which we regard as "simple" is an article of faith which can never be proved. On the other hand, all our scientific endeavours are, in any case, based on another article of faith, i.e. that of an integral creation. I am sure that somewhere the correct approach, leading to a simple treatment of the problems of life, lies already hidden in our minds. To find it must be our main task.

M. MATTHIAS: Just one very short remark to my friend Mendelssohn. We had that discussion three years ago in Colgate when I tried to tell him that in order to understand, we have to believe because the other way round, it's a hopeless affair. In my opinion, today, if a theoretical physicist talks to a biologist what he really needs is an interpreter. The interpreter should be the experimental physicist... I will really refrain from saying anything more but one thing.

I was baffled at the discussion about memory and computers and their connections, and the classic assumption that this must go one way or the other as a flip-flop mechanism like in a computer. If you consider that most of us cannot function with the speed of life, it's baffling to assume that a memory or anything that we perceive should go like an electric computer with the speed of light. Completely apart from the fact that the access to a computer of that kind would be experimentally a very difficult problem, I was amazed that nobody seems to object to the fact that it may be unrealistic to use these entirely physico-technical gadgets to treat something as complicated as a biological problem.

L. ROSENFELD: I am tempted to contradict the last objection, simply because it is very difficult to speak in general terms without defining exactly what one means by such things as "complexity", for instance. One of the aims of science at any rate is just to make it possible for us to cope with complex situations by creating a sort of shorthand symbolism which helps us to characterize them. In investigating biological phenomena, there is a challenge for us to find such simple schemes which may help us to orient ourselves in their complexity, and, to begin with, to classify the various orders of organization that we encounter in biology.

So I am more optimistic than you.

**REMARK ON THE PARAMETRIZATION
OF THE STATES OF COMPLEX SYSTEMS**

IRVING SEGAL

M.I.T., Boston, Massachusetts, U.S.A.

1. Introductory

While the mathematical approach appears to have a great deal to offer towards the solution of some of the problems discussed in this conference, both technically and in spirit, there are visible few places in the interface between theoretical physics and biology where the more sophisticated, contemporary type of mathematics appears effectively applicable at this time. Certainly non-linear partial differential equations should be applicable to transport and other relevant phenomena, but specific results seem unlikely to become accessible until some simple empirical laws have been attained concerning the fundamental interactions. Digital computer models are also qualitatively quite appealing, but suffer from similar limitations.

These limitations may be illustrated by a simple qualitative model for a phenomenon on which Professor Fröhlich remarked extensively, the self-limiting nature of the growth of a cell or other organism. Let us suppose that the state of the organism at a given time t can be represented by the Cauchy data for a second-order hyperbolic equation, admitting a positive definite temporal invariant; if at an early time the solution of the equation is small while its first temporal derivative is large, then at a late time, the solution is limited in size by the conservation law and can attain its maximum only when its temporal derivative vanishes. These considerations are exemplified by the equations of the form

$$(*) \quad \square \phi = m^2 \phi + g \phi^p \quad (g > 0, p = \text{odd integer}),$$

in which case it has even been mathematically established that there is appropriate limiting behavior for the solutions as $t \rightarrow \pm \infty$, for general choices of m and p corresponding to a growth to maturity. But there is no empirical basis for any asymptotic equations parallel to the asymptotic equation

$$\square \phi = m^2 \phi$$

in the case of equation (*), still less for the crucial interaction term $g \phi^p$, in any biological situation known to us.

The fundamental difficulty in the mathematical treatment of complex systems such as biological ones is that there is no simple parametrization, a priori or otherwise, for their state spaces; and the experience with biological systems in recent decades has not been notably encouraging in this respect. Naturally, one can hardly begin to treat the foundations of the kinematics or dynamics of systems whose phenomenology is theoretically so complicated. My feeling is however

that there are mathematical possibilities in the direction of a simplified phenomenology which have been overlooked, perhaps because of their relative sophistication, and are worthy of investigation.

2. Phenomenological generalities

Proceeding conservatively, — as well as in line with interesting models which have been proposed, — we consider a quantum-mechanical biological system. Advances in theoretical phenomenology make it easy to cover all possibilities, including those based on classical mechanics, by the definition of a “system” as an abstract operator (Jordan) algebra, whose (hermitian) elements represent the observables of the system; states of the system are then determined by the expectation values $E(X)$ of the observables X in the state E in question, and it is postulated that E is a positive normalized linear functional on the algebra \mathcal{A} of all observables; this means that

$$E(aA + bB) = aE(A) + bE(B), \quad E(1) = 1, \quad E(A^2) \geq 0$$

for any observables A and B , and real numbers a and b . The state space of the system is then represented by a convex set Σ consisting of linear functionals on \mathcal{A} . The kinematics and dynamics of the system are given by groups or families of automorphisms of the algebra, in terms of which the concepts of stationary, equilibrium, and ground states may be defined and treated, in appropriate cases.

The problem of approximating to \mathcal{A} or Σ by systems of substantially lower dimension is amenable to a number of general considerations. One could give a precise mathematical definition for the best approximation Σ' of a given dimension to the state space Σ , based on considerations of minimization of deviations in expected values of observables and maximization of the degree of temporal invariance of Σ' . In practice, tactical considerations modify such strategic ones, which are nevertheless useful for avoiding or making explicit preconceived notions concerning the state space, and for suggesting alternatives to the conventional models. These matters may be illustrated by the problem of the parametrization of

3. Molecular states

The Schrödinger wave function provides an excellent description, so far as is known, of the state of a biologically interesting molecule, and its usefulness is too well known to require any elaboration. On the other hand, even for moderately simple molecules, the wave function is an enormously complex object, whose mathematical determination within a preassigned accuracy is just beginning to become practical. In addition, one commonly does not require all the information contained in the wave function, but is concerned with a number of summary (or “collective”) aspects. Especially in the case of larger molecules, some simple mathematical alternative to the Schrödinger wave function seems highly desirable.

Since the Schrödinger wave function is in any event an approximation to the theoretical state of a molecule, one need feel no great hesitation in exploring qualitatively rather different lines. While there seems presently no indication of a significant quantitative deviation of classical non-relativistic quantum mechanics from observations in the area of molecular physics which appears relevant to biological phenomena, there is no certainty that relativistic and quantum-field-theoretic effects may not later be found to play a rôle. The phenomenon of biological amplification over long periods of time, and the delicacy of the control mechanisms already discovered for insects, birds, etc., indicate that this possibility should be born in mind. There is a possible parallel with the introduction of the spin into non-relativistic quantum mechanics; although of marginal importance energetically, it was of great importance for the understanding of selection rules and the classification of the observed states. On the other hand, for a purely classical type of analysis the Schrödinger wave function is likewise not directly applicable.

Consider therefore the more directly phenomenological generating function for the state of the molecule, defined as follows. Let $\mathbf{P}_1, \mathbf{Q}_1; \mathbf{P}_2, \mathbf{Q}_2; \dots; \mathbf{P}_n, \mathbf{Q}_n$ denote the momentum and position vectors for the n particles of which the molecule is constituted; then the expectation value of

$$T = \exp \left\{ i \sum_{j=1}^n (\mathbf{u}_j \cdot \mathbf{P}_j + \mathbf{v}_j \cdot \mathbf{Q}_j) \right\},$$

as a function $F(\mathbf{u}_1, \dots, \mathbf{u}_n; \mathbf{v}_1, \dots, \mathbf{v}_n)$ of the arbitrary fixed vectors in question is this generating function, which has been considered in quantum mechanics by Wigner, Moyal, and many others. For a quantum-mechanical system in the state given by the Schrödinger wave function Ψ , the generating function $F = \langle \Psi, T\Psi \rangle$; it completely determines Ψ , within an irrelevant constant phase factor; it has the advantage of being closer to the physics than the Schrödinger function, and of being applicable to pure and mixed states, and to classical and quantum-mechanical systems, alike; it is however no easier to determine than the Schrödinger function and it has the disadvantage, that it is not easy to determine when a given function is the generating function of a state, and for this reason is not readily approximated by simpler generating functions.

