received a diet which was supplemented with unlimited amounts of cabbage. It will be recalled that in a previous experiment cabbage was used as a source of vitamin C in the diet which prevented the development of the renal lesions.

Discussion. The lesions described in this paper are similar to those seen by Harned, Cunningham, Smith, and Clark(9) in their experiments to determine the toxicity of PGA. These workers assumed that the casts are composed of PGA. The same assumption has been made by others(10,11). It is not unlikely that this is true in so far as the yellow casts are concerned, but the hyaline, eosinophilic casts are probably of different composition. We have no information on this point. The development of dilated atrophic tubules is almost certainly due to obstruction by these casts.

The factors which govern the formation of these casts are not known; the influence of fluid intake on their formation and the manner in which a stock diet and cabbage prevent them remain to be studied.

Summary. 1. The administration of PGA to the guinea pig may lead to the development of casts in the renal tubules and to dilation of the obstructed nephrons.

2. The lesions may develop with parenteral doses of 1 mg of PGA daily for 21 days.

3. With daily parenteral doses of 5 mg of PGA the lesions may develop in 5 days.

4. The formation of these casts is not related to the feeding of tyrosine.

5. Scurvy is not a prerequisite for the appearance of the injury.

6. The lesions were not observed to occur on a stock diet containing cabbage. It appears that such a diet offers some protection against the development of the injury.

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Further Studies on Mechanism of Auricular Fibrillation.* (17775)

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The topical application of aconitine on the dog's auricle induces auricular flutter or auricular fibrillation. These arrhythmias are immediately stopped when the area of application is isolated from the rest of the auricles by a clamp, or cooled with the aid of a thermode. Removal of the clamp or cessation of the cooling leads to reappearance of the arrhythmias. The analysis of these tracings does not support a circus movement as the responsible mechanism(1-4). The presence of a focus of stimulus formation must be assumed. In ventricular flutter precipitated by the topical application of aconitine, cooling also stopped the flutter and made sinus rhythm reappear for the duration of the cooling. Ventricular fibrillation, however, never responded to cooling. Evidence was advanced to show that with higher rates of ventricular flutter many centers became active in the ventricles. Therefore, cooling of the original center on which aconitine had been applied did not change the form of the arrhythmia(5).

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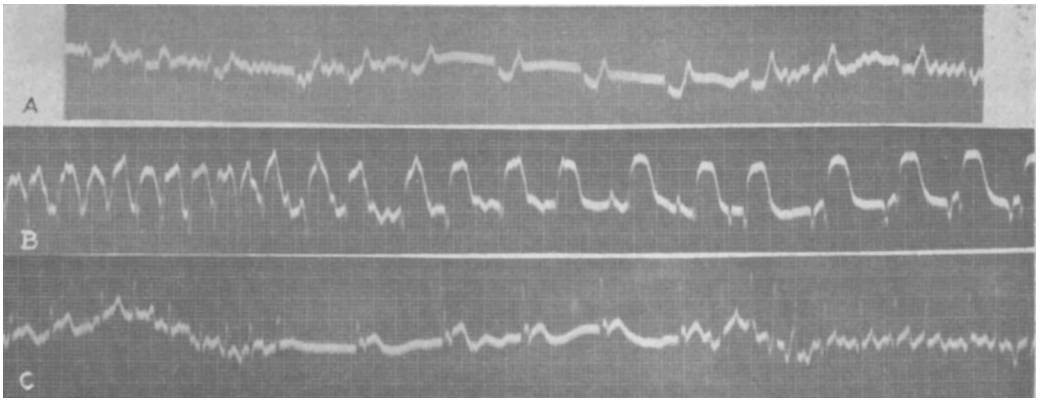

FIG. 1.

Fig. 1a shows temporary disappearance of auricular fibrillation during simultaneous cooling of sinus and A-V node. Fig. 1b shows the disappearance of auricular fibrillation caused by cooling simultaneously the sinus node and A-V node after opening of the right auricle. In Fig. 1c cooling of sinus node and A-V node abolishes fibrillation and A-V rhythm appears with inverted P waves seen after the QRS complexes.

We decided to study the effect of cooling on auricular fibrillation produced by methods other than aconitine.

