the leukemic children as well as from their family contacts. Most of the isolates were the polio type 1, 2, and 3 strains with which the community was orally vaccinated during the time of specimen collection. In addition coxsackievirus A9 was isolated from a leukemic child and from one of his siblings and an echovirus type 7 from another leukemic child. No difference was found in rate of poliovirus excretion between the leukemic children and their siblings. Usually the same virus type was isolated from the sick child and the siblings within a family and occasionally from one of their parents.

Summary. Virus isolations were attempted during a 2 year yeriod (1961-1963) from urine samples of 101 children: 42 with acute leukemia, 30 with diseases other than leukemia and 29 healthy children, most of them 2 to 10 years old. Thirty-nine cytomegalovirus isolations were made—18 from 7 of the 42 children with acute leukemia, 12 from 6 of 30 children in the "other disease" group and 9 from 6 of the 29 control children. In addition 5 isolates were obtained from 7 urines of 4 infants with cytomegalic inclusion disease. Adenovirus type 3, the only other virus found in the urine samples, was isolated from 8 of 12 specimens collected over a 5 month period from a child with hypoplastic anemia. Enterovirus recoveries from the throat and stools of the leukemic patients yielded normal patterns for children of the age group studied. Coxsackievirus A9, echovirus 7, and polioviruses 1, 2, and 3 were isolated; the polioviruses were found with high frequency as oral poliovaccines were widely distributed in the community during this study.

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Failure of Integrated Cardiac Action at Supernormal Heart Rates.* (29655)

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It is well known that as the heart rate increases, under intrinsic or imposed drive, processes within the heart accelerate. Refractory periods shorten, electrical and mechani-

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cal responses decrease in duration(1-3). There are limits, however, to how fast a heart and its tissues can be driven(4-6). Some reactions can repeat much more rapidly than can others. An extra electrical response, for example, can occur so early in the cycle that the mechanical reaction is absent or grossly subnormal(7-8). There is also an upper limit to the frequency at which atrioventricular conduction can occur(9). The purpose of the present study was to ascertain the sequence of developing cardiac abnormalities and the heart rates at which they occur as this organ is driven progressively faster. Normally the sinoatrial pacemaker maintains a regularity of heart beat and initiates the excitation which brings about coordinated activity. We wished to determine whether, as has been suggested(10), the node can influence limits of the normality of response to drive from artificial pacemakers.

Methods. The hearts of dogs, anesthetized by intravenously injected Nembutal (30 mg/kg), were exposed by a mid-sternal incision. Artificial respiration was instituted and plastic-shielded electrodes were attached to the surface of the right atrium and to the ventricles for stimulation and recording. In some experiments the sinoatrial node was crushed initially but in others this normal pacemaker was eliminated only after preliminary tests had been made of the heart's ability to maintain coordinated electrical and mechanical activity as the rate of drive was accelerated. Electrograms, electrocardiograms obtained from limb leads, pressure pulses from catheters in ventricles and aorta were registered on a 4-channel Sanborn recorder. Femoral arterial pressure was continuously monitored with a mercury manometer.

A driving stimulator with capability of providing intervals between pulses varying from 995 msec to 60 msec, with less than 1% error in timing, was used. Rate of beat was, therefore governed by control of cycle length. A strength of stimulus slightly stronger than threshold requirement was routinely used. Its strength, however, was doubled and quadrupled at times to determine the effects of driving stimulus strength on the ability of the heart to respond in a fully coordinated fashion. The general characteristics of this stimulator have been described in reports on other studies of the heart's ability to maintain integrated reactions(11).

After ascertaining the nature of mechanical and/or electrical responses at the basal heart rate, the procedure followed was to drive at progressively increasing rates. This was accomplished by a stepwise shortening (10 to 50 msec) of the cycle length. Such reductions were made only after a steady state of response had been established but this normally occurred almost instantly. Driving rates were increased even after some abnormalities of response had developed, to determine the series of changes in response pattern which could develop.

Comparisons of orthodgrade and retrograde actions were made by recording both atrial and ventricular drive effects. To determine the influence of epinephrine and other similarly acting agents on the rate limits of various responses, the drug was given by steady injection at a rate which maintained arterial pressure at 50% above control values.

Results. Hearts varied considerably in rates at which abnormalities developed but the sequence of failure was relatively uniform, though in some hearts certain phases of developing incoordination were not conspicuous. Presence or absence of the sinoatrial node did not significantly influence limits of the normal responses.

The first detectable abnormality to develop as atrial drive rate increased was a ventricular pulsus alternans which increased in magnitude until there was an alternate failure of ejection (Fig. 1). A prolongation of the P-R interval appeared shortly thereafter as driving rate continued to increase. This conduction abnormality developed into a Wenckebach periodicity followed by a 2:1 atrioventricular rhythm.

