An accelerating ventricular tachycardia ending in fibrillation can be initiated in isolated hearts by procaine injections after the administration of epinephrine, but not in untreated hearts. The run of tachycardia consists of a supraventricular or idioventricular impulse followed by an accelerating train of premature systoles coupled to it. Fibrillation results when the train reaches a frequency of 10 to 12 per second. In hearts with their bundles of His cut, epinephrine injections alone cause only a ventricular tachycardia of constant frequency. Therefore, the initiation of ventricular arrhythmias by procaine must entail the production of A-V blockade and some process which causes the tachycardia to accelerate.

Soon after quinidine was introduced into medicine as a treatment for atrial arrhythmias, it was discovered that it occasionally caused ventricular arrhythmias. In some cases these arrhythmias were fatal. Binder and Rosove have recently summarized the clinical literature on this subject from 1921 onward. Later, procaine, procaine amide and alpha-fagarine were found to behave similarly. Several explanations for this phenomenon have been offered by various investigators arguing chiefly from clinical data and experiments on whole animals. Since there have been no reports of attempts to induce ventricular arrhythmias in isolated, perfused hearts with these substances, we have undertaken to do this.

METHODS
The electric activity of isolated rabbit hearts perfused with Krebs-Henseleit solution by the Langendorff method was recorded in a manner previously described by us. Rapid injections of small volumes of solutions (1.0 cc. or less) were made directly into the perfusion stream about 7 cm. from the tip of the perfusion cannula. Solutions of l-epinephrine bitartrate were made up in one per cent ascorbic acid to prevent oxidation. The vehicle alone had no effect other than a transient one on the T wave of the ECG. Procaine hydrochloride (Novocain) was made up freshly twice a day as a two per cent solution and usually used undiluted.

The bundle of His was transected by a modification of the method of Cullis and Dixon. The right atrial wall was opened until the mouth of the coronary sinus in the septum could be seen. The interatrial septum was then cut from the posterior atrial wall to below this opening in a downward direction. The transection of the septum was continued until the ECG showed that complete heart block has been produced. At the conclusion of the experiment a solution of trypan blue was injected into the perfusion stream. When the dye began to appear in the perfusate, the perfusion was stopped and the heart removed from the apparatus. The heart was dissected to see if all parts of it were evenly colored with dye. If they were not, indicating that the circulation had been grossly damaged by the transection, the experiment was discarded.

RESULTS
The injection of procaine into the perfusion stream never induced a ventricular arrhythmia in an isolated heart which was well washed with the perfusion fluid before the injection. However, when the heart was first treated with 0.1 to 1.0 mg. epinephrine, procaine injections caused ventricular tachycardia ending in either transient or persistent fibrillation in about half of the cases studied and at least a transient ventricular tachycardia in half of the remaining cases.

Various volumes of 2 per cent procaine hydrochloride, ranging from 0.1 to 0.8 cc., were
injected into the perfusion stream in 62 experiments. A negative result occurred in 20, transient ventricular tachycardia developed in 12, ventricular tachycardia ended in transient ventricular fibrillation in 16 and ventricular tachycardia terminated in persistent ventricular fibrillation in 14 experiments. Injections of solutions of lesser concentration than this merely caused a slowing of sinus rate and of conduction, both atrioventricular and intraventricular. Stronger solutions of procaine completely stopped all electric activity of the heart for varying periods that depended on the strength of the solution injected. During recovery the sinus rate was very slow and conduction greatly prolonged, but no arrhythmias developed.

With 2 per cent procaine, 42 out of 62 hearts exhibited ventricular tachycardia at least once following one of four procaine injections. If the first injection failed to cause a persistent ventricular tachycardia, a second injection was given after the conduction effects of the first had worn off, and so on. The result was considered negative if persistent tachycardia did not result from any of four injections. It was scored as "transient ventricular tachycardia" if the tachycardia did not end in either transient or persistent fibrillation. Under the conditions of perfusion in our experiments 0.4 cc. of 2 per cent procaine solution was the dose most likely to produce ventricular tachycardia.

Figure 1 illustrates the course of events in an experiment in which the injection of procaine after treatment with epinephrine caused a persistent ventricular tachycardia and fibrillation. Tracing a shows the ECG during the control period just before the injection of 1.0 mg. of epinephrine. Three minutes later a 0.4 cc. injection of 2 per cent procaine was made at arrow 1 in tracing b. The beginning of the accelerating tachycardia caused by the injection is shown in this record. The end of the tachycardia two minutes later and the beginning of the ventricular fibrillation that ensued are seen in tracing c. The fibrillation was allowed to continue for eight minutes at which time 0.4 cc. of 2 per cent procaine was injected. This stopped the fibrillation and permitted the restoration of the normal sinus rhythm shown in tracing d. The frequency of the tachycardia at the time fibrillation began was measured in several experiments and was found to be between 10 and 12 cycles per second.