Method. Dogs were used in all experiments. Nembutal was employed for anesthesia. The sternum was removed after artificial respiration had been started, and the pericardium was opened. In half of the experiments the vagus nerves were severed in the neck. When the vagus nerves remained intact prolonged fibrillation could be more easily produced. Auricular fibrillation was induced by 3 methods. 1. Faradization of the auricles was employed lasting for 30-60 seconds. This type of fibrillation rarely persisted long enough to permit experimental study. 2. In a few experiments prolonged fibrillation of the auricles appeared following rapid stimulation with rhythmic electrical shocks. They were applied with the aid of an electrodyne research stimulator with a frequency of 500 stimuli per minute. 3. The most effective method was the application of a small strip of filter paper moistened with a concentrated solution of acetyl choline (Roche), to the area of the sinus node. The solution used contained 0.1 g of the crystals dissolved in 2 cc of distilled water. With this method(6) prolonged auricular fibrillation always appeared. Satisfactory results were also obtained when 0.05 cc of the solution of acetyl choline was injected sub-epicardially into the area near the head of the sinus node. Prolonged auricular fibrillation was necessary as only those experiments in which cessation of cooling allowed the fibrillation to reappear immediately could be evaluated. Cooling of the sinus node and of the auricular part of the A-V node was accomplished by the application of ice cold water in a glass tube, or by direct application of ice cubes on these areas. The latter method had the disadvantage that water from the melted ice spilled over the ventricular surface and deformed the ventricular complexes by depolarization currents. The A-V node was cooled in 3 ways. 1. By pressure with the thermode against the outer lateral wall of the right auricle, towards the lower wall of the right auricular septum in the area of the A-V node (coronary sinus node). 2. The heart was lifted from its bed by elevation of the apical area, and the A-V node was cooled through the thin walled coronary sinus vein at its orifice in the right auricle. It had been demonstrated before that warming this area invariably elicited coronary sinus rhythm with deeply inverted P waves(7). 3.

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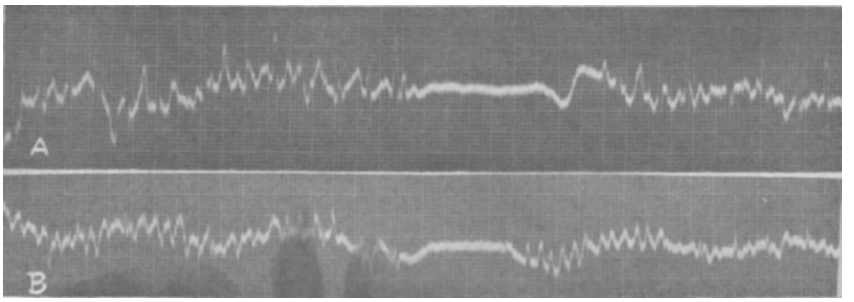

FIG. 2.
The tracings show temporary cessation of auricular fibrillation caused by cooling both the sinus node and the coronary sinus node through the coronary sinus vein. In the bottom tracing (Fig. 2b) flutter appears at the end of fibrillation and after the cooling thermode is withdrawn.

The superior and inferior vena cava were clamped and the auricle quickly opened so that the thermode could be applied on the area of the auricular part of the A-V node near the orifice of the coronary sinus vein. All electrocardiograms were taken in lead II.

Results. The experiments revealed that it was not possible to stop auricular fibrillation induced by any of the methods mentioned above, neither by cooling the stimulated area nor the area of application of acetyl choline. Even prolonged cooling of the whole sinus node was ineffective. The auricular fibrillation elicited by all three methods cited above always disappeared, however, for the duration of the cooling, when the area of the sinus node *and* of the auricular part of the A-V node were cooled simultaneously.

Fig. 1a, shows auricular fibrillation which had appeared after the application of acetyl choline to the area of the head of the sinus node. Cooling of the sinus node alone did not affect the fibrillation. Simultaneous cooling of the sinus node and of the area of the upper portion of the A-V node, through the wall of the right auricle, abolished the auricular fibrillation, and an A-V rhythm appeared. No P waves are visible. As soon as the fibrillation stopped, the cooling was discontinued and within a few seconds fibrillation started again.

In another experiment (Fig. 1b) auricular fibrillation was induced in the same way as in the experiment discussed above. The superior and inferior vena cava were clamped and the auricle was quickly opened. The sinus node area and the area around the orifice of the sinus vein were simultaneously cooled; the fibrillation stopped and an A-V rhythm appeared with deeply inverted P waves preceding the QRS complexes. The ventricular complexes are deformed because the cooling of the sinus node was accomplished by means of a small ice cube and parts of the ventricular surface became depolarized by water from the melting ice.

Fig. 1c shows auricular fibrillation which appeared after the injection of about 0.05 cc of the solution of acetyl choline subepicardially into the area of the head of the sinus node. Simultaneous cooling of the sinus and A-V nodes abolished the fibrillation and an A-V rhythm with an inverted P wave between QRS and T replaced it. After interruption of the cooling, the fibrillation started again within 2-3 seconds. In this experiment, the A-V node area was cooled by pressing the thermode towards the wall of the right auricle in the area of the orifice of the sinus vein.

The tracings in Fig. 2 were obtained in 2 experiments in which auricular fibrillation was established by the application of acetyl choline on the sinus node. The heart was lifted from its pericardial bed by elevating the apex and the sinus node was cooled with one thermode while another thermode was applied to the area of the coronary sinus node (upper A-V node), through the terminal part of the sinus vein. In both experiments the cooling was stopped as soon as fibrillation disappeared. The tracings show the immediate reappearance of fibrillation with discontinuation of the cooling. In the lower tracing the heart was

lifted out of its pericardial cradle to such an extent that ventricular complexes are almost invisible. This tracing shows the slowing of the fibrillation to flutter before its disappearance, and the appearance of flutter changing quickly to fibrillation after the interruption of the cooling.

