EXPERIMENTAL CARDIAC ARRHYTHMIAS AND QUINIDINE-LIKE DRUGS

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The purpose in writing this review has been to examine the methods for producing cardiac arrhythmias in experimental animals; firstly as evidence of the fundamental nature of these disorders of rhythm, and secondly as instruments in the quantitative assay of quinidine-like drugs. The literature on the subject is full of theories about the mechanism of these fascinating arrhythmias, but hard facts are hard to obtain. For in the whole animal there are seemingly endless variables which may influence the result of any experimental procedure.

Probably the most complex method for producing ventricular fibrillation is that which originates from the investigations of Levy (109–111) on the combined action of chloroform and adrenaline on the circulation of the cat. In this method two substances are used, both of which have direct actions upon the heart muscle, and both of which are also capable of causing reflex changes in the circulation. Yet even in such experiments in the whole animal analysis has revealed some of the individual influences which determine whether or not disorders of rhythm shall occur.

The complexities of this problem have presented such a clear challenge to investigators that it is no coincidence that so much original work has followed Levy's brilliant exposition. And it is from this work that much of our knowledge about the physiological variables in arrhythmias is drawn.

THE INFLUENCE OF CHANGES IN THE ARTERIAL BLOOD-PRESSURE

In 1914 Levy (111) wrote that "throughout a long series of experiments with adrenalin the onset of ventricular fibrillation has borne no relation to the height to which the blood pressure has been raised and the supposition of a causal relationship is thereby largely negatived." Many others since his time have made the same observation, but they, like Levy, felt that the point required further investigation.

Levy found that in cats compression of the aorta gave rise to ventricular extrasystoles, attributed to the increased intraventricular tension. But he did not believe that this phenomenon was causally related to the development of ventricular fibrillation under chloroform-adrenaline treatment in the cat, since these rhythmic ventricular extrasystoles were also observed under ether anaesthesia, during which injection of adrenaline did not lead to ventricular arrhythmias. Nevertheless he also found that "when the circulation becomes depressed, as in the case of loss of blood or some other cause" existing cardiac irregularities disappeared; and he concluded that a certain degree of intracardiac tension, about 100 mm. Hg. or over, favoured the development of ventricular extrasystoles and fibrillation. Yet a rise in blood pressure was not necessary for their appearance, as he also showed in an experiment in which the right stellate

ganglion in six cats was stimulated during light chloroform anaesthesia. Ventricular fibrillation resulted in four of these animals, and in two was preceded by no alteration in mean arterial blood pressure. Subsequent investigations have done little to make us modify Levy's original conclusions that while the absolute blood pressure level may influence the outcome of adrenaline injection into such animals, the relative change of pressure which occurs after the injection is not the crucial factor.

In 1938 Shen (177) reopened the question. The introduction of substances like F933 and F883 and the further analysis of the mode of action of yohimbine, which showed that it too possessed the property of suppressing or reversing the pressor action of adrenaline, yielded pharmacological tools for testing Levy's conclusions. In dogs under chloroform, the administration of adrenaline after a sufficient quantity of these adrenolytics had been given to abolish its vasopressor action, did not lead to ventricular fibrillation, and Shen concluded that the abrupt and intense rise of blood pressure must normally play a considerable part in its production. The next year however, van Dongen (198) showed that F933 in similar doses in cats and rabbits not only suppressed "heterotopic rhythms" caused by adrenaline and barium chloride, but also raised the resistance of the heart to fibrillation induced by electrical stimulation. These latter actions could hardly be explained by abolition of the pressor response to adrenaline and as a result in 1940 Shen and Marri (179) reconsidered the position after making further observations with a number of other substances, including F1262. Bovet, Fourneau, Tréfouël and Strickler (25) had introduced F1262 by showing that, although closely related chemically to F933, it did not abolish or reverse the pressor action of adrenaline; yet in the rabbit and dog it protected against ventricular fibrillation induced by electrical stimulation, barium chloride and aconitine, and prolonged the refractory period of the frog's heart. Shen and Marri (179) also showed under their own conditions that F1262 prevented ventricular fibrillation caused by administration of benzol and adrenaline. But they injected adrenaline at the same time as F1262, and though as Bovet *et al.* had shown, F1262 does not reverse the pressor action of adrenaline, it does itself cause a large fall of blood pressure. In those instances, therefore, where Shen and Marri obtained protection against benzol-adrenaline fibrillation, the injection had in fact caused a fall in blood pressure and not a rise. As they pointed out, this hardly constituted a fair test of the properties of F1262; on the other hand, if the adrenaline were given 5–60 minutes after the injection of F1262, fibrillation occurred. Since nothing was known of the rate of disappearance of F1262 from the blood stream, no firm conclusions could be drawn. At the same time Shen and Marri reported a further experiment in which it was shown that during benzol inhalation the introduction of 200 γ/kg. adrenaline into the pericardial sac of a dog caused a slow rise of blood pressure, some irregularities but no ventricular fibrillation; later 20 γ/kg. adrenaline intravenously caused a rapid rise of pressure, fibrillation and death. They therefore concluded, considering the evidence then available, that "the joint influence of benzol and adrenaline plus the abrupt arterial hypertension may represent the most potent stimulating

