Meetings

Contractility

A correspondence has long been suspected between the contractility of biological structures such as muscle and other proteins and the long-range elastic deformability of suitably constructed high-polymer systems. More recently, a correspondence has been recognized between the deformability of such systems and cell motility, rhythmic motions of cilia, and cell mitosis.

In view of the importance of the subject to a broad range of biological phenomena on the one hand, and of newer ideas developing in the field of polymer science on the other, an international Conference on Contractility was held at Mellon Institute, Pittsburgh, 27–30 January 1960, under the joint auspices of the Office of Naval Research, the National Institute of Arthritis and Metabolic Diseases, and the Mellon Institute. Leading scientists engaged in research in these fields joined in active discussions throughout the 4 days of the conference. About 60 scientists, representing nine nations, participated; specialties ranged from physics to cell physiology.

The emphasis of the conference was on the fundamental principles and underlying physical-chemical concepts relating to contractile mechanisms. The connection with biological structures was explored by critical discussion of various contractile processes in biological systems.

Subjects of the Sessions

Sessions were devoted to the following subjects: (i) macromolecular models and thermodynamic principles; (ii) characterization of proteins involved in biological contraction; (iii) chemistry of contraction; (iv) analysis of the muscle system; and (v) contractile systems in cells and systems other than muscle. A sixth session was devoted exclusively to discussion.

Each session was opened with one or two invited lectures, which reviewed the area under consideration and pointed out the more and the less established aspects. This was followed by shorter scheduled reports and discussion, the latter generally extending well beyond the scheduled sessions.

Physicochemical Aspects

The opening session of the conference dealt with the physicochemical aspects of contractility and the related problem of performance of mechanical work by nonliving macromolecular systems. The study of long-chain molecules has shown that it is possible to transform chemical energy directly into mechanical work and that, furthermore, the macromolecular engine provides the contractile mechanism as well. Virtually every high-polymer network consisting of long molecular chains displays the capacity to maintain very large, recoverable strains (P. J. Flory, Mellon Institute). Rotations about chain bonds endow a polymeric substance with the singular capacity to accommodate large deformations and to return under suitable conditions to the initial undeformed state. The elasticity of rubber is a good example; cross-linking of the chains prevents irreversible flow. Closely related to rubber elasticity are deformations involving changes in the degree of swelling in open thermodynamic systems.

Polymer chains of sufficiently regular structure may occur in the crystalline state (Flory; L. Mandelkern, National Bureau of Standards). Crystallization may be induced by stretching; conversely, melting may induce contraction. The transformation between crystalline and amorphous states, being a phase transition, is very sensitive to temperature and may be made correspondingly sensitive to chemical environment. Also, the deformation range of the macromolecular contractile system may be considerably increased by crystallization, or, in general, by phase transformations involving large dimensional changes at constant force.

A macromolecular contractile system which is responsive to alterations in chemical environment may serve as a macromolecular engine for transforming chemical energy into mechanical work (W. Kuhn, University of Basel). Chemical reactions made to occur on the macromolecules themselves provide a convenient means for strongly altering the shape of linear macromolecules or the swelling capacity of cross-linked systems. Reversible ionization and deionization of suitable groups attached to the macromolecular chains provide one possible mechanism leading to appreciable osmotic driving forces. Other mechanisms, such as, for instance, changes in solubility induced by the addition and removal of complexing agents (for example, Ca^{++} ions to anionic polyelectrolyte systems), are not excluded.

In general, any thermodynamic system capable of transforming chemical energy directly into mechanical work or, conversely, of transforming mechanical into chemical energy can be described as a mechanochemical engine (A. Katchalsky, Weizmann Institute). These transformations are usually carried out by contractile fibers, which may operate cyclically, reverting after each cycle to their initial state. A thermodynamic analysis of such cycles is rewarding, as it leads to an evaluation of mechanochemical performance and establishes some general conditions for the feasibility and efficacy of mechanochemical transformations. Cycles with phase transitions at constant potential of the reactants are shown to be particularly efficacious converters of chemical energy into mechanical work.