A convenient mode of approximation may however be based on the following feature of generating functions. For simplicity, let us write simply z for the $6n$ -vector $\mathbf{u}_1, \mathbf{u}_2, \dots, \mathbf{v}_1, \mathbf{v}_2, \dots$. Then z is an element of a linear vector space, and the notion of a "positive definite" function of z is well-defined, for example as the Fourier transform of a positive mass distribution. We may now state the

Theorem: If $F(z)$ is the generating function of a state, and if $G(z)$ is any continuous positive definite function, then $F(z)G(z)$ is again the generating function of a state.

Now a particular type of positive definite function, as is well known, is one

of the form

$$G(z) = e^{if(z) - Q(z)},$$

where $f(z)$ is a linear function of z and $Q(z)$ is a positive definite quadratic form in z . On the other hand, the general second approximation to a given generating functional $F(z)$ can be put in the form

$$F'(z) = F(z) e^{if'(z) - Q'(z)}$$

for some linear and quadratic functions $f'(z)$ and $Q'(z)$, where however $Q'(z)$ is not necessarily positive definite. Experience in these matters indicates that the positive definiteness of Q' corresponds to the generating functional $F'(z)$ being at a higher level than $F(z)$. In other terms, the generating functional for two (or more) systems in interaction (with a positive interaction energy) should differ from the product of the respective generating functionals, to within second order, by a factor of the indicated type with a positive definite quadratic form; so that *this second approximation is again the generating functional of some state*.

Consider for example the case of two systems S_1 and S_2 which are spatially separated and in states represented by the generating functionals $F_1(z_1)$ and $F_2(z_2)$; suppose that they interact as they come closer, producing a compound system with generating functional $F(z_1, z_2)$. Now a generating functional transforms in a very simple way under euclidean spatial displacements, or more generally, under any linear inhomogeneous transformation in phase space which is canonical (i.e. preserves the fundamental commutation relations between the P 's and the Q 's; in mathematical terms, such a transformation is "symplectic"). An approximation to $F(z_1, z_2)$ which should give somewhat more than the geometrical disposition of the systems S_1 and S_2 within the compound system, corresponding to such a transformation, is then of the form

$$F^{(1)}(z_1, z_2) = F_1(T_1 z_1) F_2(T_2 z_2) e^{if_1(z_1) + if_2(z_2)},$$

where T_1 and T_2 are the linear transformations corresponding to the basic linear transformations in 3-dimensional configuration (or more generally, 6-dimensional phase) space, and f_1 and f_2 correspond to the vector displacements in these spaces. The next approximation to $F(z_1, z_2)$ is obtained by multiplication with $\exp\{-iQ(z_1, z_2)\}$, where Q is a positive definite quadratic form, chosen to minimize the energy variance as determined from the generating functional $F^{(1)}(z_1, z_2) \exp\{-iQ(z_1, z_2)\}$; this approximation $F^{(2)}(z_1, z_2)$ should give, hopefully, a good first-order account of bond strength, among other information. Any number of systems, such as the atomic constituents of a molecule, or monomers in a polymer, may be treated in the same way.

This should be a relatively simple approximation scheme to explore, either analytically or numerically. The number of free parameters is easily adjustable, according to the number of parameters on which the quadratic form Q is per-

mitted to depend, and on whether one goes beyond the usual displacements in configuration space to the admissible ones in phase space. Its main qualitative advantage is that the approximating generating functional is always the generating functional of some bona fide state; this means essentially that all probabilities computed through the use of the functional will be non-negative, and in the case of mutually exclusive compatible events will add up to unity as they should. Additional qualitative advantages are:

(1) Symmetry is never lost; the approximating generating functional can easily be made to be invariant or transform appropriately in the same fashion as the exact generating functional, under the compact or finite groups relevant to molecules;

(2) Additional information concerning the actual generating functional can be incorporated into the initial approximation, before correction by the exponential quadratic factor, providing a more accurate approximation;

(3) The generating functional is relatively convenient for Fourier analysis, computation of moments, and adaptation to higher approximations, such as may be obtained by replacing the exponential quadratic factor by the Fourier transform of a Gaussian function multiplied by a non-negative polynomial of given degree (the degree 0 corresponding to the case here discussed);

(4) The present approximation scheme provides a relatively uniform and consistent method and formalism, adaptable to a wide range of physical systems, including relativistic and quantum-field-theoretic ones. In particular, it is adaptable to the treatment of states which do not contain an exact number of particles; a special class of such states, introduced mathematically in 1960, has since been found useful for the study of optical coherence, and their fermion analogue, recently developed by Shale and Stinespring, may prove relevant to electron phenomena (including possibly that reported by Dr. Szent-Gyorgi).

On the other hand, it may well be that some difficulties may arise upon further investigation of the present scheme, or in its application to molecules of biological interest. Our purpose has been simply to attempt to start the ball rolling, so to speak, by giving a theoretical indication of the possible existence of interesting mathematical alternatives to the Schrödinger wave function for the approximate description of complex molecules. While the accuracy of the indicated description may be significantly less than that which is theoretically possible with the use of fully delocalized molecular orbitals, it should be practically attainable relatively conveniently, and may yet be sufficiently precise for some interesting quantum biological purposes. The mathematical questions which arise, — for example, that of the choice of the T 's, f 's, and of Q , for simultaneous minimization of $E(H^2) - E(H)^2$, with supplementary side conditions (where H represents the energy operator and E the expectation value functional corresponding to these choices), — should be well within the range of contemporary mathematical techniques.

S. L. SOBOLEV: Je ne suis pas d'accord sur le fait que les mathématiciens n'ont rien fait au niveau des conceptions et au niveau des cas techniques. Et je veux donner quelques exemples qui se rattachent aux problèmes biologiques.

Le premier exemple: qu'est-ce que l'organisme humain? ou, peut-être, l'organisme animal? C'est un automate, qui a un état, dans lequel il se trouve, et selon lequel il peut réagir d'une façon ou d'une autre sur chaque action qu'il extériorise. Il y a quelque chose qui n'est pas tellement pauvre dans la théorie des automates. Nous n'avons pas traité, dans ce colloque, de cette théorie. Car je doute, maintenant, que ce soient des résultats tellement développés qu'ils puissent être appliqués immédiatement à la biologie. Mais je ne doute pas pour autant que la technique et la théorie des automates, comme leurs concepts, soient inapplicables. Je suis sûr, cependant, que nous ne pouvons pas trouver la solution de nos problèmes dans cette théorie. Mais nous pouvons en tirer des choses très utiles pour le développement de la biologie.

Il y a aussi d'autres questions. Il y a un très intéressant paradoxe. D'un ordinateur pour "curatives" électroniques (je ne sais pas comment mieux dire en français), nous ne connaissons rien sur la façon dont il marche. Ce problème "devinez comment il marche" est beaucoup plus compliqué que de construire le nouvel automate, car la question surpasse mille fois et davantage toutes les possibilités de ce même automate, de ce même ordinateur. Ce que je dis est un théorème déjà bien démontré: c'est un fait dont il faut tenir compte.

Nous ne pouvons pas, maintenant, construire un automate qui fonctionne comme le cerveau humain, ou même comme le petit organisme de quelque microbe très primitif. C'est dire qu'il est très difficile de penser que nous puissions déchiffrer, maintenant, tout ce qui se fait dans la biologie. Mais nous avons déjà un très bel exemple au niveau de la physique classique, qui a créé la théorie des probabilités et la physique statistique, qui n'a rien de commun avec le mouvement des particules singulières et vous donne les méthodes pour décrire et résoudre tous les problèmes se rattachant aux grands ensembles. La position est beaucoup plus difficile, maintenant. Car ni la théorie des grands ensembles de la physique statistique, etc. . . ., ni la théorie des petits ensembles, qui contient seulement les opérations en nombres finis, ne sont applicables. L'une est trop générale, quoique pourvue de quelques propriétés très importantes, l'autre, trop pauvre, ne peut opérer avec tel nombre d'opérations qu'on peut effectuer par une calculatrice moderne. Il s'agit toujours de nombre d'opérations qui se perdent dans l'espace vu le nombre de molécules dont le globe terrestre est construit.

