It has, of course, been known for a long time that when you work you get tired, and that if you work hard you breathe hard, and when you stop working you keep breathing hard for a while as you recover. It is also clear that walking up a mountain is more tiring than walking down a mountain, although the reason for this is not so obvious as it might appear. Chemical changes in the muscles during exercise have been studied for a remarkably long time. For instance, an increase of lactic acid in the muscles of deers which have been run to exhaustion was discovered by Berzelius in 1841, and as far back as 1871, Weiss showed that the glycogen content of muscles decreased with work. Even the fact that creatine was formed by working muscles was observed by Monari in 1889 and the liberation of inorganic phosphate from an organic compound during activity was recorded by Salkowski in 1890. The work of Fletcher & Hopkins (1907) supported the lactic acid theory of muscle contraction which was based on the belief that the breakdown of glucose to lactic acid was the immediate energy source.

It became known largely through the work of Meyerhof (1920) and his school that inorganic phosphate was required for the metabolism of muscle extracts, but it was not until 1930, when Lundsgaard investigated the metabolism of muscles treated with iodoacetate, that it became clear that muscles could contract and work without making lactic acid.

These treated muscles that did not make lactic acid did, however, liberate inorganic phosphate. The source of this phosphate was called phosphagen. This was quite soon identified as N-phosphorylcreatine in vertebrates and N-phosphorylarginine in most invertebrates. A variety of other phosphate-liberating compounds
have also been found in many different animal species especially worms and leeches (see Ennor & Morrison, 1958). These compounds such as N-phosphoryltaurocyamine, N-phosphorylglycocyamine, N-phosphoryllombricine, etc., are all closely related. They contain a substituted guanidine group which can react with ATP to make a phosphoryl derivative.

Investigations starting 40 years ago showed that these compounds have virtually no separate metabolism of their own and were not broken down enzymically by dialysed extracts of muscle. The material in the muscle which allowed these phosphogens to breakdown was identified first as adenosine monophosphate (AMP) and then finally as adenosine diphosphate (ADP) by Lohmann (1934). The original incorrect identification occurred because of the presence of the myokinase reaction in muscle which can cause an interchange of the adenosine mono, di and triphosphates. Thus it seemed likely that the real energy source and the phosphagen which liberated inorganic phosphate was adenosine triphosphate (ATP). Phosphoryl-creatine was thus an energy store used to replenish ATP as quickly as it was used.

Under conditions of poisoning with iodoacetate, a breakdown of phosphorylcreatine was found to be related to long continued muscle work (Lundsgaard, 1934). However, it proved exceedingly difficult to find any change in a single contraction and impossible to observe significant changes in ATP at that time (Davies, Cain & Dellaqua, 1959; Cain, 1960).

Much work with myosin isolated from muscle by Engelhardt & Lyubimowa (1939) and Szent-Györgyi (1953) with mixtures of myosin and actin showed that the myosin, the main structural protein of muscle, is also an enzyme and can break down adenosine triphosphate. In the presence of actin this reaction is accompanied by mechanical changes which could be related to changes in intact muscle. About the same time, studies on intermediary metabolism showed that ATP is a source of energy. It is made as a result of the breakdown of glycogen by the pathway called anaerobic glycolysis. Later it was also found to be the end product of oxidative phosphorylation. The problem was to show directly that it was the source of inorganic phosphate in working muscle, was directly related to the work done and whether it was used for contraction or relaxation.

The situation was so unsatisfactory in 1950 that Professor A. V. Hill issued his famous "Challenge to Biochemists" to prove that ATP really was associated with contraction in muscle. He pointed out that "---no change in the ATP has ever been found in living muscle except in extreme exhaustion, verging on rigor." Many attempts were made to solve this challenge. Many other sources of inorganic phosphate besides ATP were investigated such as the carnosine di- and mono-phosphates, all the inosine, guanosine and