Further contributions to this session dealt with the thermodynamics of the stretching of swollen fibers (W. Prins and J. J. Hermans, Syracuse University); recent work on the reversible supercontraction of β-keratose with change of *p*H (F. G. E. Pautard, University of Leeds); elastic properties of muscle proteins (C. A. J. Hoeve, Mellon Institute; Flory); evidence for a phase transition in muscle contraction (Hoeve and Flory); and the rates of configurational change in macromolecules and their dependence on concentration and charge (J. D. Ferry, University of Wisconsin).

Muscular Contraction

The study of muscular contraction illustrates different approaches to the analysis of contractibility in biological systems. Experimental methods fall into five broad categories: (i) analysis of structure; (ii) chemical characterization of component proteins; (iii) enzymatic activity of the proteins; (iv) study of simpler, model systems; and (v) physiology of the intact system. The following general picture emerged from the sessions.

Electron micrographs of skeletal muscle show two morphologically distinct sets of filaments, thick (A band)

and thin (I band). At normal muscle length, the thin filaments extend beyond the I band and interdigitate with thick filaments in the A band. In longitudinal sections the interdigitating array can be seen directly; it can also be deducted from counts of the number of filaments in successive cross sections. Although some recent micrographs suggest that the two sets of overlapping myofilaments are not always separate (F. S. Sjostrand, Karolinska Institute), most subsequent discussion of contractile mechanism was premised on the interdigitating anatomy.

Of the structural proteins that can be extracted from muscle, myosin and actin are fairly well characterized (K. Laki, National Institutes of Health). However, it is difficult to work out exact relationships among operationally defined muscle proteins because the preparations are not homogeneous, especially when tested immunologically. The heterogeneity can be reduced considerably by making ammonium sulfate precipitations in the presence of lithium choride (J. Marshall, University of Pennsylvania).

Myosin and actin appear to be localized in the thick and thin myofilaments, respectively. This assignment is based on differential extractibility of A- and I-band material (J. Hanson, University of London) and staining studies with fluorescent antibodies (Marshall).

The muscle proteins are chemically reactive: they form complexes with each other and also interact with smaller molecules, notably the nucleotides. Although it is not clear how these reactions relate to the contractile process, they are of interest because they reflect properties of components of muscle. One such reaction frequently implicated in the contractile process is the hydrolysis of adenosinetriphosphate (ATP) by myosin and actomyosin. Studies with labeled substrate suggest that the terminal phosphate of the nucleotide is transferred to the enzymatic site of the protein before being liberated as inorganic phosphate (D. Koshland, Brookhaven National Laboratory).

Under appropriate conditions, actin alone splits ATP (F. Oosawa, Nagoya University). The G-F transformation, from globular actin to fibrous aggregates, can be regarded as a reversible fibrous condensation. The apparent equilibrium state depends on magnesium concentration and temperature; it is accompanied by a continuous dephosphorylation of ATP and is, therefore, a steady state maintained by ATP hydrolysis. Another aspect of the interaction of actin with nucleotide is the exchange of bound nucleotide with labeled ATP or adenosinediphosphate in the solution. In the G form, exchange of ATP takes place; however, the nucleotide in the F form is not exchangeable (J. Gergely, Massachusetts General Hospital).

Many properties of living muscle can be demonstrated after the physiological regulatory mechanisms have been destroyed by treatment with glycerol. The contractile response of the glycerol-extracted preparation is elicited by ATP and other triphosphorylated nucleotides; both actin and myosin are required (A. Szent-Gyorgyi, Institute for Muscle Research). The nature of the forces leading to this contraction is not known.

Further contributions to the biochemistry of muscle dealt with studies on the structure of myosin which indicate that it is a triply stranded polypeptide chain (W. Kielley and W. F. Harrington, National Institutes of Health); the inhibition of adenosinetriphosphatase activity of myosin A with trinitrobenzene sulfonate (a specific ϵ-amino group reagent) and the interaction of myosin B with pyrophosphate and ATP (Y. Tonomura, Hokkaido University); the activation and inhibition of myosin A (J. J. Blum, Baltimore City Hospitals); the intrinsic contractibility of the myosin B system (M. F. Morales, Dartmouth Medical School); and the dependence of the rate of creatine phosphate hydrolysis on the rate of muscular contraction (W. F. H. M. Mommaerts, University of California).

