COMPREHENSION of the ultimate nature of muscular contraction is of great importance to the cardiologist. In view of the rapid and highly specialized progress in the study of myosin, actin and adenosine triphosphate as the agents of contractile activity in various types of muscle, it may be desirable to give a brief orientation as to what this progress means. What are the main trends in its development? What does the evidence consist of? What conclusions have been reached? How do the new facts connect with other phases of metabolism and function?

Most work in this field has been performed with substances derived from skeletal muscle. Anyone desiring to investigate the same problems for the myocardium will meet peculiar difficulties in regard to low yield or abnormal behavior of the material. This is due to our lack of knowledge and experience in cardiac biochemistry, it does not necessarily indicate that these two kinds of muscle are fundamentally different. To say, for example, that the amount of myosin in the heart is only one-twentieth of the total protein, means only that one has not yet learned to obtain it quantitatively.

All muscular activity relies, eventually, on the consumption of oxygen. This does not mean that the contraction process itself is of an aerobic nature; indeed, many kinds of skeletal muscle can work anaerobically (through glycolysis) for a considerable time. The purpose of respiration, and of glycolysis, is to synthesize so-called energy-rich phosphate compounds, two of which occur in muscular tissues in marked concentration: adenosine triphosphate (ATP) and phosphocreatine (PC). The former substance is the immediate energy donor for all cellular processes. It occurs in mammalian muscles, including the heart, in the rather constant concentration of about 5 µM per gram fresh tissue. Phosphocreatine occurs in more varying amounts; in typical skeletal muscles it may exceed the adenosine triphosphate about four-fold, but in the heart there is considerably less than that. Phosphocreatine can transfer its phosphate group to adenosine diphosphate (ADP), thus turning it into adenosine triphosphate. In this sense, phosphocreatine acts as a reserve of adenosine triphosphate, but it may well have a more fundamental function in connection with relaxation or diastole.

Adenosine triphosphate makes its energy available when it is dephosphorylated to adenosine diphosphate, and presumably this is the reaction which supplies the energy for the contraction process. It would be of importance to establish this directly by demonstrating the breakdown of adenosine triphosphate during or before contraction. Such work is in progress, but it advances slowly on account of the experimental difficulties. A crude approximation to this experiment consists of immersing the tissue suddenly into liquid air: the intense cold acts as a stimulus and causes the tissue to be frozen in the contracted state. In this way, we find that about 0.5 µM of adenosine triphosphate per gram tissue undergoes chemical change in contraction, but the experiment is so crude
that it is of limited value. There are, however, physiologic data which permit calculation of the amount of adenosine triphosphate dephosphorylated in one maximal contraction; and these calculations likewise show that 0.5 µM of adenosine triphosphate is involved in the full activation of one gram muscle.

We arrive, then, at the conclusion that each full contraction of a muscular tissue is correlated with the breakdown of a definite amount of adenosine triphosphate, and that it is the task of respiration—or, to a limited extent, glycolysis—to resynthesize the adenosine triphosphate which has been used in this manner. In the absence of contractile activity, there is only a low rate of adenosine triphosphate-utilization constituting the basal metabolism of the tissue. Activity and the performance of work cause a great increase in the breakdown of adenosine triphosphate, and metabolism increases sharply. In some muscles, the capacity of the oxidative enzyme system is such that the adenosine triphosphate can be synthesized as fast as it is used. Such muscles, of which the heart is an example, can perform continuous duty, and need not develop facility for glycolysis. Other muscles, like most voluntary muscles in the human body, do not have such well-developed provisions for oxidative phosphorylation; upon intense activity, they contract an oxygen debt during which glycolysis covers the demand for adenosine triphosphate somewhat, but in which the store of adenosine triphosphate and phosphocreatine is finally used up till exhaustion.