Mechanical dissociation and failure of atrioventricular conduction occurred at much lower rates of drive than those producing abnormality in electrical responses (Table I). Alternation in electrical responses developed at rates ranging from 293 beats per minute

TABLE I. Rates of Drive at Which Response Abnormalities Appeared.

Occurrence	No. of exp	Rate threshold (beats/min) Range	Avg
A—Accelerating atrial drive			
Ventricular "Pulsus Alternans"	32	154-264	210
PR conduction abnormality	28	256-388	308
2:1 AV rhythm	22	265-445	355
Alternation in auriculogram spike amplitude	24	293-525	446
2:1 Stimulus-atrial electrical response ratio	25	303-575	482
Atrial fibrillation	6	324-575	482
B—Accelerating ventricular drive			
Ventricular "Pulsus Alternans"	24	179-284	220
PR conduction abnormality	19	184-268	235
2:1 VA rhythm	15	197-308	288
Alternation in ventriculogram spike amplitude	15	210-365	290
2:1 Stimulus-ventriculogram response ratio	11	246-480	318
Ventricular fibrillation	5	415-483	449

in some animals to 525 in others. Ultimately, alternation in amplitude changed to a 2:1 stimulus-response rhythm as drive rates were raised to still higher levels (Fig. 2—Table 1-A). This alternate failure or "break off" of response to very rapidly applied stimuli occurred in 25 tests at rates between 303 to 575 beats per minute while atrial fibrillation developed in 6 other tests at rates between 324 and 575 per minute and ventricular fibrillation in one other at a drive rate of 550 per minute. It is commonly thought that fibrillation invariably occurs in cases in which such rapid excitation is applied but in the present experiments it was not an invariable result.

At very fast rates of stimulation 3:1 or even 4:1 ratios developed in a few cases. Drastic increases in stimulus strengths converted 4:1 rhythms back to a 2:1 ratio or a 2:1 rhythm back to a 1:1 response ratio showing alternation in spike amplitude. Epinephrine, norepinephrine and metaraminol bitartrate (Aramine) likewise increased the rate at which integrated responses could be maintained.

When the ventricle was driven directly at increasing rates, essentially the same sequence of phenomena was observed (Table I-B). An alternation in mechanical response occurred first and then a failure of conduction between ventricle and atrium (R-P conduction). Complete dissociation was preceded by a reversed Wenckebach type phenomenon. As shown in Table II, R-P block occurred at a lower rate of drive than did P-R conduction alternation. The rate threshold for mechanical pulsus al-

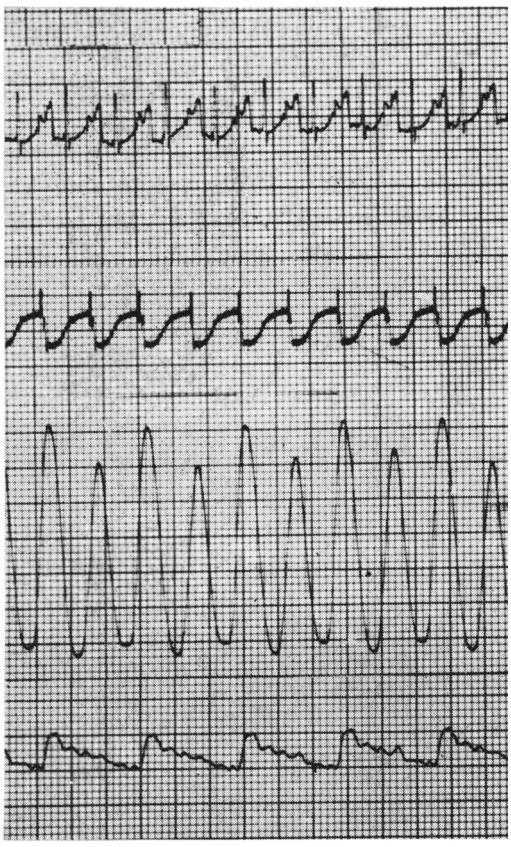

FIG. 1. Atrial drive cycle length 285 msec (210 beats/min). Upper to lower tracings: ECG, atrial electrogram, ventricular and aortic pressure pulses. Note alternation in mechanical response of ventricle and alternate failure of ejection. All electrical phenomena normal.

