The presence of an extinct felid highly convergent with the cheetah (*Acinonyx*) in the development of long legs and other specializations for running also draws attention to this aspect of the fauna.

In 1941, Simpson (*1*) reviewed the large Pleistocene felines of North America and concluded that only three groups were present: pumas, jaguars, and *Panthera atrox*. Simpson regarded *Panthera atrox* as a giant form of jaguar, but later work (*2*) has established that it is better interpreted as an American lion. Some of the taxa that he regarded as pumas, such as *Felis inexpecta* and *"Smilodontopsis" mooreheadi* have reduced protocones on the P^4. This same condition is also present in *Felis studeri* and *F. trumani*. Among living felids only the cheetah (*Acinonyx*) has a strongly reduced protocone.

Felis trumani was first described from a late Pleistocene cave deposit in Nevada (*3*). It resembles *Acinonyx* in having (i) small upper canines, (ii) a short face and a broad domed forehead (Fig. 1, a and b), and (iii) enlarged external and internal nares. The skull and mandible of the felid from Natural Trap Cave can be matched almost exactly with that of *F. trumani*, and it is to this species that we refer the Wyoming material. However, it is possible that one of the older names applied to North American cats with reduced protocones on P^4 may prove to be the senior synonym of the late Pleistocene form. The other taxa range in age from late Pliocene (Blancan) to middle Pleistocene. The skeleton of *F. trumani* has the distal segments of the leg elongated as in *Acinonyx* (Fig. 1, c–e). This is especially shown in the metatarsals, which are straight and much elongated.

In spite of the close similarity between *F. trumani* and *Acinonyx*, we regard it as an example of parallelism rather than as a member of the latter genus. The shapes of many of the muscle scars and many details of the skull and skeleton suggests that it may be more closely related to the puma, *Felis concolor*, than to *Acinonyx*. It probably has a long independent history in North America, perhaps derived from Blancan forms related to *F. studeri* (*4*). The history of the cheetah-like cat from the Natural Trap and its North American relatives has been disguised by previous confusion with the puma.

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Possible Cyclic Nucleotide Regulation of Calcium Mediating Myocardial Contraction

Abstract. *An inhibitor of adenylate and guanylate cyclases was tested on strips of left atria from rabbits. Effects of catecholamines (cardiotonic) and of acetylcholine (cardiodepressive) were blocked, and positive force-frequency was converted to negative. Ouabain produced only contracture without positive inotropy. The cardiotonic effect of increased calcium remained. Data suggest that cyclic nucleotides modulate calcium associated with these stimuli.*

It is generally accepted that the effects of a variety of autonomic agonists on myocardial contractility involve alterations of cyclic nucleotide metabolism (*1*). Cyclic adenosine monophosphate (AMP) is thought to exert its inotropic effect through activation of protein kinases with the subsequent phosphorylation of several control sites. Among the suggested effects of cyclic AMP are augmentation of calcium influx associated with a "slow-current" phase of the action potential (*2*), phosphorylation of sarcoplasmic reticulum leading to an increase in calcium accumulation, and beat-to-beat regulation of myocardial contraction (*3*, *4*). It has been proposed that protein kinase catalyzed phosphorylation of sarcoplasmic reticulum may mediate the increase in rate of contraction and relaxation of heart muscle induced by catecholamines (*4*).

The positive force-frequency relationship (Treppe) (*5*) is a fundamental control mechanism for cardiac contractility (*6*). It is generally agreed that an alteration in intracellular calcium concentration plays a significant role and, while several mechanisms have been suggested, the exact cellular mechanism or mechanisms are not yet clearly defined (*7*).

We have studied an inhibitor of adenylate cyclase and guanylate cyclase (*8*) that is capable of blocking glycogenolysis and calcium uptake in cardiac sarcoplasmic reticulum. Cyclic AMP reverses the inhibition (*9*). We now report the effects of the inhibitor on a variety of agonists and perturbations that affect myocardial contractility, presumably, by different mechanisms, but all of which involve calcium (*1*, *2*, *7*).