Sixteen of the 30 hearts that fibrillated showed only a transient fibrillation. Figure 2c is an example of this showing both the start and end of a short interval of fibrillation which followed approximately two minutes of accelerating tachycardia. The beginning of the latter is shown in 2a and tracing b shows the extent to which it had accelerated 40 seconds later. Spontaneous reversions usually occurred...
Fig. 2. Accelerating tachycardia ending in transient fibrillation. At arrow 1 in a, 0.4 cc. of 2 per cent procaine was injected three and one-half minutes after 1 mg. epinephrine. At arrow 2, the lost supraventricular impulse to which an extrasystole was coupled can be seen; 40 seconds later; c: one and one-half min. later.

within the first minute of fibrillation in these experiments or they did not occur at all.

An invariable feature of the ECG's at the start of the tachycardia caused by procaine in epinephrine-treated hearts is a disturbance of atrioventricular conduction. In some cases there is a complete A-V block lasting for several seconds, the auricles continuing to beat at an only slightly diminished rate. The period of ventricular quiescence is terminated either by automatic idioventricular beats or by supraventricular impulses that finally get through the A-V node. The first ventricular complexes appear to us to be supraventricular in origin; but since, as will be seen later, the same effect was obtained after procaine in hearts with their bundles of His severed, the beats could theoretically also have been idioventricular in origin.

Control observations on the effect of epinephrine injections in more than a hundred normal isolated hearts showed that no premature systoles or arrhythmias were ever produced. They are regularly seen, on the other hand, in epinephrine-treated hearts after the A-V block, just mentioned as due to the injection of procaine, was relieved (arrows marked 2 in figs. 1 and 2). These premature systoles are the first of an accelerating train apparently emanating from the same focus. The excess of procaine required to initiate the accelerating ventricular tachycardia in the epinephrine-treated heart slows the conduction of these premature impulses so that an exact electrocardiographic analysis of them is not possible. However, a dose of acetylcholine that was able to stop the heart completely in the control period had no effect whatsoever on the ventricular tachycardia and fibrillation caused by the epinephrine-procaine sequence of injections, showing that they were ventricular in origin. The statement that all of the oscillations throughout the tachycardia represent premature beats emanating from the same focus is chiefly based on the identical appearance of all of the oscillations with the first few which would generally be considered to be premature systoles, a fact which our records confirm.

Half of the 20 negative results listed in Table 1 were failures to exhibit premature systoles in the first place. The others were cases in which the train consisted of less than six premature systoles.

Injections of epinephrine in hearts whose bundles of His were cut did not cause an accelerating ventricular tachycardia or fibrillation. However, they did cause a discharge of extrasystoles which were coupled to the slow automatic idioventricular beats occurring under these conditions (fig. 3b and c). The premature systoles occurred either singly or in trains which, unlike those caused by epinephrine-procaine injections in normal hearts, reached a constant, relatively slow frequency after a brief initial acceleration (fig. 3b and c). Trains of premature systoles, such as that shown beginning in figure 3b, only occurred after a period of ventricular silence which in this case began in the middle of tracing a seven seconds before the automatic beat and the premature systole coupled to it shown in b. The period of silence usually occurred between 30 seconds and one minute after the injection of 1.0 mg. of epinephrine under our experimental conditions.

The trains of premature systoles shown in figure 3 could be ended by the injection of small amounts of procaine. However, the injection of procaine after epinephrine did not always revert the control to the idioventricular pacemaker. Figure 4 illustrates that in some hearts procaine could initiate an accelerating
The effect of epinephrine on a heart with transected bundle of His. a: 32 seconds after the injection of 1 mg. of epinephrine. Arrow 1 marks the beginning of a seven second period of ventricular silence ending at arrow 2 in record b. c: 26 seconds later. Thirty-six seconds after the end of this record, an injection of 0.4 cc. of 2 per cent procaine stopped the tachycardia.

Tachycardia just as it could in intact hearts. Tracing a shows the train of premature systoles caused by epinephrine one and one-half minutes after the injection had been made. Three and one-half minutes later 0.4 cc. of 2 per cent procaine was injected. This immediately stopped the train of premature systoles and caused a period of ventricular silence that lasted 45 seconds. The end of this period is shown in b. An accelerating train of premature systoles began at this time coupled to an automatic beat arising in the same focus. Tracing c shows the increased frequency of the tachycardia one minute later and the beginning of the brief period of fibrillation that occurred shortly afterwards.