Alors, il faut espérer — j'espère: je suis très optimiste quand même, bien que j'aie émis quelques paradoxes sur ces théories — que le développement de quelques nouvelles branches de la mathématique: la théorie des automates, la logique mathématique, peut-être quelques nouvelles branches qui sont entre la logique mathématique, et l'analyse classique, et l'analyse fonctionnelle, qui sont déjà bien développées, bien qu'on ne puisse résoudre quelques problèmes difficiles —

j'espère, je crois que le développement de ces branches, encore insuffisamment en progrès, nous donnera enfin la possibilité de résoudre non pas sans doute tous les problèmes biologiques, mais ceux qui, d'entre eux, sont les plus importants.

G. CARERI: I would like to continue perhaps on the same way as Mendelssohn; I am also an experimental physicist. I find some difference between the way we see things and the way theoretical physicists do.

There is a question I will try to put; I am afraid nobody can answer. Is it true that what exists inside a living cell is a kind of organization which can also operate between many cells in an organ, and between many organs in the individual, and between many individuals in a society and so on? Then there is a common pattern perhaps. I agree with you Sobolev, the analytical way we should describe this pattern, this hierarchic order between subunits and units, is perhaps what is missing today. Hierarchy of interactions this is what we are looking for. This is what attract some physicists, which are used to think in this way, in low temperature and in solid state physics. That is essentially why I am here. I believe that in this search for things that happen inside a cell and that are similar to the major ones that happen even in a human society, we must be open minded, we must use also our private moral life, in the sense that we should learn something so general to be applied in all life that surrounds us. I do not expect everybody to agree with me, of course. I see here people who do not. But I would like to use a phrase by the painter Georges Braque: "I do not aim to convince you, all I want is to let you think about it".

Concerning the extreme improbability for existence of life that Mendelssohn was saying, let me quote that in Florence five hundred years ago, a committee of six people joined around a table. One was Michelangelo, the other was Leonardo da Vinci, and among others I remember Botticelli, Perugino, Filippo Lippi. Now how could these very improbable events happen? There is perhaps one possible reason: these people were very much influencing each other. Whenever life operates, we see strongly interacting members! And I think this is something that should be explored, and deeply, in all possible systems, from the cell to men and to the society.

W. M. ELSASSER: Ma remarque sera très courte. Je reviendrai de cette conférence avec une nouvelle conception. Tout le monde sait que l'organisme est une structure. Mais, de toutes les indications de M. Fessard et de M. Halberg, j'ai déduit ce que je savais déjà d'une façon générale mais pas du tout de façon précise: que l'organisme, ayant une structure quadridimensionnelle, ne peut être considéré comme une structure à trois dimensions. Si j'ai raison de généraliser les données de ces messieurs, c'est parce que nous savons que par exemple dans l'hydrodynamique, il y a une différence radicale entre les dimensions de l'espace, selon qu'on en ait deux ou trois. On peut prouver, d'une manière mathématique, qu'il

n'y a pas de turbulence dans un espace de deux dimensions. Mais tout le monde sait qu'il y a de la turbulence dans trois dimensions. De sorte que la différence entre une structure à trois dimensions et une structure à quatre dimensions pourrait bien être une chose fondamentale. C'est donc aux mathématiciens et à nous, les physiciens mathématiques, d'élaborer cette différence. Sans cela, l'on tirerait des conclusions, à partir des structures à trois dimensions, et l'on commettrait des erreurs qui sembleraient ridicules dans cinquante ans.

H. FRÖHLICH: Dr. Pullman in his talk has told us that there are two types of approach to this kind of physics. One was that of quantum chemistry whereby you specify detailed problems which he and others have been able to solve so nicely and to make very much progress. But there is also a physics concerned with general features. In the preceding discussions a number of people have come up to ask, are there some general principles? In other discussions some statements were made which one might call very vague. In physics, however, one speaks about general principles in a very exact way. Both Dr. Prigogine and I tried to do this in a certain way on the first day. I turned out when we met that we both had used overlapping concepts as if we had actually prepared our relative contribution—which was not the case. I think that many of the biologists and also of the physicists have not been really aware of what we have said because they were not all up to date in what has happened during the last five years.

What Prigogine said was something very general but nevertheless exact. Namely that big systems have an equilibrium state, and if we take it slightly out from this equilibrium state, they tend to fall back into it. This is on what physics had previously mainly been concentrated. He has found in a very general way without being specific that if we take such a system very far from equilibrium then another way of stabilisation can arise. But this is a stabilization which requires always a flux of energy through the system. That is what he thought resembles the state of some biological systems.

I have started with the concepts we are trying to derive in a more intuitive way. When I started I said to you that in my opinion biological systems are large systems, where a few degrees of behaviour are far from equilibrium and stabilized in a nearly stationary way. Now each big system consists of many atoms; the single atom does not see really a large size organization and it practically oscillates with very minute deviations as if it were in an equilibrium system. This is the reason for considering a few degrees of freedom.

Now I tried to link up this general concept with some developments that have taken place in recent years in physics. They start out from super-conductivity, superfluidity where we found that a few modes of motion have exceptional behaviour. But these are systems in equilibrium. Later it was found that in lasers for instance something occurs which is related to this macroscopic order of very subtle nature. It is closely connected with certain phase correlations and we found

that for instance lasers show this correlation as do superfluids and superconductors.

We had a discussion whether this was a classical or quantum concept. It is both! while it builds up it's quantal, but later on the quantal aspects are suppressed, I then tried to see whether biology seen in a naive way, offers such a possibility, namely, to excite few modes of a certain behaviour in a way in which it can be stabilized. Here I think arises a most striking possibility out of the phantastic dipolar properties of biological molecules. So I made an estimate, I introduced a concept that in physics is extremely well known though very little use is made of it namely that of longitudinal electric modes. I assumed, that they be strongly excited and asked whether they can be stabilized. The answer is that there is the possibility of stabilization if we introduce deformations of a general nature, and so go from the usual linear behaviour into the nonlinear region. Then we went down a step further and we found that the estimate I made of the frequencies are in the region which according to Careri may also be expected to obtain resonances of biological molecules.

Je veux donner une idée du raisonnement que suit le physicien. Nous nous éprouvons sur des principes établis et définis, et, à moment-là, nous fabriquons un modèle. Le modèle a été une invention, quelque chose qui présente une corrélation avec une réalité bien plus complexe. Et puis, nous essayons de traiter ce modèle, aussi exactement que possible. Puis, nous repassons à l'objet réel.

Je crois que les concepts de la physique quantique vont se vérifier dans la biologie. Il n'y a pas de doute. Mais alors il faut faire des modèles, pour étudier certaines suggestions expérimentales. J'ai la joie de pouvoir vous dire que quelques laboratoires vont s'attaquer à vérifier ces suggestions. Je voudrais terminer en disant quelques mots sur la nature générale de ces discussions.

D'une part, il y a un domaine de la physique qui s'attache au détail et qui se donne pour tâche d'élucider certains phénomènes explicites, qui ont été découverts (ce qui a été très long à étayer . . .). Il y a autre chose: il faut le courage de faire des prédictions, de faire quelque chose qui ne soit pas tout à fait orthodoxe. Il y a, par exemple, la superconductibilité, dont on a tant parlé ici, pendant de nombreuses heures. On a dit que c'était un système très obscur. Les gens ne le comprenaient pas très bien. Il y avait un principe sur lequel tout le monde était d'accord: inversant la tendance, on ouvrirait la voie au progrès; donc, il ne faut pas faire de prédictions en partant d'hypothèses, mais garder toute la précision nécessaire sur le plan mathématique; il faut respecter tous les principes généraux de la physique. Mais, ceci assuré, il ne faut pas hésiter à faire des prédictions, en demandant à l'expérimentateur de les vérifier, bien que les résultats ne viennent pas toujours confirmer les prédictions. Cela peut toujours être un moyen d'ouvrir la voie à des progrès. C'est ce que M. Prigogine et moi-même avons essayé de vous suggérer de faire, en vous proposant des façons nouvelles d'aborder ces problèmes.

Cela rejoint ce qu'a suggéré M. Mendelssohn et ce qu'a suggéré M. Careri. Mais il faut d'abord essayer de faire des prédictions et les étudier avec beaucoup de précision et de rigueur.