Rabbits of either sex were stunned by cervical dislocation; the hearts were excised, and the left atria were rapidly prepared according to the methods of Levy (*10*), with one modification. The muscle was cut longitudinally, with one half serving as the experimental tissue and the other as a control. Relative contractile force (F) was measured; its first derivative (dF/dt) was electronically calculated and calibrated. While our data are in the form of dF/dt as the index of contractile response, the same conclusions were reached when relative force was the parameter assessed (data not shown). Excitation voltage was set at 10 percent above threshold (3 to 6 volts), the pulse duration was 3 msec, and the frequency 90 pulses per minute. The preparations were equilibrated for 20 minutes, and during that time the chamber was drained and refilled twice. The total volume of the chamber was 5 ml, and the temperature was maintained at 37°C. Test doses of the agonists (isoproterenol and norepinephrine, 10^{-8} to $10^{-6}M$; calcium chloride, 6 mM; and acetylcholine, $10^{-7}M$) were added sequentially to the chamber allowing force to return to the control level between each agonist. Treppe (that is, force-frequency, Bowditch, or staircase) was elicited by increasing the stimulus frequency suddenly from 90 to 240 pulses per minute and also by progressive increments from 90 to 180, 240, and 300 pulses per minute. After the frequency was lowered to that of the control, the contractile force returned to normal within 5 seconds. Adenylate cyclase inhibitor (ACI) was then added in 100-μl portions. A ve-

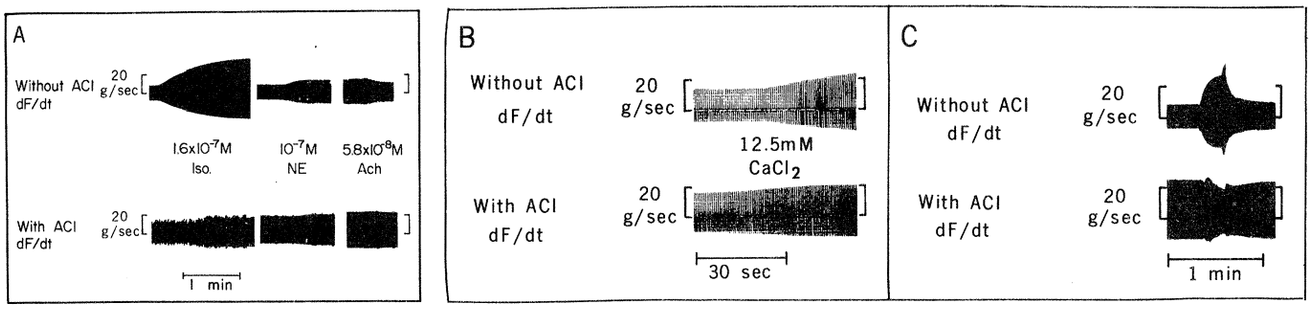

Fig. 1. The effect of adenylate cyclase inhibitor (ACI) on the velocity of contraction (*dF/dt*) as affected by inotropic stimuli. There was no significant difference in the mean values of controls and experimentals. Significant variation occurred so that, in some experiments, day-to-day initial force was higher in control and in others both were approximately equal. The effects of ACI illustrated in these figures were qualitatively the same and were reproduced in 8 to 12 separate experiments. The paper speed is indicated in this and in Fig. 2 by the bar. (A to C) Traces taken from separate experiments. (A) Effects of isoproterenol, norepinephrine, and acetylcholine. (B) Effect of calcium. (C) Influence of ACI on force-frequency (staircase phenomenon). Frequency of stimulation was increased from 90 to 240 beats per minute. Note that ACI converted a positive staircase to a negative one. After increasing the frequency, there was a slight tendency toward a rise in force, but this rapidly led to a negative inotropic state that gradually returned to control after restoration of normal stimulation frequency. The effect of ACI on *dF/dt* as affected by increases in frequency was the same as illustrated in (C) when the stimulation rate was increased in increments from 90 to 180, 240, and 300 beats per minute (data not shown).

hicle solution of 58 m*M* ammonium chloride and 10 m*M* acetic acid was added to the control atrial strip. In some of the experiments an ion-free aqueous preparation of ACI was employed, and the results were identical to those obtained with the buffered preparation. Alkali-digested ACI was prepared as described by Levey and colleagues (*8*). The force-frequency was restudied 10 minutes after each dose. After the positive force-frequency was converted to a negative one, test doses of isoproterenol, norepinephrine, acetylcholine, and $CaCl_2$ were added. After each washing to remove the agonist, the preparations were tested again for a positive force-frequency response; if a response was observed, more inhibitor (100 μl at a time) was added until it was completely abolished. Ouabain was added after the response was abolished.