An important feature of record b of figure 4 with respect to the initiation of an accelerating tachycardia by procaine is the widening of the QS complex and the prolongation of the Q-T interval. In this record, the timing of the first three premature systoles is not much different from the control before procaine (record a), but the Q-T interval is lengthened to such a degree that the succeeding extrasystoles take off from the peak of the T wave. In the control (record a), they take off from the isoelectric line.

The response to an injection of epinephrine or to the epinephrine-procaine sequence of injections in hearts with their bundles of His severed was quite variable. Since the response of intact normal hearts to procaine is quite constant, the variability of the response of intact hearts to the epinephrine-procaine sequence of injections noted previously is apparently due to the variable response of the ventricles to epinephrine.

**DISCUSSION**

These experiments indicate that the initiation of ventricular arrhythmias by procaine in epinephrine-treated hearts is due to the production of some degree of A-V block by procaine thereby making it possible for epinephrine to initiate a train of premature ventricular systoles of constant frequency and finally their transformation into an accelerating ventricular
tachycardia by a further action of procaine. In normal isolated hearts, epinephrine alone only causes a sinus tachycardia and procaine alone only a slowing of sinus rate and conduction velocity. When A-V block is produced by cutting the bundle of His, epinephrine can cause a ventricular tachycardia but never an accelerating one ending in fibrillation. It is apparent, therefore, that for procaine to initiate an accelerating tachycardia ending in fibrillation it would first of all have to cause A-V block and secondly, to transform the epinephrine-induced ventricular tachycardia into an accelerating one. Ventricular fibrillation, when it occurs, is a consequence of the accelerating tachycardia reaching a certain critical frequency.

It has been shown previously by others that epinephrine causes ventricular arrhythmias in situations where the ventricles are divorced from atrial control. Rothberger and Winterberg showed that simultaneous stimulation of the cardiac sympathetic nerves and of the peripheral ends of the vagi in dogs caused ventricular premature systoles and tachycardia. Segers found that the perfused frog ventricle isolated from the auricles ordinarily responded to a single shock with only one response. When epinephrine was added to the perfusion medium, a premature systole coupled to the usual response was also obtained. Finally, a run of paroxysmal tachycardia outlasting the stimulation could be obtained if the electrolyte content of the medium were suitably altered besides the addition of epinephrine.

The ability of antifibrillatory drugs to transform ventricular tachycardias of constant frequency into accelerating ones capable of ending in fibrillation has also been observed previously. Scherf and Siedek found that quinine could transform a bigeminal rhythm induced by the injection of small amounts of aconitine into an accelerating ventricular tachycardia and fibrillation, in some dogs at least. In other dogs, however, the same injection caused the aconitine-induced premature systoles to disappear. They found it impossible to predict which effect would be produced by a given injection. Drury, Horsfall, and Munly also found that injections of quinidine in dogs caused the appearance of ventricular tachycardia ending in fibrillation when the ventricles were being stimulated with slow rhythmic shocks which alone only sufficed to drive the ventricles rhythmically at a rate slightly above the sinus rate. They found, by suitable testing, that the doses of quinidine producing this result lengthened the absolutely refractory period and reduced the rate of conduction in the ventricles.

The transformation of a paroxysmal tachycardia into an accelerating one that can end in fibrillation seems to depend on succeeding impulses falling into the recovery phase of the ones preceding them. This could be effected by procaine if it delayed recovery without concomitantly slowing the rate of the tachycardia to an equivalent extent. According to Hoff and Stansfield's analysis of the initiation of ventricular fibrillation in the dog heart by extra impulses fired into a cooled focus, an ectopic beat arising during the recovery phase of a normal beat makes the second of a pair of closely spaced impulses which is the necessary and, in most cases, sufficient condition for the initiation of an accelerating tachycardia and fibrillation. These investigators found that, in quiescent ventricles, two impulses could initiate an accelerating tachycardia when fired into a cooled focus, if the impulses arrived sufficiently closely together at the focus. In some instances three impulses were necessary. Since these experiments show that as few as two closely spaced impulses can immediately cause ventricular fibrillation, it is apparent that the tachycardia initiated by the procaine-epinephrine sequence of injections which starts slowly and accelerates gradually over a period of minutes before fibrillation begins is an artifact due to the presence of an excess of procaine in the tissue fluid. Hoff and Stansfield also pointed out that ventricular fibrillation is the consequence of an accelerating tachycardia no matter how it is produced. The present experiments confirm this assertion and show in addition that the acceleration can be greatly slowed without affecting the outcome. According to Scherf, Schaffer, and Blumenfeld, a
ventricular tachystolic center recruits other similar centers which then become self-sustaining, the result being fibrillation. A single tachystolic center would only result in ventricular flutter.