H. C. LONGUET-HIGGINS: I hope Dr. Fröhlich didn't take me to say that one should never make predictions. But there is a difference between predicting things that *might* happen and things that *should* happen. May I speak in a lighter vein for a minute or two?

The virtues of physics as a mental discipline are very great. So, at one time, were thought to be the virtues of a study of the Classics. The classical education opened all doors; one was enabled to think logically, and to distinguish between the good and the bad argument.

There is a story which dates from forty or so years ago, of a dinner party in Oxford. The wife of a distinguished classical scholar was introduced to her neighbour, and asked him "And what do you do?" He said "Madam, I am a physicist." The lady replied: "Oh, indeed. My husband says that anyone with a classical education can get up physics in a fortnight."

M. MARGENAU: Although I am grateful to be called upon for comments in this final session, I speak with a sense of embarrassment since I do not have sufficient knowledge in the field of biology to contribute positively to the solution of the problems that have been raised. I have found myself mainly on the receiving end during the exchange of information in our interesting discussions. But I shall make bold once more to speak briefly as a philosopher of science with basic concerns about the integration of physics and biology.

As I view past efforts at establishing union between disparate disciplines, I am impressed by the circumstance that such attempts have never succeeded in the plane of observational facts. The manifest phenomena in any given science are rarely similar to those in another and attempts at comparison and classification almost never provide common ground. Integrative qualities lie in the texture below the surface of facts, in the realm of principles and theories in terms of which the facts are explained. Only these theoretical roots, the axiomatic foundations of different disciplines are likely to unite them, and I am happy to observe that in most of the discussions during the last few days, basic theories like quantum mechanics and thermodynamics, not specific facts, have been called upon to provide a synthesis. The deeper you go into the theoretical bases of biology and physics, the better will be your prospect at unification. And here, perhaps, even the philosopher can play a role. For the deepest roots of all science are found within certain philosophical premises.

I shall not try to confirm or contradict any of the things some of my colleagues have said, even though I have been at times prompted to do so. If I were to level criticism it would be directed against the cocksureness I perceived in the attitude of some of the theoretical physicists at these meetings.

Interesting epistemological problems have been raised. I was especially impressed by the paper presented by Dr. Fessard who outlined for us one of the most basic problems of the theory of knowledge in very definite scientific terms. When he discussed the connection between the unobserved responses of a subject and the external stimuli that occasion them, when he spoke of the merely conscious modes of awareness of a subject in contradistinction to the observer's observation or knowledge of them. I drew from his comments the conclusion that you can not avoid facing the serious problem of the meaning and the role of consciousness in biological processes. Nothing has been said about it at these meetings; yet I think it ought to be in the minds of physicists who are interested in the problems of life. Specifically, I am raising the question as to the feasibility of the pretended union so long as the phenomenon of consciousness is neglected.

What I wish to say next may seem heretic and out of place. Practically all discussions this week have been based on the premise of mechanistic causation. I use this phrase in a rather general and generous sense, including the statistical form of causality that is peculiar to quantum mechanics. Perhaps it is an insult to this audience to inject the word teleology on this occasion. While I do not want to talk like an Aristotlian, referring to vague notions of purposiveness or to the even vaguer ideas of du Nouy who coined the phrase telefinality, I am anxious to propose something a little more specific and articulate. What I have in mind is the kind of teleology which inheres in the exclusion principle of Pauli. Let me explain. If physicists had limited their studies to the laws controlling the behavior of individual particles they would never have discovered the Pauli principle or its antithesis, the principle of symmetry for bosons. These principles of symmetry have no relevance to individual particles but become significant and coercive in the interplay between particles of the same kind. As is well known, they are sources of organization in the non-living world, providing explanations for all the so-called cooperative phenomena. The lesson I wish to draw is this. Just as the Pauli principle regulates occurrences involving many particles and could never have been discovered on the plane of individuals, it may well be that biological organization is tied to principles which can not be discovered within physics because they have no applicability to phenomena in the inorganic (perhaps I should say unconscious) world. What these principles are is difficult to predict, but I would guess that they are laws of invariance, laws of symmetry of a novel kind. However, in the sense which I have tried to outline in earlier remarks they must not be in conflict with the laws of physics, just as the Pauli principle is not in conflict with Schrödinger's equation.

Thus, I plead for open mindedness and for the maintenance of an expectation that the unravelling of problems in biological science may well expose principles of physics which the physicist, even the expert in quantum mechanics and statistical mechanics, could not derive from his present knowledge.

I am prompted to conclude with this memento. Let us not try to force physics

and biology together. The natural symbiosis of these two disciplines can not help but be fruitful. But if you take over ideas from physics too literally and install them in biology you may contract the same difficulties which confronted people who, some years ago, formed a group of eager disciples of a discipline called social physics. It took concepts like force, pressure, temperature, entropy and tried to formulate in terms of them a theory of social behavior. I believe this movement has failed because it did not recognize that concepts are not completely interchangeable between different disciplines. It would be most astounding to me if a science like biology would not ultimately have to develop concepts of its own, concepts with no counterparts in physics. On the other hand, this open-mindedness, this liberal expectation should never prevent us from staging the sort of fruitful intercourse which to me has made the present occasion unusually memorable.

R. KUBO: Since I have not spoken yet in this conference, I would like now to make a very brief remark from a physicist's point of view, although I doubt a little if I should talk after the last remark of Dr. Margenau.

The point I like to make is concerned with a general theorem about the relationship between response of a system to outside stimulus or disturbance. The concept of response to stimulus is very often talked about in physics and also in biology. Now, there is a well-established theorem [1] in statistical physics which has been proved extremely useful in recent years in analysis of many body problems, which are typically complex problems in modern theoretical physics. If the external stimulus is an external force F which is defined by the additional term, $-AF$, in the Hamiltonian (energy) of the system and if the response of the system is observed in a physical quantity B , the relationship between the stimulus and the response is represented by such an equation as

$$B(t) = \int_{-\infty}^t \varphi_{BA}(t-t') F(t') dt',$$

provided that the response is linear in the stimulus. Here $\varphi_{BA}(t-t')$ is the response at the time t to a preceding pulse stimulus at t' . It is a function of $t-t'$ if the system is in a stationary state. If the force is periodic, then the linear response is described by an admittance (susceptibility) which is defined by

$$\chi_{BA}(\omega) = \int_{-\infty}^{\infty} \varphi_{BA}(t) e^{-i\omega t} dt.$$

This is just a generalization of admittance function which is familiar in electric net work theories.

A general theorem now states that the response is very closely related to the fluctuation within the system in the absence of such external disturbances. This is the *fluctuation-dissipation* theorem. In fact, it is generally shown that the response

function $\varphi_{BA}(t)$ is given in terms of a correlation of two fluctuating quantities A and B at different time points; namely

$$\varphi_{BA}(t) = \langle A(t_0) B(t_0 + t) \rangle / kT,$$

where k is the Boltzmann constant and T the temperature and $\langle \rangle$ means a statistical average. This fluctuation-dissipation theorem is very fundamental in the non-equilibrium statistical mechanics. It should be emphasized particularly that the theorem should apply more generally to systems in stationary states, not necessarily in thermal equilibrium [2]. Then the response function should be determined by fluctuation in a stationary state of the observed system. This observation is important for biological applications of the fluctuation-dissipation theorem if such should be possible, since a biological system can be regarded stationary, though not in thermal equilibrium.

[1] R. Kubo, *J. Phys. Soc. Japan* **12** (1957) 570.

[2] R. Kubo, *Rep. on Progress in Physics* **24** Part I, 255 (1966); Tokyo Summer Lectures in Theoretical Physics 1965, Part I. Many-Body Theory, Ed. R. Kubo (Shokabo, Tokyo, and W. A. Benjamin, New York).

A. LICHNEROWICZ: Nous avons retouché, si j'ose dire, des choses relativement concrètes, bien qu'elles soient encore abstraites.