Epinephrine, norepinephrine, isoproterenol, and the Bowditch frequency effect all produced significant increases in contractility; acetylcholine produced a negative inotropic effect (Fig. 1A). Addition of ACI had no effect on force but after a 10-minute incubation the rabbit atrium showed virtually a complete loss of responsiveness to the above agonists. The preparation was still qualitatively sensitive, however, to an increase in exogenous calcium (Fig. 1B). An increase in frequency which ordinarily augmented contractility (positive force-frequency) resulted in a negative inotropic response after treatment with the inhibitor (Fig. 1C), whether rate was increased in one increment or in multiple increments. In the presence of ACI, ouabain, which is a water-soluble cardiac glycoside, was without effect on contractility when the control atrial strip responded with significant positive inotropy (Fig. 2A). In addition, in every experiment, ouabain produced, in the ACI-treated tissue, a gradual decrease in developed force and an increase in the resting tension to a point of contracture. The contracture phenomenon is illustrated by the upward slope of the base line (Fig. 2B). This effect was independent of electrical stimulation since, once the contracture developed, it persisted although the stimulator was turned off. The mechanism may involve an inhibition of sarcoplasmic reticulum function by the cyclase inhibitor (*9*). These experiments suggest that the toxic action of digitalis, evidenced by contracture, can develop even when not preceded by a positive inotropic phase.

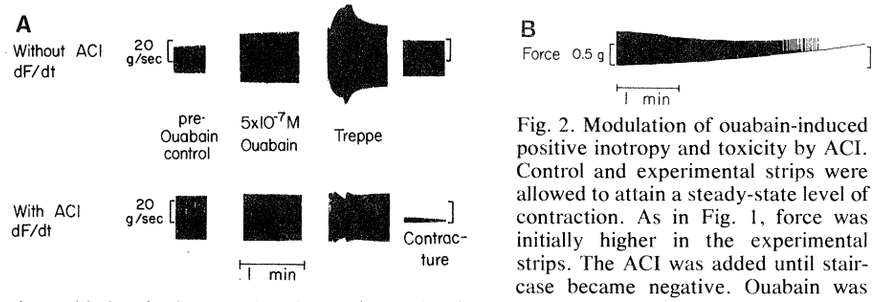

Fig. 2. Modulation of ouabain-induced positive inotropy and toxicity by ACI. Control and experimental strips were allowed to attain a steady-state level of contraction. As in Fig. 1, force was initially higher in the experimental strips. The ACI was added until staircase became negative. Ouabain was then added to both control and experimental strips; the untreated tissue always developed a significant augmentation of *dF/dt* approximately 15 minutes after addition, as illustrated. The ACI-treated strip did not develop positive inotropy. Maximum contraction in the case of the control had not been reached even after a full ouabain effect, since increase in frequency of stimulation (90 to 240 beats per minute) still elicited an increase in force. The ACI-treated strip responded with only negative inotropy. Always, the experimental strip finally produced contracture as illustrated in the force trace of (B). These results were repeated in eight separate experiments.

Alkali-treated ACI, which was inactive on adenylate cyclase (*8*), was also without effect on the atria, and the ACI did not alter the binding of ^{3}H-labeled alprenolol to isolated cardiac membrane fragments (data not shown).

These experiments describe what may be a direct involvement of the adenylate and guanylate cyclases in the mechanism of cardiotonic and cardiodepressant action, respectively, of several agonists and suggest the possibility of a relation between digitalis action and a pool of calcium affected by cyclic nucleotides. The data also suggest that one of the fundamental control mechanisms of heart, namely force-frequency (the response to an increase in frequency), may also relate to this same calcium pool which appears to be responsive to changes in adenylate and guanylate cyclases. While it is possible that changes in frequency alter the availability of catecholamines which in turn interact with the adenylate cyclase causing an increase in contractility, this is unlikely because the positive force-frequency phenomenon does not appear to depend on autonomic innervation or on the presence of catecholamines, and catecholamines are not depleted by increased frequency (*7, 11*).

The relationships of the activator calcium pools, the drug effects, and the positive force-frequency response to functions linked to cyclic nucleotides will be better understood after the active prin-

ciples in the inhibitor fraction have been purified. However, the alkali treatment known to destroy ACI inhibition of adenylate cyclase (*8*) destroys all the biologic effects we describe. Although it is possible that the demonstrated effects are nonspecific, ACI itself had no major effect on basal cardiac contractility and calcium exerted its normal inotropic effect. It seems unlikely, therefore, that nonspecific effects on membranes or other tissue components are responsible for the observations described.