The physiology of striated muscle can be interpreted in terms of both *sliding* and *folding* mechanisms (R. J. Podolsky, Naval Medical Research Institute). According to the former interpretation, contraction is brought about by mechanical interaction of the two sets of filaments seen in electron micrographs. In the folding model, the contractile force arises from molecular rearrangement of a single filament. Feedback between the mechanical motion and the chemical process which leads to this molecular rearrangement can account for both the steady-state and transient properties of the living fiber.

Smooth muscle also has two morphologically distinct myofilaments; this suggests that, if the contractile force arises from interaction between filaments, the same fundamental mechanism might work in both smooth and striated muscles (J. Hanson, University of London).

Other examples of contractibility in biological systems are the movement of chromosomes in cell division (S. Inoue, Dartmouth Medical School), the injection of virus genetic material into bacteria (L. Kozloff, University of Chicago), the movement of sperm tails (B. Afzelius, Wenner Grens Institute), and protoplasmic streaming (N. Kamiya, Osaka University). Several similarities to the muscle system were noted. For example, some physical-chemical properties of the fibers that control chromosome movement resemble those of actin (D. Mazia, University of California). Also, the protein which moves virus material into the host cell is similar to actomyosin; ATP is hydrolyzed when the protein contracts. Lastly, cellular contractile elements can be studied as model systems after glycerol extraction (H. Hoffman-Berling, Max Planck Institut für Physiologie). As in similar preparations of muscle, motility can be influenced by the concentration of ATP, calcium, and mercurial inhibitors.

Sliding versus Folding

The final session of the conference was largely devoted to discussion. The issue of a sliding mechanism versus one of chain "folding" in muscular contraction evoked spirited response. According to the former view, contraction is brought about by interactions at the surfaces of filaments revealed in electron microscopy; both the molecular arrangement and the linear dimension of the filaments are considered to remain unaltered. Opponents preferred one or another of several mechanisms involving configurational rearrangements at the molecular level, these rearrangements occurring within the filaments of the sarcomere. According to these views the linear dimensions of the filaments decrease as the muscle shortens. Electron micrographs of muscles stopped at different stages of isotonic contraction offer the possibility of distinguishing between the two mechanisms; several laboratories are undertaking studies of this nature.

A contractile force could be generated, it was stated, by a sliding model in which the number of filament bonds increases with the extent of interdigitation (W. Kauzmann, Princeton University). Flory questioned the sufficiency of simple surface interactions to generate forces and deformations of the magnitudes observed, stating that linkages capable of sustaining the required tensions would probably not be labile enough to facilitate the observed rapid alterations in lengths. Podolsky noted that it would be difficult to reconcile such a sliding model with the kinetics of muscular contraction. Sliding kinematics in which the moving filaments have complementary sites which, as they pass each other, form a mechanochemical engine remains a possibility. In this case, although the contractile force would be produced by changes in molecular configuration, the filaments on which the force-generating elements are situated would "slide" past each other.

If chemical reactions can be reversed in contracting muscle during an applied stretch, as suggested by A. V. Hill, forcible stretching apparently brings about *microscopic* reversal of the con-

tractile process. This is easy to understand if contraction of a fiber is brought about by the adsorption of a substance distributed between fiber and immersing solution, as discussed earlier by Katchalsky. However, it is not easy to visualize the microscopic reversal (by sudden stretch) of a process consisting of several cycles of dephosphorylation, as in some mechanisms proposed for shortening by sliding filaments (M. F. Morales).

Other Discussion

Further discussion posed the question of how to differentiate the several molecular mechanisms whereby long molecules may induce major changes in dimensions through interaction with a chemical reagent. One mechanism, discussed earlier by Flory and Mandelkern, depends on the existence of the polymer in two forms, crystalline and amorphous, the one form being converted into the other upon alteration of the chemical environment. Coexistence of the two forms would, under the simplest circumstances, be evidenced by a horizontal region in the isothermal stress-strain curve. T. Hill (University of Oregon) pointed out that such a stress-strain curve does not necessarily imply a crystalline-amorphous transition; there are other molecular mechanisms which result in similar stress-strain curves. J. J. Hermans said that whether a one- or two-phase description of a system is used is a matter of convenience. If a cooperative transition is involved, it is generally expeditious to treat the phenomenon as a phase transition.

