going on while the blood phosphate is still in the rachitic range. We therefore conclude that a definite deposition of calcium salts may occur before the blood phosphorus regains its normal level. We have as yet no experiments in which the rats were carried through till the healing process was complete, but if we may draw analogies from the work of Howland and Kramer on human rickets, we ought to find that when healing is complete the blood phosphate will regain and maintain its normal level. It seems therefore that calcification is not directly controlled by the level of the blood phosphate. Experiments are, however, in progress to determine the nature of the relation between these two factors.

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Experiments with quinidine on conduction and on the refractory period in the dog's heart.

By ALFRED E. COHN and ROBERT L. LEVY.

[*From the Hospital of the Rockefeller Institute for Medical Research, New York City.*]

These experiments are based on the theory of fibrillation developed by Garrey and Mines on the suggestion of A. G. Mayer and recently elaborated by T. Lewis. The theory, although it illustrates best the condition known as flutter, is directly applicable also to the state of fibrillation. In the normal heart the stimulus for contraction arises at the sinus node and passes in a radial fashion to the rest of the muscle of the auricle. In flutter, and in fibrillation, there is apparently no fixed point at which the stimulus originates. It appears to be dislocated from the node but it is not yet known what activity goes on in this structure when the abnormal rhythm prevails. Instead of the usual arrangement, an excitation wave courses continuously through the muscle of the auricle, usually over a circular path about the openings of the great veins, as Lewis's experiments show. In order that a continuous circuit may be maintained it appears to be necessary (1) that the path shall have a sufficient length; (2) that the rate of passage shall be sufficiently slow, and (3) that when the stimulus returns to its starting point, the muscle is ready to receive it. It is clear, on this plan, that: (1) if the muscle

mass involved is too small, a path long enough to permit the development of a circus becomes impossible; (2) if the rate of conduction is too fast, the stimulus returns to its starting point before the muscle at that point is ready for its reception; (3) if the refractory period of the muscle at the starting point is prolonged beyond the time consumed by the stimulus to make its circuit, the muscle cannot be reëxcited. The establishment and maintenance of circus movement depends then on (1) a large mass of muscle; (2) a slow rate of conduction, and (3) a brief duration of the refractory period.

When it became clear to us after trial in patients that with quinidine one could terminate the state of fibrillation in about half the individuals afflicted, we began early in 1921 to examine the nature of the activity of this drug. Certain effects which we found the drug to possess on the heart and circulation we reported to this Society at its meeting on May 18, 1921. At that time we reported that the study of its effect on the rate of conduction of impulses through the muscle was under way. We have since added to these studies an investigation of its effect on the duration of the refractory period. On these two phases of the subject we report now.

During the course of our work, Lewis's report dealing with the same phases of the subject has been published. Although the general viewpoints of the two researches are the same, they show a certain difference in that we have attempted to maintain the conditions of the experiments as nearly natural as possible and have, perhaps, in consequence of this difference in plan, arrived at somewhat different results.

These experiments were carried out on dogs, anesthetized with ether only. Artificial respiration, at constant pressure and volume, was maintained by the method of Meltzer and Auer. The chest was split and the right auricle exposed by an incision of the pericardium. A wick was sewed to the heart near the base and another near the apex of the auricular appendix. The two wicks led to non-polarizable electrodes. These electrodes formed parts of two separate galvanometer circuits which were completed by indifferent electrodes inserted in the muscle of the chest wall. Electrodes were also placed on the right fore and left hind limbs.

Records at suitable times and for different purposes were then obtainable of the usual lead 2, and of excitation at the base and at the apex of the auricle. A combination of any two records could be taken. Electrodes for sending break shocks into the auricles were permanently fixed in the auricle near the sulcus terminalis. The vagi remained undisturbed. The rate of the heart was natural. By taking simultaneous records of the excitation at the base and apex of the auricle, the distance between the electrodes being known, the rate of conduction could be calculated. The refractory period could be known exactly by obtaining and arranging in series the duration of the periods after the waves of auricular activity which the break shock terminated (Table I). These periods fall into two groups: those in which the break shocks fail to elicit a response, and those which bring about a response. The longest of the periods after which a shock fails to elicit a response is the refractory period. The break shocks were signalled by a special device to the camera and were photographed. They were likewise signalled and inscribed on the smoked record of the blood pressure. Records were made before and after injecting quinidine.

We report now on six experiments (Table II). The refractory period rose in four: 0.0042 sec. (Exp. 39), .0502 sec. (Exp. 47), 0.0336 sec. (Exp. 48), 0.0120 sec. (Exp. 46), and fell in two: 0.0101 sec. (Exp. 41) and 0.0084 sec. (Exp. 42). In two the change, one upward and one downward, was insignificant (Exps. 39 and 42). The rate of conduction fell in four (Exps. 39, 42, 46 and 47), and remained practically unchanged in one (Exp. 48). In experiment 41, the change in this rate is unknown. It is important to point out that after injecting quinidine the heart rate rose 4 times (Exps. 39, 46, 47 and 48). In experiment 46, the rate fell after subsequent injections. In two experiments (Exps. 41 and 42) the rate fell though the change was slight. In the cases in which the rate rose there was an increase in the duration of the refractory period. This result is contrary to what is anticipated, for with a rise in rate, Lewis's experiments lead one to expect a fall in this measurement. In cases in which the rate fell, there was a fall also in the length of the refractory period.