pattern for the production of ventricular fibrillation." Perhaps it would be fair to say that a number of observations had been made consistent with the hypothesis that the rise in pressure after adrenaline-injection was important; on the other hand, it had also quite clearly been demonstrated that the substances involved did have a direct action on the myocardium.

The war then intervened and put a stop to this work. It was started again in the United States with two minor changes. The widespread use of cyclopropane had attracted the attention of investigators to its action upon the myocardium, and cyclopropane rapidly displaced chloroform or benzol as the "sensitising" inhalant anaesthetic in Levy's classical manoeuvre, and dogs were therefore substituted for cats. The reason for using dogs is due to the observation that cyclopropane is more effective than chloroform in the dog (8, 125) and perhaps also to the impression that the reactions of the dog might be more akin to those of man. Secondly, the adrenolytics used before the war were replaced by dibenamine.

Moe, Malton, Rennick and Freyburger (130) and Nickerson and Nomaguchi (142) simultaneously published in 1949 a very interesting analysis of the problem. It was found that in dogs larger doses of dibenamine and priscol were required to protect against cyclopropane-adrenaline induced ventricular irregularities than were required to reverse the pressor response to the same dose of adrenaline. Conclusions of a similar nature were also arrived at in man. On the other hand, ergotamine 0.16 mg./kg. was found to protect against four times the previously effective dose of adrenaline without preventing the pressor effect. Clearly then, the protective action of these adrenolytics was not necessarily related to their ability to abolish the pressor response. Nevertheless, conclusive proof followed that the level of the blood pressure was of importance in relation to this phenomenon. It was found that if dibenamine or a similar blocking agent were given in a dose just adequate to prevent ventricular arrhythmias on administration of adrenaline in presence of cyclopropane, then elevation of the blood pressure, either by means of a regulator in the peripheral circulation or by compression of the aorta, caused the reappearance of ventricular tachycardia or even ventricular fibrillation. A sudden rise of pressure was not necessary; an elevation of the mean pressure was quite effective provided it was of sufficient duration. Nickerson and Nomaguchi (142) emphasize this point, that short periods of hypertension lasting 5–10 seconds lead to few irregularities, and that irregularities persist for up to 10 seconds after a prolonged rise of pressure has been released. Conversely, Moe, Malton, Rennick and Freyburger (130) showed that if the pressor response to adrenaline were limited to only 5–10 mm. Hg. by their peripheral pressure-regulator, then the ventricular tachycardia was prevented. In some experiments eight times the previously effective dose of adrenaline caused no irregularity when the pressure-regulator was in operation. These observations are not in fundamental disagreement with those of Murphy, Crumpton and Meek (136) who found that ventricular tachycardia can still occur when the pressure rise has been virtually prevented by a similar type of stabilizer, since they also found in other dogs treated with cyclopropane and adrenaline that ventricular tachycardia did

not occur unless the blood pressure was allowed to rise. There seems little doubt from the published accounts of these experiments that the part played by the level of the blood pressure varies considerably according to the experimental conditions, the quantity of adrenaline used, perhaps the depth of anaesthesia and the individual animal. If we accept the view that the general level of the blood pressure is only one of many variables in determining whether or not ventricular arrhythmias may ensue, then the various observations are mutually reconcilable. It is quite clear that it is not the crucial factor under all circumstances, and so far it has only been incriminated as a factor at all in cyclopropane-adrenaline arrhythmias.