The participation of adenosine triphosphate in the contractile event itself was demonstrated by the epoch-making observations of A. Szent-Györgyi in the early 1940's. These consisted, first, of a better characterization of the structural protein, myosin. It had been realized that, in order to explain the intricate mechanism of contraction, one has to assume that the fibrils consist of a special protein which is able to execute some intra- or intermolecular rearrangement leading to macroscopic shortening or tension, and it was suspected that a certain protein fraction, myosin, might be an important constituent of this system. The classic work of von Muralt and Edsall had shown that myosin consists of long, possibly rod-shaped, molecules, well suited to act as the structural protein of a fibrous structure, while Weber demonstrated that fibers made out of such myosin possess an optical anisotropy similar to that of the A-band of the fibril. Szent-Györgyi and Straub, however, found that the contractile fibril consists of two major proteins, myosin and actin, which form a complex named actomyosin, which is now held to be the building stone of the fibril.

Interactions between actomyosin and adenosine triphosphate can be demonstrated experimentally. On the one hand—as had previously been discovered by Engelhardt and Ljubimova for "myosin" in the old sense—actomyosin can act as an enzyme which hydrolyzes adenosine triphosphate, an adenosinetriphosphatase or ATPase. This property is localized in the myosin moiety, but the presence of actin modifies its action in some respects. The middle 1940's witnessed eloquent developments of the idea that (acto)myosin is a contractile enzyme, which "picks up" the energy liberated in the reaction it catalyzes and uses it to perform work. The value of this type of consideration has become doubtful, but it is obvious that the adenosine triphosphatase activity of myosin reflects some more intricate interplay between the protein and the nucleotide of which, in the isolated system, only some remnant, namely the hydrolysis of adenosine triphosphate, has been retained. A second type of interaction which demonstrates its applicability to the problem of contractility more directly was discovered by Szent-Györgyi in 1942. Threads spun from an actomyosin solution will contract to one-third of their length upon the addition of adenosine triphosphate in an electrolyte medium of appropriate composition (potassium and magnesium ions). The threads become thinner instead of thicker when contracting and develop practically no tension, but these imperfections are due to the lack of spatial molecular organization. A preparation dis-
covered later by Szent-Györgyi approaches muscle more closely in that the actomyosin structure of the fibril is fully preserved in the original configuration. This is the "extracted fiber bundle" made from the rabbit psoas muscle, which becomes thicker when contracting under the influence of adenosine triphosphate and develops about the same tension as the original muscle. Similar fibers have now been made from the myocardium, and their study holds promise (Taeschler and Bing, Robb and Mallov).

Recently, an important development in Cambridge has for the first time also made the process of relaxation accessible to experimental analysis. Marsh and Bendall discovered a soluble protein in muscle which, when added to a contracted psoas-fiber in the presence of adenosine triphosphate, causes immediate relaxation.

If the actomyosin system is responsible for so many properties of the living muscle, the chemical and physical study of its component proteins becomes a matter of interest. Much of the knowledge in this field is of a highly technical nature and cannot be related in a few words. Some properties of actin, however, are of special interest. This protein can exist in two forms, named globular (G) and fibrous (F) actin. The former is a globular protein with a moderate molecular weight (57,000), the latter is a linear polymer of the G-protein. In the transition of G to F, adenosine triphosphate is dephosphorylated to adenosine diphosphate and causes the transition of actin from the G to F state:

\[ \text{Actin} + \text{ATP} \rightarrow \text{(Actin)}_{\text{polym.}} + \text{ADP} + \text{Phosphate} \]

If all the actin present in 1 Gm. muscle would polymerize once, this would involve the breakdown of 0.5 µM. of adenosine triphosphate, exactly the amount which is dephosphorylated in a fully activated contraction of 1 Gm. muscle. We suppose, therefore, that the polymerization of actin is one of the chemical reactions constituting the contraction process, presumably occurring before and during the rise of tension, and coincidently with the initial heat production.

We can summarize these trends of research in the following four statements: (1) The purpose of metabolism is to generate adenosine triphosphate as it is used. (2) The building stones of contractile fibrils are actin and myosin. (3) Adenosine triphosphate can cause the contraction of actomyosin fibers and also cause various physical changes in less organized actomyosin systems. (4) Adenosine triphosphate is broken down in the polymerization of actin in an amount exactly equivalent to the amount involved in one contraction.

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