W. REICHARDT: In relation to Dr. Fessard's paper some remarks were made concerning the repetitive structure of retina units, neuronal units in the first optical ganglion (lamina) of the housefly *Musca* and the nervous projection of the retina onto the lamina. In this connection it was shown in our laboratory that the dioptics of the *Musca* ommatidium acts as an inverting lens system. The distal endings of the rhabdomers at the basis of the dioptic apparatus are separated and arranged in a typical asymmetric pattern. The optical axes of the individual rhabdomers of one ommatidium are the geometrical projection of the distal rhabdomer endings into the environment, inverted by 180° by the dioptic apparatus. The divergence angles between optical axes of the rhabdomers of one ommatidium correspond to divergence angles between the appropriate set of ommatidia in such a way, that seven rhabdomers of seven ommatidia are looking at one point in the environment (in the intermediate region between dorsal and ventral part of the eye: 8 to 9 rhabdomers of a set of 8 to 9 ommatidia). These facts were established from sections of living eyes and confirmed by using special optical methods in the intact animal.

The pattern of decussation of individual retinula cell axons between retina and lamina was predicted adopting the hypothesis that the fibers of retinula cells No. 1 to 6, whose rhabdomers are looking at one point in the environment, project into a single "cartridge" in the lamina. These predicted connections were confirmed

by Braitenberg. We have therefore a one to one correspondence between a lattice of points in the environment and the lattice of "cartridges" in the lamina.

It was shown that the unfused rhabdomer structure of the *Musca* ommatidium increases the effective entrance pupil of the eye by a factor of seven (respective 8 to 9 in the intermediate region between dorsal and ventral part of the eye) compared to the classical apposition eye. – The *Musca* compound eye can be regarded as a "neural superposition eye".

P. O. LÖWDIN: I have been asked to try to make some general comments from theoretical points of view on the relation between physics and biology. Let me start by mentioning the great importance of biology for physics by reminding you of the little frog which, in 1791, led Galvani to the discovery of the electric element—an event which has certainly been of fundamental importance for the development of the entire theory of electric phenomena.

In physics, one deals with phenomena in nature which are as simple as ever possible, whereas, in biology, one studies systems of extreme complexity. It seems clear, however, that the basic phenomena in biology follow the laws of physics and chemistry. In science, one should remember that "theory" is nothing which exists by itself, and that "theory" is essentially the quintessence of experimental experience expressed in mathematical form. The last hundred years of experiments in physics and chemistry have led to the formulation of the fundamental laws which are now expressed in concise form by quantum theory.

From the time of Newton, the laws of nature have usually been expressed in differential calculus, but there is now a trend to shift over to "modern mathematics" and set theory. The experimental data are collected in "sets", and correlation between various data are then explained in terms of "mappings" of sets on each other. Of particular importance are the linear sets (or linear spaces) and their mappings in terms of linear operators. The modern language is essentially geometrical and, starting out from the ordinary 3-dimensional space, one constructs n -dimensional spaces or ∞ -dimensional spaces of the type introduced by Hilbert. A child crawling around on a floor is living in a 2-dimensional space, when it rises on its feet, it enters the 3-dimensional world, and when it becomes a scientist, it may use all these experiences to enter the multi-dimensional spaces of mathematics and modern physics. The properties of a space may be described by means of a specific reference system, but, since the laws of nature must be independent of any specific choice of this reference system, one has a "general principle of relativity" which is even more general than the principles formulated by Einstein.

In connection with classical physics and modern quantum theory, one should remember that they both require "initial conditions" which are usually only prescribed by the experimental set-up. If the physical situation at the initial time t_0 is given by the wave function Ψ_0 or the density matrix I_0 , the situation

at the time t is described by the wave function Ψ or the density matrix Γ , respectively, according to the laws

$$\Psi = U\Psi_0, \quad \Gamma = U\Gamma_0U^\dagger,$$

where $U = U(t, t_0)$ is the evolution operator for the system. It should be observed that this operator U is, in principle, determined by the theoretical laws of physics, whereas the information about Ψ_0 or Γ_0 has to come from the experimental situation under consideration. In biology, the initial conditions and the boundary conditions must come from biology, and theory is hence essentially a tool for handling biological data according to laws found under simpler conditions. The application of theoretical physics to biology may thus also be considered as an interesting extrapolation procedure from simple to extremely complex systems.

This procedure may be more complex than one anticipates. For example, let us consider a master skier going down a slalom hill on skis and ask for an explanation of his motion on the basis of the laws of nature. One should study the motion of the center of mass, the motion of the skier with respect to this center, and the physiological processes underlying what is going on. The interesting point is that one has considerable difficulties in explaining even the pure mechanical aspects of the motion, since it is hard to get hold of sufficient experimental information about what is really going on. Even if the entire motion is divided into small parts, it is hard to get hold of the "initial conditions" for each part — even if the skier believes that he knows how to "initiate" various turns and swings. If one puts a theoretical physicist who knows everything about the laws of mechanics (but nothing about skiing) on a pair of skis and asks him to go down the slope, the result will be rather startling, but the interesting point is that, even if he later learns to ski, he may not know what he is doing mechanically. Even an analysis by means of slow-motion picture has not yet revealed the full details of all the dynamical processes involved, and still skiing is a very slow process in comparison to the physiological processes in the body.

I have chosen this example to indicate that one should not expect too much of theory itself in connection with biological phenomena; it is essentially a tool for handling biological data, and it may provide a useful conceptual framework for discussing the elementary processes going on.

In three excellent lectures by Fröhlich, Prigogine, and Pullman, we have heard about various theoretical aspects on biology referring to different levels of "molecular sophistication", which are supplementing each other in a most interesting way.

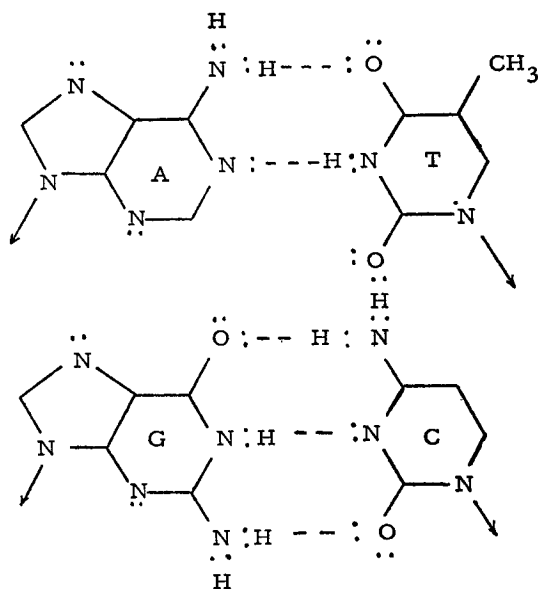
Transport phenomena are of fundamental importance in biology, and one has to understand energy and momentum transfer as well as charge transfer on a macroscopic as well as a microscopic level. Prigogine has chosen to discuss transport phenomena and basic properties of certain systems far away from equilibrium, and our general understanding of these things are of great importance also in biology. Fröhlich has pointed out the possible importance in biology of

the so-called "intermediate region" in the electro-magnetic theory—the region in which usually both the longitudinal and transverse components of the field strengths are of importance, and he has emphasized the effects of the existence of "longitudinal waves". It should perhaps be observed that he is not suggesting the introduction of any strange new phenomena, but a careful analysis of the consequences of Maxwell's equations for the intermediate region which may lead to results of direct importance in cellular biology. By means of the Hückel-method, Pullman has finally given a first analysis of the over-all properties of the conjugated systems, which are planar molecules of essential importance in biochemistry due to the occurrence of mobile π -electrons.

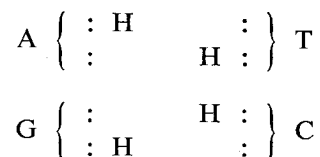
The main point is perhaps that, as time goes on, biologists are making better observations and finer measurements and they have now reached a level where the fundamental particles come in. The transport phenomena are now dealing with electrons and protons, and Szent Györgyi speaks here of electron transfer as one of the most important physiological processes.

To me, it is particularly fascinating that the memory unit in biochemistry is connected with a hydrogen bond, and that it seems to consist of an electron lone-pair: which is either empty or has caught a proton H and formed the structure: H. This leads to a flip-flop mechanism with two possibilities which correspond to the symbols 0 and 1 in a digital electronic computer.