**Summary**

The ability of procaine hydrochloride to initiate ventricular arrhythmias was studied electrocardiographically in isolated rabbit hearts, perfused with Krebs-Henseleit solution in the Langendorff apparatus.

In about two-thirds of the 60 hearts studied, a gradually accelerating ventricular tachycardia, leading in the majority of cases to a transient or persistent fibrillation, could be initiated by injections of procaine into the perfusion stream after treatment of the hearts with epinephrine, whereas in untreated hearts, procaine had no such effect. The accelerating tachycardia began with a premature ventricular systole, coupled to an idioventricular or supraventricular impulse arising during a period of A-V block caused by the action of procaine, and consisted of a train of premature systoles coupled to the first one. Fibrillation occurred when the tachycardia reached a frequency of 10 to 12 per second. When A-V block was produced by severing the bundle of His, epinephrine only caused the discharge of single premature systoles or trains of premature systoles of constant and relatively slow frequency.

It was concluded that procaine initiates tachycardia and fibrillation in the epinephrine-treated heart, first, by causing A-V block and, secondly, by delaying the recovery of ventricular excitability so that at least one epinephrine-induced premature ventricular systole, appearing by virtue of the A-V block, can fall in the recovery phase of a preceding impulse. This sequence of events is known to be sufficient for initiating a self-sustaining accelerating tachycardia ending in fibrillation.

**Summario in Interlingua**

Le capacitate de hydrochlorido de procaina de initiare arrhythmias ventricular esseva studiate electrocardiographicamente in isolate cordes de conilio, perfundite del solution de Krebs-Henseleit in le apparato de Langendorff.

In circa duo tertios del 60 cordes studiate, un tachycardia ventricular que se accelerava gradualmente e dueva in le majoritate del casos a un fibrillation transiente o persistente poteva esser initiare per le injection de procaina in le fluxo perfusional post que le corde habeva esse tractate con epinephrina. In cordes non tractate con epinephrina, le procaina non produceva un tal effecto. Le tachycardia accelerante comenciava con un systole ventricular prematur, copulate a un impulso idioventricular o supraventricular que se formava durante un periodo de bloco atrio-ventricular causate per le action del procaina, e consisteva de un serie de systoles prematur attachate al prime. Fibrillation occurreva quando le tachycardia attingeva un frequencentia de 10 a 12 per secunda. Quando un bloco atrio-ventricular esseva producite per secar le fasce de His, epinephrina causava solmente le discarga de systoles prematur individual o de series de systoles prematur a constant e relativemente basse frequentias.

Nos concludeva que procaina initia tachycardia e fibrillation in cordes tractate con epinephrina (1) per causar un bloco atrio-ventricular e (2) per retardar le recuperation del excitabilitate ventricular de manera que al minus un prematur e epinephrinogene systole ventricular, que appare gratis al bloco atrio-ventricular, pote cader in le phase de recuperation del impulso precedente. Iste sequencia de eventos es cognosciteinente sufficiente pro initiare un tachycardia accele-rante auto-supportante que se termina in fibrillation.

**REFERENCES**

Heart Rate as a Factor in Production of Vascular Turbulence

Direct observations of flow in femoral arteries of dogs by high-speed cinematography failed to reveal the existence of a transient turbulence during the fast forward flow previously found in the rabbit's aorta (McDonald, 1952). This proved intriguing since the vessels were of approximately the same diameter and the blood of the two species had the same Reynolds' number, calculated in the usual way.

A detailed study of oscillatory flow suggested an explanation: The velocity profile is not parabolic in form as in the case of steady flow; the more peripheral layers move more nearly in phase with pressure gradients than those near the center of the stream. As pulse frequency increases the velocity becomes more nearly uniform toward the center of a tube, the lateral variation in velocity being crowded nearer and nearer to the boundary. This increases the rate of shear in the boundary layers. Since instability occurs when the rate of shear exceeds a critical value an "effective Reynolds number" which takes frequency into account is defined as that of a steady flow having the same maximal drag.

The authors conclude that the critical limit of stability of an oscillating stream depends not only on velocity and diameter of the vessel, but also on pulse frequency. These studies are said to have a predictive value in relation to the nature of flow of blood in arteries of different animals and man.

For details see J. F. Hale, D. A. McDonald and J. R. Womersley; J. Physiol. 121: 629, 1955.
The Initiation of Ventricular Tachycardia and Fibrillation by Procaine in the Isolated-Perfused Rabbit Heart
LEONARD GRUMBACH and V. I. Merrill

_Circ Res._ 1956;4:112-118
doi: 10.1161/01.RES.4.1.112

_Circulation Research_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1956 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/4/1/112