If the circus movement, as it is now believed, underlies the state of fibrillation, and if it depends on the factors which have

TABLE I.

EXPERIMENT 48.

Male Dog—8.0 kgm.

Refractory Periods.

	Before Quinidine.	After Quinidine. 0.02 gm. (Intravenous).
No responses.....		.0825
		.0844
	.0560	.0876
	.0601	.0904
	.0605	.0915
	.0607	.0917
	.0653	.0917
	.0655	.0941
	.0663	.0950
	.0666	.0985
	.0678	.0989
	.0695	.1000
	.0699	.1061
	.0700	.1066
	.0708	.1078
	.0754	.1079
Ref. period.....	.0763	.1099
Responses.....	.0766	.1106
	.0770	.1114[1]
	.0792[1]	.1123[1]
	.0812	.1129
	.0827	.1135[1]
	.0844	.1138
	.0855	.1145
	.0859	.1161[1]
	.0861	.1194
	.0868	.1200
	.0892[1]	.1207
	.0960	.1211
	.0970	.1219
		.1222
		.1228
		.1232
		.1234

[1] No responses.

been discussed, an action of quinidine calculated to bring this activity to an end should consist in increasing the rate of conduction and in lengthening the refractory period. In point of fact our experiments show that quinidine affects one of these factors (the refractory period) favorably, but not the other (the rate of conduction). And it affects the refractory period favorably in the doses we have used, in spite of the rise in rate which the drug

TABLE II.
EXPERIMENTS WITH QUINIDINE.

	Exper. 39. Male 19.9 kgm.		Exper. 41. Male 11.6 kgm.		Exper. 42. Male 15.5 kgm.		Exper. 46.				Exper. 47. Male 13.0 kgm.			Exper. 48. Male 8.0 kgm.	
	Before Quinidine.	After Quinidine 5×0.05 gm.[1]	Before Quinidine.	After Quinidine 0.05 gm.[1]	Before Quinidine.	After Quinidine 0.06 gm.[1]	Before Quinidine.	After Quinidine 0.05 gm.[1]	After Quinidine 0.07 gm.[1] Total 0.12 gm.	After Quinidine.	Before Quinidine.	After Quinidine 0.01 gm.[1]	After Quinidine 0.03 gm.[1] Total 0.04 gm.	Before Quinidine.	After Quinidine 0.02 gm.[1]
Heart rate	150	180	220	210	185	165	154	178	128	110	140	215	220	165	205
Refractory period	0.0982	0.1024	0.0792	0.0691	0.1066	0.0982	0.0572	—	0.0692	—	0.0434	0.0812	0.0936	0.0763	0.1099
Rate of conduction (mm. per sec.)	1,728	1,351	—	—	1,033	957	1,121	1,082	744	824[2]	2,637	—	2,474	769	762

[1] Quinidine was injected intravenously.

[2] 12 minutes after the preceding conduction rate.

brings about. Under the circumstances, it is necessary to conclude that the effect on the refractory period is the more important. It is also a matter of interest that the dogs are not affected uniformly by the drug. It is to be recalled that a similar lack of uniformity in action exists in patients. We have, as yet, no explanation of this phenomenon. Muscular irritability is a third factor which must be considered in this connection, but a discussion of this, as well as of the details of the experiments now described and of those formerly reported, we reserve for the full account of our studies.

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The acid base equilibrium of the blood following vigorous muscular exercise.

By DAVID P. BARR.

[*From the Russell Sage Institute of Pathology and the Second Medical Division of Bellevue Hospital, New York City.*]

Immediately following short periods of vigorous muscular work, there is a marked reduction in the bicarbonate content of the blood, a phenomenon observed by Christianson, Douglass and Haldane in 1914.[1] The initial purpose of the present investigation has been to discover what changes in the reaction and the CO_2 tension of arterial blood accompany the diminution in bicarbonate. For this purpose, four individuals without demonstrable organic defects but of varying grades of apparent fitness were selected for experiment. Each did on a Krogh bicycle ergometer a standard amount of exercise which consisted of the performance of approximately 3,500 kilogrammeters of work in three and a half minutes. The method employed upon the blood is that introduced by Henderson and Haggard[2] and consists in the simultaneous determination of the carbon dioxide absorption curve of blood at body temperature and the carbon dioxide content of the arterial blood as it occurs in the body. The reaction of the arterial blood is calculated from the $H_2CO_3/BHCO_3$ ratio after the formula of Hasselbalch. Arterial blood was drawn from the brachial or

[1] Christianson, J., Douglass, C. G., and Haldane, J. S., *Jour. Physiol.*, 1914, xlviii, 244.

[2] Henderson, Y., and Haggard, H. W., *J. Biol. Chem.*, 1919, xxxix, 163.