There are, however, a number of considerations which suggest that it may be profitable to explore the possibility that the blood pressure level is of importance in the development of other forms of ventricular and perhaps of auricular disorders. There is to start with, the often quoted observation by Rothberger and Winterberg (1910) (158) of ventricular premature contractions and a bigeminal rhythm following a rise of systemic arterial pressure due to aortic occlusion in an otherwise normal and untreated animal. This type of observation has often been confirmed, by Levy in 1914 (111) and others since (9, 108, 130) even in the dog heart-lung preparation. While this disturbance is mild compared with ventricular tachycardia, there are perhaps circumstances in which the former might precipitate the latter. There is also at least a suggestion that prolonged rises of intra-auricular pressure may lead to auricular disorders of rhythm. And it has already been reported that increased stretch of the auricles predisposes to arrhythmias induced by aconitine (170). It would therefore be interesting to see whether the general level of the blood pressure affects the "fibrillation threshold" as measured by the method of Wiggers and Wégria (210), or whether a change in intra-auricular pressure alters the ability of electrical stimulation to induce flutter or fibrillation in the auricles.

Finally one may well wonder by what means it is that a rise in systemic arterial pressure influences the ability of adrenaline to induce arrhythmias in a heart under cyclopropane anaesthesia. Nickerson and Nomaguchi (142) have shown that bilateral vagotomy or minimum blocking doses of atropine do not protect against ventricular irregularities, nor does bilateral vagotomy alter the effect of aortic occlusion in inducing irregularities after small protective doses of dibenamine. The effect of a rise in pressure is therefore likely to be direct upon the heart itself. This would be in accord with the observation by Moe *et al.* (130) of a bigeminal rhythm in the dog heart-lung preparation on a *sudden* elevation of systemic pressure. And one is reminded of the work of Segers (174, 175) in which he found that, in the frog's heart, a rise of intracardiac pressure favoured the appearance of extrasystoles and diminished the "cellular polarisation." Increase or decrease of the degree of distension changed the level of polarisation either so that extrasystoles always occurred or so that they never occurred. In his view the effect of changes in pressure were to be explained by the alteration caused in the degree of polarisation of the cells of the heart.

THE ROLE OF ADRENALINE IN THE DEVELOPMENT OF ARRHYTHMIAS

In the original experiments of Levy in 1911 (109) adrenaline was used in conjunction with chloroform to produce disorders of the rhythm of the ventricles. Since that time it has proved effective after treating a cat or dog with other substances, of which benzol (139, 140) and cyclopropane (126) have been studied most extensively, though many other unsubstituted or halogenated hydrocarbons (35) and iminoazole derivatives (60, 61) possess similar properties. On the other hand, other sympathomimetic amines besides adrenaline can be used in combination with these hydrocarbons to precipitate ventricular arrhythmias. Levy himself used epinine and tyramine (111) and noradrenaline was also shown to be effective by Tournade and Raymond-Hamet (193), Meek (124) and Garb and Chenoweth (65). Meek and his colleagues (124) also found that cobefrin and kephrine were active, but not ephedrine, benzedrine, paredrine, synephrin or neosynephrin. Even simpler aliphatic amines have been shown to possess this type of activity (137). However, of these amines adrenaline has been used far the most widely, and there is no reason to believe that the others differ from it in their mode of action.

Levy (111) also pointed out that adrenaline (to which we should now also add noradrenaline) of endogenous origin may account for those instances of ventricular arrhythmias which occur on the administration of chloroform alone. This was supported by his observation that nicotine, which he knew "accelerated the secretion of the adrenal glands," also could precipitate ventricular fibrillation under chloroform anaesthesia (see also 125). And he emphasized the significance of sympathetic nervous activity still further by experiments in which fatal ventricular fibrillation was precipitated by stimulation of the right stellate ganglion.

Nickerson and Nomaguchi (142) concluded from their observations that the tendency for the heart of an animal exposed to cyclopropane to develop arrhythmias is greatest shortly after adrenaline first reaches it. Thus ventricular fibrillation was precipitated by occlusion of the aorta, and hence a rise in left intraventricular pressure, 15–20 seconds after injection of adrenaline, but not thereafter. Moreover, as they and others have observed, when ventricular fibrillation develops spontaneously in otherwise untreated dogs exposed to chloroform or cyclopropane with adrenaline, it occurs very shortly after the injection of adrenaline, in their experience after only 8 seconds as an average. This would restrict the period of susceptibility from somewhat less than 8 seconds up to 15–20 seconds after injection of adrenaline. Similarly Fawaz (62), although finding it more difficult to produce ventricular fibrillation in the isolated dog heart-lung preparation than in the intact animal, observed that when fibrillation did occur, it did so less than 30 seconds after the injection of adrenaline. Since the peripheral circuit time of the preparation was about one minute, the effect must have been produced by a single passage of adrenaline through the coronary system. And in this instance, as in the experiments of Murphy, Crumpton and Meek (136) quoted above, the fatal ventricular fibrillation occurred in spite of

the fact that there was no substantial alteration in systemic arterial pressure. It would therefore appear that that action of adrenaline which predisposes to or initiates the development of ventricular arrhythmias on intravenous injection is of a fleeting character.