H. Eisenberg (Mellon Institute) discussed the profound difference in the effects of potassium chloride and sodium chloride in producing phase transitions in some synthetic polyelectrolytes, under conditions of identical charge density; F. Oosawa reported similar findings in the influence of magnesium and calcium on the phase transition of polyacrylic acid.

In the course of the conference it became clear that a number of biological processes can be interpreted in terms of long-range elastic deformation of polymers. In no case, though, is the evidence for this mechanism conclusive; contraction preceded by an interaction *between* polymers could not be excluded. However, the lines of research by which these mechanisms might be distinguished were brought into sharper focus.

WILLIAM R. CARROLL
National Institutes of Health, Bethesda, Maryland

H. EISENBERG
Mellon Institute, Pittsburgh, Pennsylvania

RICHARD J. PODOLSKY
Naval Medical Research Institute, Bethesda, Maryland

Forthcoming Events

September

6–10. Lower Metazoa, Comparative Biology and Phylogeny, 2nd symp., Asilomar, Pacific Grove, Calif. (M. B. Allen, Kaiser Foundation Research Inst., 14th and Cutting Blvd., Richmond, Calif.)

8–9. Technical Comunications, 2nd annual, Dayton, Ohio. (D. G. Peterson, Jr., Soc. of Technical Writers and Editors, 4564 Marlin Ave., Dayton 16, Ohio)

8–10. American Political Science Assoc., New York, N.Y. (E. M. Kirkpatrick, 1726 Massachusetts Ave., NW, Washington 6, D.C.)

8–10. Great Issues of Conscience in Modern Medicine, Hanover, N.H. (G. O'Connell, Dartmouth College News Service, Hanover)

8-10. Parapsychological Assoc., 3rd. annual, New York, N.Y. (W. G. Roll, Parapsychology Laboratory, Duke Univ., Durham, N.C.)

8–18. History of Medicine, 17th intern. cong., Athens and Isle of Cos, Greece. (S. Oeconomos. Faculty of Medicine, National and Capodistrian Univ. of Athens, Odos panepistimiou, Athens, Greece)

10–11. Air Pollution, intern. cong., New York, N.Y. (A. B. Conlin, Jr., ASME, 29 W. 39th St., New York 18)

11–15. International College of Surgeons, 12th intern. cong., New York, N.Y. (M. Thorek, ICS, 850 W. Irving Park Rd., Chicago 13, Ill.)

11–16. American Chemical Soc., 138th annual, New York, N.Y. (A. T. Winstead, ACS, 1155 16th St., NW, Washington 6)

11–16. Illuminating Engineering Soc., natl. technical conf., Pittsburgh, Pa. (A. D. Hinkley, IES, 1860 Broadway, New York 23)

12–13. International Conf. on Trichinellosis, Warsaw, Poland. (Z. Kozar, Polish Parasitological Soc., Zaklad Parazytologii, PAN, Warszawa, Pasteura 3, Poland)

12–14. Entomological Soc. of Canada—Entomological Soc. of Saskatchewan, annual joint meetings, Saskatoon, Sask., Canada. (L. L. Reed, ESC, K. W. Neatby Bldg., Carling Ave., Ottawa, Canada)

12–15. Atomic Masses, intern. conf., Hamilton, Ontario, Canada. (H. E. Duckworth, Dept. of Physics, McMaster Univ., Hamilton)

12–15. Society of Automotive Engineers, Milwaukee, Wis. (R. W. Crory, SAE, Meetings Operation Dept., 485 Lexington Ave., New York 17)

12–16. International Council of the Aeronautical Sciences, 2nd intern. cong., Zurich, Switzerland. (J. B. Bidwell, Inst. of the Aeronautical Sciences, 2 E. 64 St., New York 21)

12–17. World Federation of Occupational Therapists, Sydney, Australia. (Liverpool School of Occupational Therapy, Victoria Rd., Huyton, Liverpool, England)