In the genetic code, according to the Watson-Crick model, the information is contained in the four base pairs AT, TA, GC, and CG, which are nitrogen bases joined by hydrogen bonds according to the diagrams:



An analysis of the formulas shows that the genetic template consists of patterns of electron lone-pairs and protons, and that the normal nitrogen basis are characterized by the following combinations



If a proton is misplaced and one gets a "tautomeric" form, the genetic code is also changed, and one may obtain a mutation.

Each hydrogen bond is a proton shared between two electron lone-pairs, and, since each electron-pair offers the proton an attraction represented by a potential well, the proton in the hydrogen bond is actually situated in a double-well potential with two minima separated by a barrier. The proton may move from one minimum to the other above the barrier or through the barrier by means of the quantum-mechanical "tunnel effect", and this process leads to a deterioration of the genetic code [1]. The tunnel-effect depends on the fact that the proton is a de Broglie wave-packet, which may penetrate classically forbidden regions.

In Uppsala, we have recently calculated the shape of the energy potential surfaces for the mobile protons in the genetic code under the assumption that they simultaneously polarize the electronic clouds of the base pairs involved, and the results indicate that the minima are so asymmetric that the protons stay where they are supposed to be in the genetic code with a thermal error due to the tunnel effect which, at $T = 310 \text{ K}$, is of the order of magnitude 10^{-10} for the GC-pair and 10^{-11} for the AT-pair [2]. Since the biological mutation rates per base pair and generation are in the region 10^{-8} to 10^{-12} , the theoretical figures obtained are almost "too good to be true", but it would certainly be of some interest if one could predict the spontaneous mutation rates in biology on the basis of the laws of physics and biology.

The main conclusion seems to be that, when the biologists refine their observation and measurements to the extent that they approach the level of the fundamental particles, they are bound to find quantum effects, and personally I believe that the field of "quantum biology" is here to stay — irrespective of whether this extension of biology is really desired or not. In such a case, theoretical physics is going to be of even greater importance for biology in the future.

It is always difficult for new ideas to come into science, and even cross-fertilization is a very slow process. Max Planck discovered quantum mechanics around 1900, and it is said that in the next decade the new approach conquered physics completely — however, the truth seems to be that Planck's older opponents died one after each other, leaving space for the new ideas to develop. Something similar happened to Einstein and his theory of relativity.

I think that the main importance of a conference of this type is to diminish the inevitable friction which occurs when two scientific fields approach each other, particularly when they are as different as theoretical physics and biology. Both the biologists and the theoreticians are sincere scientists which may have completely different or even controversial aspects on one and the same problem, but both fields may still gain immensely by a closer collaboration which is based on some form of compromise and understanding and not on the death of one of the parts involved. We have hence all reasons to be grateful to the organizers of this conference for the contact they have established.

- [1] P. O. Löwdin, *Advances in Quantum Chemistry* (Ed. P. O. Löwdin, Academic Press, 1965): 213.
- [2] P. O. Löwdin, Proc. Study Week on Intermolecular Forces at Pontifical Academy, Rome (1966); Pontif. Acad. Scie. Scripta Varia No. 31.

Mrs. GRENE: Dr. Lloyd mentioned about one of his experiments that it worked better if the subject did not know what the experiment was about. Perhaps it's better that you didn't know that the philosophers among you were using you as their subject so that we could try to see how you go on and what your methods of thinking and of handling problems are. In this sense, philosophical problems have been implicit in much of the conference. At the same time there were also explicit philosophical problems that arose on occasion, and a good many have come out this afternoon. Perhaps I could just summarize what seem to me to be the principal philosophical problems that ought to be dealt with, not necessarily at such a conference as this — since I gather that most of you prefer to deal with the detailed problems of interaction between the disciplines — but certainly by philosophers who are thinking about more general problems.

First, Dr. Margenau mentioned what I should certainly want to mention also at the head of my list, the very beautiful model of epistemology which Dr. Fessard gave in his talk: Dr. Fessard spoke of the problem that arises when one considers the observer of any piece of animal behavior; this can be generalized to include the behavior of theoretical physicists or biologists or any other knowers. In all these cases there is not only the "input" from the external world in the subject and his output; there is also an input in the observer and his output, and in between there is what happens in himself, which he has to use as a kind of model for what he takes to go on in his subject. He can't get inside his subject, but he has to use the structure of his own experience to model the experience of his subject. Dr. Fessard described this situation as the physiologist confronts it; insofar as the epistemologist is (as Polanyi calls him) an "ultrabiologist", he is faced with exactly the same situation. He is interpreting a piece of human behavior — knowing physics or biology or what you will — and he can do so only by using the transition from his input to his output to model what he imagines takes place in his subject.

Not only does Dr. Fessard's model shed light, moreover, on the central situation

of the epistemologist; it also gives the philosopher something to think about in connection with the question of the relation, philosophically speaking, between physics and chemistry on the one hand and the biological sciences on the other. Several people, Dr. Careri for instance, and Dr. Margenau, have mentioned the distinction between levels of organisation in the organic vs. the inorganic world. There seem to be hierarchies of structure and function not only as between the non-living and the living, but in the living world itself. It seems to me that Dr. Fessard's little diagram showed very clearly how this may be, especially for the study of behavior. There seems to be a fundamental difference here in the way in which biological knowledge is organised in relation to its subject from the way in which physics is related to its subject. If you are talking about protons and electrons, for example, you do not have the double relation that Dr. Fessard described, for you are not dealing with a subject which is itself responding to its environment as you are also doing. The reference to the responding organism seems to introduce into biology a new logical level which is missing in physics and chemistry. How is one to talk about this problem adequately? Does the proliferation of levels arise already in physics, or is there something different about it in biology? I would have gathered from the remarks both of Dr. Margenau a few days ago and of Dr. Careri today that both of them think that there is a continuity here. You just start with the Pauli principle, and go on multiplying complexities, all along the same line. On the other hand, Dr. Fessard's example and others that I have dealt with on other occasions lead me to believe that perhaps there is a different kind of complication of levels when one comes to organic beings, that there is a qualitative change in the kind of hierarchy one is dealing with. The problem here is one which no one has yet, so far as I know, definitively solved, but which is a matter of lively controversy at the moment.

And this leads on to the question whether one can give a proof of nonreducibility for living things, that is, a proof that there is a greater logical richness in biological than in non-biological subject-matter. I was impressed by Dr. Löwdin's way of putting this: that is, that when you are dealing with biological material you have a vast number of starting points and that in this way biology is more complex than physics. I think there is a job for logicians here, to try to demonstrate what kind of logic is entailed here. Again, this may be done perhaps in terms of some kind of mathematics, as Dr. Sobolev mentioned a couple of times. It might be done perhaps in terms of the logic of parts and wholes, which again logicians and philosophers of science have dealt with very inadequately. At any rate there is clearly an important field here in which philosophers and mathematicians should collaborate.

Another philosophical question that, again, was touched on only today in connection with the relation between physics and biology is the question of the temporal organisation of living things. Maybe the physical world, viewed relativistically, is itself four-dimensional, but certainly the four-dimensional character

of living beings is something pretty complicated and perhaps it has to be dealt with, as Dr. Halberg suggested strikingly this morning, with different tools. Here again there is a whole nest of philosophical problems.

Finally, there is another question which was touched on this afternoon by Dr. Careri. That is the question of the structure and function of communities, not only the complexity of a single organism and of its morphogenesis and life history, but the question of the way in which an organism enters into and is controlled by its community. I hoped that we would hear something of this from Dr. Lindauer. It's certainly a subject that people in insect behavior and other ethological fields are concerned with. This again is certainly one of the places where biology ought to touch on philosophical questions and I was very glad that Dr. Careri mentioned it.

A. LICHNEROWICZ: Il nous est revenu que vous désiriez savoir s'il pourrait y avoir une suite à ce colloque. Ce colloque a eu le mérite de réunir des gens que la vie ne faisait pas se rencontrer. Ils avaient tort, nous le savons tous aujourd'hui, de ne pas se rencontrer. Certains d'entre vous ont proposé le principe d'une nouvelle conférence, dans environ deux ans. La spécificité de notre actuelle Conférence est qu'elle a été vraiment pluridisciplinaire tout en couvrant un large éventail, peut-être trop large. La nouvelle conférence pourrait continuer à s'intituler, en précisant davantage, peut-être: "De la Physique Théorique à la Biologie". Bien entendu, pour l'organiser l'actuel Comité serait élargi à toute l'Europe d'une part, et, d'autre part, à l'Amérique et à l'Asie.