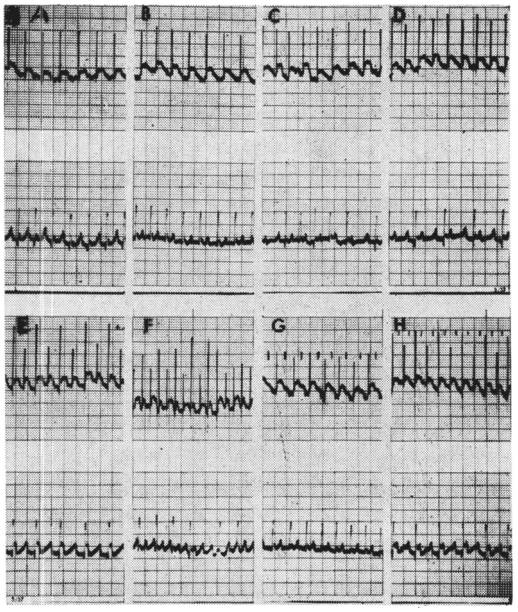

FIG. 2. Atrial electrograms (spikes retouched) and ECG at accelerating rates of atrial drive. Cycle lengths: A = 305 msec (196 beats/min); B = 275 msec; C = 255 msec (note Wenckebach effect); D = 235 msec (2:1 rhythm); E = 195 msec (marked alternation in atrial electrogram); F = (AV 2:1 to 3:1); G = 135 msec (stimulus-atrial 2-1, AV 1:1); H = 105 msec (570 beats/min) (stimulus-atrial 2:1, AV 2:1).

ternans, during direct ventricular drive, however, was higher than in atrial drive even in the same hearts (Table I).

Responses to drive were not always regular particularly when rates were reduced from very high levels. In instances in which 2:1 stimulus-response ratios were attained, sudden reduction to moderately fast rates resulted in irregularities rather than the 1:1 ratio previously seen. Quick jumps upward and downward rather than gradual changes were not well tolerated and fibrillation of atrium and/or ventricle frequently resulted.

Catecholamines and Aramine administration enabled faster follow of a drive. Rate thresholds for failure of V-A conduction, full regular mechanical response, and electrical follow were raised by approximately 10 to 20%.

Discussion. Reviews of cardiology(12) and textbooks of physiology have much to say about the abnormalities of function produced by spontaneous or artificially produced tachycardias. It appears, however, that the heart is quite resistant to disorganization and failure of function if the rate of drive is increased progressively and relatively slowly.

The first process to fail was excitation-contraction coupling. It was not anticipated that atrial drive would produce a ventricular "pulsus alternans" at a lower rate than from direct ventricular drive. This difference might be due to a partial A-V conduction failure though records of the electrical response gave no evidence of such an occurrence.

The observation of Scher *et al*(13) that a V-A conduction failure begins to develop at lower rates of drive than A-V conduction abnormality was confirmed. It is difficult to state just how and where V-A conduction block occurs because it does not appear to interfere with A-V conduction an instant after ventricular drive terminates. The fact that catecholamines can raise the level of rate response abilities is not surprising. It is known that applied drive causes release of catecholamines from cardiac tissue stimulated (14).

Cardiac tissue makes an adjustment to slowly augmenting rates of stimulation if pulses are regular. Ultimately they fall in refractory periods rather than vulnerable periods and a "break off" of response rather than an arrhythmia is the result. It would seem that a sudden change in rate or an irregularity of rate of firing would be the most

TABLE II. Rates at Which AV and VA Conduction Begin to Fail.

Exp No.	Rate threshold atrial drive: Wenckebach effect (beats/min)	Rate threshold ventricular drive: "Reversed" Wenckebach effect (beats/min)
11	324	227, 227, 268
13	293, 293	219
15	293	184
18	347	200
19	375	193
22	285	216
	2:1 Block (A–V)	2:1 Block (V–A)
11	344	308
13	388	279
15	308	209
18	375	285
19	400	214
22	316	230

dangerous defects of an artificial cardiac pacemaker.

The rate thresholds for various abnormalities differed enormously from animal to animal but remained relatively constant in the same heart. Since there was considerable overlap in frequency ranges, the averages obtained were merely approximations of the rates at which particular types of abnormality might be expected. Calculations of deviations from the mean were no more helpful.

Summary. Hearts of anesthetized dogs were driven at slowly accelerating rates from atrial or ventricular electrodes. The rate thresholds for various abnormalities and failures were determined for both types of drive. Pulsus alternans occurs at a slower rate during atrial than during direct ventricular drive. Conduction from ventricle to atrium fails at slower rates than does A-V conduction. Alternation in electrical response voltage and ultimately 2:1 stimulus-electrical response ratios develop at high rates of drive in both atrium and ventricle much more commonly than do fibrillation or other irregularities of response. Sudden changes in rate and irregularities of stimulus pulse spacing are more apt to disorganize cardiac function than are progressive rate changes.

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Excitable Cycle of the Heart as Determined by Mechanical Stimuli.* (29656)

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The excitable cycle of the heart has been defined almost entirely by electrical stimulus testing. This method has shown that absolute and relative refractory periods are followed by a phase of supernormality(1). Within the terminal portion of the relative refractory period there is also a phase of relative supernormality to anodal current. This was referred to originally as a "dip" in the excitability recovery curve(2). During this "dip" phase the myocardium is also vulnerable to fibrillation by supra-threshold electrical pulses(3) and this concept of a vulnerable period in the excitability cycle is generally accepted. The question rises as to whether this is a specific vulnerability to electrical shock only or to all types of stimulation as well.

The period of refractoriness is possibly more correctly spoken of as an unresponsive period since stimuli applied during the relative refractory phase do evoke a response

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