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First Occurrence of the Garnet-Ilmenite Transition in Silicates

Abstract. *Pyrope garnet ($Mg_3Al_2Si_3O_{12}$) has been found to transform to an ilmenite-type phase at a loading pressure between 240 and 250 kilobars and at about 1000° to 1400°C in a diamond-anvil press coupled with laser heating. The lattice parameters for the ilmenite-type phase of $(Mg_{.75}Al_{.25})(Si_{.75}Al_{.25})O_3$ are $a_0 = 4.755 \pm 0.002$ and $c_0 = 13.360 \pm 0.005$ angstroms. The zero-pressure volume change associated with the garnet-ilmenite transition is calculated to be −7.1 percent. This result verifies the prediction that pyrope garnet would transform to the ilmenite structure at high pressure first suggested in 1962 by Clark* et al. *and Ringwood.*

Ferromagnesian garnet $(Mg,Fe)_3Al_2Si_3O_{12}$, especially the magnesium-rich variety, is an important mineral in the earth's upper mantle. Accordingly, studies of phase transformations of pyrope garnet ($Mg_3Al_2Si_3O_{12}$ or $3MgSiO_3 \cdot Al_2O_3$) at high pressure have an important implication for our understanding of the earth's transition zone and the lower mantle.

Clark *et al.* (*1*) and Boyd (*2*) have suggested that pyrope garnet might transform to an ilmenite-type structure at high pressures. This parallels the suggestion by Ringwood (*3*) that the ilmenite-type phase of $MgSiO_3$ would probably display extensive solid solution with Al_2O_3 (corundum, a disordered ilmenite structure in which the cations are identical).

Ringwood and Major (*4*) investigated the system $Mg_3Al_2Ge_3O_{12}$–$Mg_3Al_2Si_3O_{12}$ to 170 kbar at 1000°C in attempting to establish the garnet-ilmenite transition. They observed a series of ilmenite-type solid solutions containing up to 20 mole percent $Mg_3Al_2Si_3O_{12}$. Extrapolation of phase boundaries suggests that pressures of 200 to 300 kbar would be required to transform pyrope to an ilmenite structure (*5*).

I have previously reported that pyrope garnet disproportionates into a mixture of the orthorhombic perovskite phase of $MgSiO_3$ plus Al_2O_3 (corundum) at loading pressures greater than 300 kbar and at about 800° to 1200°C (*6*). Since the zero-pressure density for the assemblage $MgSiO_3$ (perovskite) plus Al_2O_3 is greater than the estimated density for the ilmenite modification with the pyrope composition, it is expected that the pyrope garnet-ilmenite transition, if one exists, should take place before the pyrope garnet breaks down to the assemblage perovskite plus corundum.

Kawai *et al.* (*7*) synthesized a hexagonal form of $MgSiO_3$, which was later confirmed as the ilmenite-type structure by me (*8*). Success in synthesizing the ilmenite-type phase of $MgSiO_3$ would lend considerable support to the possibility of pyrope garnet transforming to the ilmenite structure, representing a solid solution

Table 1. X-ray diffraction data (room temperature and 1-bar pressure) for the ilmenite-type phase of $MgSiO_3 \cdot \frac{1}{3}Al_2O_3$ quenched from a loading pressure of about 300 kbar and temperature of 1000° to 1400°C of pyrope-garnet ($Mg_3Al_2Si_3O_{12}$) with CoK_α radiation; obs, observed; cal, calculated.

I/I_{100}*	d_{obs} (Å)	d_{cal} (Å)†	*hkl*
5	4.46	4.45	003
85	3.51	3.51	012
10	2.98		‡
95	2.592	2.594	104
5	2.48		‡
15b	2.44		‡
40	2.380	2.378	110
100	2.097	2.097	113
< 5	1.93		‡
< 5	1.86		‡
40	1.752	1.753	024
15	1.723		‡
90	1.623	1.625	116
5	1.546	1.548	018
		1.546	211
5	1.518	1.516	122
35	1.410	1.411	214
5	1.392		‡
45	1.373	1.373	030
5	1.269	1.271	1, 0, 10
5	1.258	1.259	119
5	1.188	1.189	220
< 5	1.12	1.126	312
		1.121	0, 2, 10
10	1.080	1.081	134
20	1.049	1.050	315
		1.049	226
		1.017	042
10	1.013	1.014	2, 1, 10
		1.008	1, 1, 12
10	0.9570	0.9575	1, 2, 11
5	0.9430	0.9427	318

*Estimated visually; "b" denotes broad line. †Calculated from a hexagonal lattice cell with $a_0 = 4.755$ and $c_0 = 13.360$ Å. ‡Corresponding to the lines for the orthorhombic perovskite modification.