(Assentiment général, se traduisant par un oui unanime)

Il en sera donc ainsi décidé.

F. HALBERG: Je vote une ovation au Professeur Marois, pour l'accueil qu'il nous a réservé.

A. LICHNEROWICZ: Je voudrais dire à chacun d'entre vous, au nom du Comité d'Organisation, notre gratitude pour être venus ici, pour avoir créé cette atmosphère à la fois de très haut niveau scientifique et particulièrement amicale. Au nom de ce Comité, merci. C'est vous qui avez assuré ce que l'on peut appeler le succès de cette Conférence. Je laisse maintenant la parole à l'Institut de la Vie, sans lequel rien n'aurait pu avoir lieu.

F. DE CLERMONT-TONNERRE: C'est par l'amitié du Pr Marois et la confiance du Comité d'organisation que le Vice-Président, co-fondateur de l'Institut de la Vie, a l'insigne honneur de parler devant vous.

Permettez-moi, au nom du Conseil d'administration de l'Institut de la Vie, au nom du grand Conseil et au nom du Comité de Patronage de notre Institut, de vous remercier tous! . . . Tous les participants à ce Colloque, les uns arrivés

de tellement loin! Et vous êtes venus pour nous. Croyez que nous en sommes profondément reconnaissants et émus.

Reconnaissants, particulièrement, de la confiance que vous nous témoignez par votre présence. Et d'avoir répondu, comme vous l'avez fait, à l'invitation de notre jeune Institut; d'avoir pendant six jours travaillé en son nom, avec autant d'ardeur! C'est pour nous une responsabilité lourde, tant dans l'organisation actuelle que pour l'avenir.

Votre confiance, je n'en veux qu'un témoignage. Lorsque M. Lichnerowicz, tout à l'heure, évoquait le lieu où se tiendrait le futur Colloque, j'ai remarqué, dans cette salle, ce que plusieurs murmures et suggestions laissaient entendre: que vous ne seriez pas fâchés de revenir à Versailles. Nous ne savons pas quelle sera la décision du Conseil élargi, mais je suis sûr que cette décision vous l'appréciez tous, car je tiens à vous dire ceci: où que se tienne ce Colloque, l'Institut de la Vie sera fier de vous y voir participer. Puis-je ajouter que la caractéristique essentielle qui me paraît, du point de vue de l'Institut, s'être dégagée de notre confrontation, pourrait être son étonnant esprit de liberté intimement associé à la plus grande rigueur. Comment ne pas penser que les conséquences en seront fructueuses!

Permettez-moi, pour conclure, d'ajouter un mot au nom de la discipline que je représente, puisque, aussi bien, c'est la seule occasion que j'aurai d'en parler devant vous.

. . . L'Histoire aussi est une science de la vie. Et, de plus en plus, elle se tourne vers vous, vers votre aide. D'abord, pour augmenter ses possibilités d'investigation. Pour développer encore davantage son esprit de critique, son ambition est, sous votre égide, à son tour de connaître la rigueur des lois et d'arriver à des résultats certains.

Merci, au nom de cette discipline, de l'aide que vous lui apportez tous les jours! Croyez que, pour un historien, avoir assisté à vos débats est l'expérience la plus enrichissante qu'il puisse avoir. Ainsi sommes-nous devenus des amis, au sein et par-dessus nos disciplines respectives. Cette amitié anime nos travaux futurs et garde vivant le souvenir des heures exaltantes que nous avons passées ensemble.

Ce n'est qu'un au revoir que nous vous disons, Amis de l'Institut de la Vie!

LIST OF PARTICIPANTS

M. AGENO,
Istituto Superiore di Sanità,
Laboratori di Fisica,
Viale Regina Elena 299,
ROME (Italie).

P. AUGER,
Professeur à la Faculté des Sciences de
Paris, Président de la Commission des
Sciences de l'U.N.E.S.C.O.
12, rue Emile Faguet,
75 - PARIS 14e (France).

S. BENNETT,
University of Chicago,
Laboratories for Cell Biology,
939 East - 57th street,
CHICAGO - Illinois 60637 (U.S.A.).

E. D. BERGMANN,
Laboratoire de Chimie Organique,
Université de Jérusalem,
JERUSALEM (Israël).

M. A. BOUMAN,
National Defense Research Organiza-
tion TNO,
Institute for Perception RVO-TNO,
Kampweg 5,
SOESTERBERG (Pays-Bas).

S. E. BRESLER,
Institute of High Molecular CPDS,
Academy of Sciences,
LENINGRAD B. 164 (U.R.S.S.).

G. CARERI,
Università degli Studi - Roma,
Istituto di Fisica "Guglielmo Marconi",
Piazzale delle Scienze 5,
ROME (Italie).

B. CHANCE,
Johnson Research Foundation,
Department of Biophysics and Physical
Biochemistry,
School of Medicine,
University of Pennsylvania,
PHILADELPHIA - Penn. (U.S.A.).

F. DE CLERMONT-TONNERRE,
Vice-Président du Conseil d'Admini-
stration de l'Institut de la Vie,
14, rue du Conseiller Collignon,
PARIS - (France).

E. G. D. COHEN,
The Rockefeller University,
NEW-YORK - N.Y. 10021 (U.S.A.).

M. H. COHEN,
Institute for the Study of Metals,
University of Chicago,
5640 Ellis Avenue,
CHICAGO - Illinois 60637 (U.S.A.).

A. Cournand, Prix Nobel,
College of Physicians and Surgeons,
Columbia University,
Department of Medicine,
630 West 168th Street,
NEW YORK - N.Y. 10032 (U.S.A.).

J. D. COWAN,
University of Chicago, Chairman,
Committee on Mathematical Biology,
937 E. 57th Street,
CHICAGO - Illinois 60637 (U.S.A.).

D. M. CROTHERS,
Yale University,
Department of Chemistry,
Sterling Chemistry Laboratory,
225, Prospect Street,
NEW-HAVEN - Connecticut 06520
(U.S.A.).

- C. CRUSSARD,
 Directeur Scientifique de la Société
 Péchiney,
 23, rue Balzac,
 75 - PARIS 8e (France).
- A. DALCQ,
 Secrétaire Perpétuel de l'Académie
 Royale de Médecine de Belgique,
 Palais des Académies,
 1, rue Ducale,
 BRUXELLES (Belgique).
- K. H. DEGENHARDT,
 Institut für Humangenetik und Ver-
 gleichende Erbpathologie
 der Universität Frankfurt,
 Paul-Ehrlich-strasse 41,
 6 - FRANKFURT (R.F.A.).
- P. DEJOURS,
 Faculté de Médecine de Paris,
 Laboratoire de Physiologie,
 45, rue des Saints-Pères,
 75 - PARIS 6e (France).
- Rév. Père A. DOU, S.J.,
 Catedra de Ecuaciones Diferenciales,
 Facultad de Ciencias - C.U.,
 Departamento de Ecuaciones Funcio-
 nales,
 MADRID - 3. (Espagne).
- J. DUCHESNE,
 Université de Liège,
 Département de Physique Atomique et
 Moléculaire,
 Institut d'Astrophysique,
 COINTE-SCLESSIN (Belgique).
- M. EIGEN, Prix Nobel,
 Max-Planck-Institut für Physikalische
 Chemie,
 Bunsenstrasse 10,
 3400 - GÖTTINGEN (R.F.A.).
- W. M. ELSASSER,
 University of Maryland,
 Institute for fluid Dynamics and Applied
 Mathematics,
 MARYLAND - 20740
 (U.S.A.).
- A. FESSARD, de l'Académie des Sciences,
 Collège de France,
 Institut Marey,
 Laboratoire de Neurophysiologie Gé-
 nérale,
 4, avenue Gordon-Bennett,
 75 - PARIS 16e (France).
- H. FRÖHLICH, F.R.S.,
 University of Liverpool,
 Chadwick Laboratory,
 LIVERPOOL 3 (Grande-Bretagne).
- P. GLANSDORFF,
 Université Libre de Bruxelles,
 Faculté des Sciences,
 Pool de Physique,
 50, avenue F. D. Roosevelt,
 BRUXELLES - 5. (Belgique.)
- P. P. GRASSÉ,
 Président de l'Académie des Sciences,
 Laboratoire d'Evolution des Etres Or-
 ganisés,
 Faculté des Sciences,
 105, boulevard Raspail,
 75 - PARIS 6e (France).
- Mme. M. GRENE,
 University of California,
 Department of Philosophy,
 DAVIS - Cal. 95616 (U.S.A.)
- F. GROS,
 Institut de Biologie Physico-Chimique,
 Fondation Edmond de Rothschild,
 13, rue Pierre Curie,
 75 - PARIS 5e (France).