13–14. Bionics, symp., Dayton, Ohio. [Commander, Wright Air Development Division, Attention: WWRDA (Maj. J. E. Steele, Wright-Patterson Air Force Base, Ohio)]

13–15. Instruments and Measurements, 5th intern. conf., Stockholm, Sweden. (Tekn. Lic. Helge von Koch, Kungl. Tekniska Högskolan, Stockholm 70)

14–15. Aspects of Internal Irradiation of Mammals, Saratoga, Wyo. (T. F. Dougherty, Univ. of Utah, Salt Lake City)

14–16. Tube Techniques, 5th natl. conf., New York, N.Y. (D. Slater, College of Engineering, Research Div., New York Univ., 346 Broadway, New York 13)

15–16. Engineering Management Conf., 8th annual, Chicago, Ill. (E. O. Kirkendall, AIME, 29 W. 39 St., New York 18)

15–17. Radio Soc. of Great Britain, natl. convention, Cambridge, England. (Secretary, RSGB Convention Committee, 37 Metcalfe Rd., Cambridge, England)

16–18. Cori's Ester and Phosphorylated Glucides, 1st intern. symp., Milan, Italy. (Segreteria Organizzativa del 1st Symposium Internazionale sull'estere di Cori e sui glucidi fosforilati, Via Modica 6, Milan)

16–21. European Cong. on Infantile Neuro-Psychiatry, Paris, France. (G. Belaubre, 14 rue Drouot, Paris)

16–22. World Medical Assoc., Berlin, Germany. (General Secretary, WMA, 10, Columbus Circle, New York 19)

18–21. Forensic Pathology, 2nd intern., New York, N.Y. (C. Larsen, Tacoma General Hospital, Tacoma 5, Wash.)

18–25. Inter-European Cong. of Cardiology, 3rd, Rome, Italy. (V. Puddu, Clinica, Medica, Università-Policlinico, Rome)

19–21. Space Electronics and Telemetry, 5th natl. symp., Washington, D.C. (H. W. Royce, Glenn L. Martin Co., Mail Stop H–2035, Baltimore 3, Md.)

19–22. Research in Burns, 1st intern. cong., Bethesda, Md. (American Inst. of Biological Sciences, 2000 P St., NW, Washington 6)

20–23. Conf. on Pure Food Laws, London, England. (Secretariat, Pure Food Centenary 1960, 14 Belgrave Sq., London S.W.1)

20–24. Aeronautics, 4th European cong., Cologne, Germany. (Wissenschaftliche Gesellschaft für Luftfahrt, Eberplatz 2, Cologne)

20–7. International Atomic Energy Agency, 4th general conf., Vienna, Austria. (IAEA, 11 Kärntner Ring, Vienna 1)

21–22. Industrial Electronics, 9th annual symp., Cleveland, Ohio. (G. E. Hindley, Reliance Electric & Engineering Co., 24701 Euclid Ave., Cleveland 17)

21–23. National Power Conf., Philadelphia, Pa. (A. B. Conlin, Jr., ASME, 29 W. 39 St., New York 18)

22. Society of Plastics Engineers, Binghamton, N.Y. (T. A. Bissell, SPE, 65 Prospect St., Stamford, Conn.)

22–23. High Temperature Resistance and Thermal Degradation of Polymers, symp., London, England. (Symposium Subcommittee, Plastics and Polymer Group, Soc. of Chemical Industry, 14, Belgrave Sq., London, S.W.1)

22–26. Cancer Cytology, intern. conf., Madrid, Spain. (Miss E. L. Hughes, Pan American Cancer Cytology Soc., P.O. Box 633, Coral Gables, Fla.)

23–25. Inter-Society Cytology Council, annual, Chicago, Ill. (P. A. Younge, ISCC, 1101 Beacon St., Brookline 46, Mass.)

24–2. American Soc. of Clinical Pathologists, Chicago, Ill. (A. H. Dearing, 2115 Prudential Plaza, Chicago, Ill.)

25–28. American Inst. of Chemical Engineers, Tulsa, Okla. (F. J. Van Antwerpen, AICE, 25 W. 45 St., New York 36)