These results are the more remarkable because stretch and pressure tend to prolong the fibrillation or to establish it again once it disappears. Stretch and pressure were unavoidable during the cooling. The combined cooling was successful in 16 experiments on dogs weighing about 6.5 kg in which acetyl choline was used to initiate auricular fibrillation. Only in 3 large dogs, all weighing over 18 kg, were we unsuccessful in stopping the fibrillation induced by acetyl choline, by the combined cooling of the sinus and A-V nodes. In 2 experiments long lasting auricular fibrillation following faradization was abolished by the combined cooling and returned a few seconds after discontinuation of the cooling. The same observation was made in 2 experiments in which persistent auricular fibrillation appeared after the intravenous administration of pilocarpine and faradization. Whenever the fibrillation reappeared after it had been abolished by cooling, the renewed simultaneous cooling of the sinus node and the auricular parts of the A-V node re-established sinus rhythm. In one experiment prolonged auricular fibrillation had appeared after the subepicardial injection of Veratrine in the area near the head of the sinus node and in 3 experiments it followed rapid rhythmic stimulation of the auricle with 500 stimuli per minute. Combined cooling of the sinus and the A-V nodes abolished temporarily the fibrillation in each of these experiments.

Discussion. Auricular flutter and fibrillation elicited by the focal application of aconitine on the dog's auricle disappears when the focus is cooled. However, the auricular fibrillation caused by faradization, or by rapid rhythmic stimulation of the auricle, or by the focal application of acetyl choline are not stopped by cooling either the area of stimulation or the area of application of acetyl choline. This different response suggests that we are not justified in considering fibrillation to be due to a single mechanism. Different forms with different mechanisms may exist as has been known for some time regarding extrasystoles. However, combined cooling of the sinus node and the auricular portion of the A-V node repeatedly abolished the fibrillation in 24 of 27 experiments. Only in 3 dogs with large hearts were we unsuccessful in changing the fibrillation to sinus rhythm by this method. Interruption of the cooling brought forth fibrillation again within a few seconds. Since in almost all dogs investigated by Lewis the circus wave moved up or down the sinus node, it is interesting to note that cooling of the whole length of the sinus node did not abolish the types of auricular fibrillation discussed in this paper. The reappearance of the fibrillation once the cooling was interrupted is not compatible with a circus movement mechanism. A circus movement once arrested cannot later continue its way. A rapid stimulus formation in a center or centers is the other alternative. We consider it probable on the basis of these experiments that a rapid stimulus formation in one center leads to the same process in other centers, and thus, a rapid stimulus formation in the sinus node may also cause rapid stimulus formation in the A-V node. The possibility of rapid stimulus formation in the A-V node being responsible for auricular fibrillation has been stressed before. Haberlandt found the sinus beat regularly during auricular fibrillation caused by faradization of the frog's heart(8). Since the magnitude of the negative after potential is increased by rapid stimulus formation under certain conditions(9), the awakening of several centers is possible. The possibility that fibrillation is due to multifocal stimulus formation was often discussed before the circus movement theories were developed. It has been demonstrated that rapid stimulation in one ventricle may lead to the awakening of heterotopic centers in the other ventricle(5). The reason why the activation of other centers is so rare when aconitine is employed and is so common when fibrillation is caused

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by the measures discussed in this paper is not known. Aconitine, according to our results, causes auricular fibrillation by rapid stimulus formation in *one* center while in the other types of auricular fibrillation investigated by us more than one center is active.

Summary. Auricular fibrillation caused by electrical stimulation of the auricles or by the application of acetyl choline to the area of the sinus node is not stopped by cooling the area of stimulation or cooling of the site of application of the drug. In 24 of 27 experiments, however, the simultaneous cooling of sinus and A-V nodes terminated the auricular fibrillation. Interruption of the cooling caused the auricular fibrillation to recur.

The experiments are evidence which tends to support the theory that in some forms of auricular fibrillation more than one center of rapid stimulus formation is active. They speak against the presence of a circus movement.

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Gonadectomy and Ovarian (Spleen) Grafts and Growth of Normal Male and Female Mice.* (17776)

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The more obvious end results of castration have long since been recognized as the complete failure of humans or the lower animals to undergo the body changes of normal puberty. Although individuals in the condition of acute gonad deficiency will continue to grow to or beyond adult proportions, the resulting state represents the persistence of a neutral or asexual form. It is in effect an expression of the growth impulse of the body in the absence of functioning gonads and their physiology. The effects of castration on body vigor lend themselves to objective experimental investigation. There is some degree of controversy among investigators concerning the effect which gonadectomy has on the growth of laboratory rodents. Slonaker(1) observed greater body weight in castrated male rats although Stotsenburg(2), and Hatai (3,4) working with albino rats, reported that castration did not make any material difference in the body. Masui and Tamura (5) reported that castration did not affect growth of mice. Tang(6), Evans and Simpson(7), van Wagenen(8), Korenchevsky and Dennison(9), and Lawless(10), all of whom worked with rats, found that castrated male rats were lighter than their controls. Mice bearing active androgenic ovarian grafts do not assume a growth pattern comparable to that of normal males(Hill)(11).

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