- H. HAKEN,
Institut für Theoretische Physik der
Technischen Hochschule Stuttgart,
Azenbergstrasse 12,
7 - STUTTGART 1. (R.F.A.).
- F. HALBERG,
University of Minnesota,
Medical School,
Chronobiology Laboratories,
Department of Pathology,
MINNEAPOLIS - Minnesota 55455
(U.S.A.).
- T. L. HILL,
University of Oregon,
Department of Chemistry,
College of Liberal Arts,
EUGENE - Oregon 97403 (U.S.A.).
- A. KATCHALSKY,
Weizmann Institute for Sciences,
REHOVOTH (Israël).
- O. KLEIN,
Ringen 21,
MORBY-STOCKSUND (Suède).
- M. KOTANI,
Osaka University,
Faculty of Engineering Science,
TOYONAKA - OSAKA (Japan).
- R. KUBO,
University of Tokyo,
Department of Physics,
Faculty of Science,
BUNKYO-KU - TOKYO (Japan).
- A. D. McLACHLAN,
University Chemical Laboratory,
Lensfield Road,
CAMBRIDGE - (Grande-Bretagne).
- A. LICHNEROWICZ,
de l'Académie des Sciences,
Collège de France,
- Chaire de Physique mathématique,
Place Marcellin Berthelot,
75 - PARIS 5e (France).
- M. LINDAUER,
Zoologisches Institut der Universität,
Siesmayerstrasse 70,
6 - FRANKFURT a.M. (R.F.A.).
- B. B. LLOYD,
University Laboratory of Physiology,
OXFORD (Grande-Bretagne).
- H. C. LONGUET-HIGGINS, F.R.S.,
Department of Machine Intelligence
and Perception,
University of Edinburgh,
Forrest Hill,
EDINBURGH - 1. (Grande-Bretagne).
- P. O. LÖWDIN,
Quantum Chemistry Group for Re-
search in Atomic, Molecular, and
Solid-State Theory,
University of Uppsala,
UPPSALA (Suède).
- F. LYNEN, Prix Nobel,
Max-Planck-Institut für Zellchemie,
Karlstrasse 23-25,
8 - MÜNCHEN 2. (R.F.A.).
- O. MAALØE,
Det Mikrobiologiske Institut,
Øster Farimagsgade 2 A,
COPENHAGUE (Danemark).
- M. MAGAT,
Laboratoire de Physicochimie des Ra-
yonnements,
Faculté des Sciences,
91 - ORSAY (France).
- H. MARGENAU,
Yale University,
Physics Department,
217 Prospect Street,
NEW-HAVEN - Conn. 06520 (U.S.A.).

- M. MAROIS,
Professeur Agrégé à la Faculté de
Médecine de Paris,
Président du Conseil d'Administration
de l'Institut de la Vie,
89, boulevard Saint-Michel,
75 - PARIS 5e (France).
- B. MATTHIAS,
University of California, San Diego,
Department of Physics,
Revelle College,
P.O. Box 109,
LA JOLLA - California 92038 (U.S.A.).
- P. MAZUR,
Instituut Lorentz voor Theoretische
Natuurkunde,
Nieuwsteeg 18,
LEIDEN (Pays-Bas).
- K. MENDELSSOHN, F.R.S.,
University of Oxford,
Department of Physics,
Clarendon Laboratory,
Parks Road,
OXFORD (Grande-Bretagne).
- J. MONOD, Prix Nobel,
Institut Pasteur,
25, rue du Docteur Roux,
75 - PARIS 15e (France).
- R. S. MULLIKEN, Prix Nobel,
University of Chicago,
Laboratory of Molecular Structure and
Spectra,
Department of Physics,
1100 East - 58th Street,
CHICAGO - Illinois 60637 (U.S.A.).
- S. OCHOA, Prix Nobel,
New-York University Medical Center,
Department of Biochemistry,
550 First Avenue,
NEW-YORK - N.Y. 10016 (U.S.A.).
- L. ONSAGER, Prix Nobel,
Yale University,
Department of Chemistry,
Sterling Chemistry Laboratory,
225, Prospect Street,
NEW-HAVEN - Connecticut (U.S.A.).
- J. POLONSKY,
Compagnie Générale de Télégraphie
sans Fil,
Directeur du Département Télévision,
132, avenue de Clamart,
92 - ISSY-les-MOULINEAUX
(France).
- I. PRIGOGINE,
Université Libre de Bruxelles,
Faculté des Sciences,
Service Chimie-Physique II,
50, avenue F. D. Roosevelt,
BRUXELLES - 5. (Belgique).
- B. PULLMAN,
Professeur à la Faculté des Sciences de
Paris,
Administrateur de l'Institut de Biologie
Physico-Chimique,
Université de Paris,
Faculté des Sciences,
Laboratoire de Chimie-Quantique,
13, rue Pierre Curie,
75 - PARIS 5e (France).
- W. REICHARDT,
Max-Planck-Institut für Biologie,
Spemannstrasse 34,
TÜBINGEN (R.F.A.).
- A. REINBERG,
Laboratoire de Physiologie,
Fondation Adolphe de Rothschild,
29, rue Manin,
75 - PARIS 19e (France).

S. A. RICE,
Director of the Institute for the Study
of Metals,
University of Chicago,
5640 - Ellis Avenue,
CHICAGO - Illinois 60637 (U.S.A.).

L. ROSENFELD,
Nordisk Institut for Teoretisk Atom-
fysik,
Blegdamsvej 17,
COPENHAGUE Ø (Danemark).

M. P. SCHÜTZENBERGER,
Institut Blaise Pascal,
23, rue du Maroc,
75 - PARIS 19e (France).

I. SEGAL,
Massachusetts Institute of Technology,
Department of Mathematics,
CAMBRIDGE - Mass. 02139 (U.S.A.).

S. L. SOBOLEV,
Académie des Sciences de l'U.R.S.S.,
NOVOSIBIRSK (U.R.S.S.).

A. SZENT-GYORGYI, MD. PH. D., Prix
Nobel,
Laboratory of the Institute for Muscle
Research at the Marine Biological
Laboratory,
WOODS-HOLE - Massachusetts
(U.S.A.).

A. TAVARES DE SOUZA,
Instituto de Histologia e Embriologia
da Faculdade de Medicina,
Universidade de Coïmbra,
COIMBRA (Portugal).

L. TISZA,
Massachusetts Institute of Technology,
Department of Physics,
CAMBRIDGE - Massachusetts 02139,
(U.S.A.).

Mme TONNELAT,
Faculté des Sciences,
Institut Henri Poincaré,
11, rue Pierre Curie,
75 - PARIS 5e (France).

H. H. USSING,
Institute of Biological Chemistry,
University of Copenhagen,
2 A, Øster Farimagsgade,
COPENHAGUE K. (Danemark).

TH. VOGEL,
Directeur du Centre de Recherches
Physiques,
Centre National de la Recherche
Scientifique,
31, chemin Joseph-Aiguier,
13 - MARSEILLE 9e (France).

E. WOLFF,
de l'Académie des Sciences,
Administrateur du Collège de France,
Laboratoire d'Embryologie Expérimen-
tale,
49 bis, avenue de la Belle-Gabrielle,
94 - NOGENT-sur-MARNE (France).

R. WURMSER,
de l'Académie des Sciences,
Institut de Biologie Physico-Chimique,
Fondation Edmond de Rothschild,
13, rue Pierre Curie,
75 - PARIS 5e (France).

Directeur de la publication: M. Maurice MAROIS
Imprimé en Hollande