Hoff and Nahum (80, 138) in 1934 gave an account of their views on one of the mechanisms which may bear on this problem. They observed that administration of large doses of adrenaline to cats caused two phenomena, firstly a profound reflex cardio-depressor effect, with bradycardia, slowed auricular conduction and migration of the pacemaker to A-V node and bundle of His, and secondly the appearance of ventricular extrasystoles from one or more foci. When the reflex depressor mechanism was eliminated by cutting the vagi, the ventricular arrhythmias also disappeared. And they drew the conclusion that, for the production of ventricular rhythms, the ventricular rhythmicity must be greater than that of the supraventricular (sinus node or auricular) mechanisms. They had previously observed that benzol "increases the sensitivity" of the ventricle to adrenaline normally present in the body, so that ventricular arrhythmias might occur in the absence of any reduction of the rhythmicity of pacemaker or auricles. And they also found that administration of admittedly large doses of acetyl-β-methylcholine completely suppressed abnormal ventricular rhythms during inhalation of benzol or chloroform. This was attributed to the ability of such a cholinergic drug to reduce to a safe level the increased rhythmicity of the ventricle. Similarly it has been observed that administration of pilocarpine will prevent chloroform-adrenaline syncope (146), perhaps due to the fall of blood pressure. Thus in the first type of experiment reflex vagal stimulation caused by a rise of blood pressure is presumed to reduce the rhythmicity of the auricles more than the ventricles, whereas in the second experiment acetyl-β-methylcholine reduces the rhythmicity of the ventricles more than that of the auricles. (This action of a substance possessing the properties of acetylcholine should not be confused with the well-established ability of such drugs to precipitate arrhythmias under very different circumstances, a phenomenon which is quite distinct and which is discussed elsewhere.) These observations of Nahum and Hoff serve to enlighten the proposition that the distinctive property of adrenaline in precipitating ventricular arrhythmias under appropriate conditions is one of enhancing the rhythmicity of single cells or groups of cells in the ventricular muscle. But since there are many observations of ventricular fibrillation occurring in animals in which both vagi have been cut, the reflex vagal mechanism can only be of subsidiary importance in the mode of action of adrenaline.

Observations by Moe, Harris and Wiggers (129) on the vulnerable period of cardiac muscle suggested to Fastier (60) that "adrenaline syncope might occur when the heart's capacity to respond to a fast rate is so impaired (by treatment with agents like benzene and amarin) that the cardio-acceleration produced by injecting adrenaline results in the stimulus of a new beat coming during the vulnerable period of the preceding cardiac cycle." This was also suggested by the observation that immediately before "adrenaline syncope" the T waves of

the electrocardiogram were interrupted by R waves of succeeding complexes. This analogy with Moe, Harris and Wiggers' experiments is difficult to concede, for the latter had to use electrical stimuli hundreds of times greater than threshold in order to produce ventricular fibrillation. Moreover Fastier found that driving the auricles at an accelerating rate by means of a stimulator was much less effective than a small dose of adrenaline in producing idio-ventricular rhythms in animals treated with amarin or benzol. In fact, after amarin conduction was depressed and the ventricles responded with increasing difficulty to the accelerating auricular discharge. This evidence also points to the probability that the lethal action of adrenaline under these circumstances is due to a direct action on the ventricular muscle. The crucial time has been shown to be that at which the injected adrenaline has just reached the myocardium, and presumably at which the concentration of adrenaline is highest at its site of action. One may also reasonably suppose that, because of the natural vagaries of the coronary circulation, it is the time at which the greatest variations in concentration of adrenaline around the myocardial cells is likely to obtain; one would then also expect the greatest variation in myocardial rhythmicity. The other possible factor in producing such local variations is that of myocardial damage.

THE EFFECTS OF VARIOUS FORMS OF DAMAGE TO THE MYOCARDIUM

In various forms, myocardial damage, provided it is not too severe, has been shown, in some instances very conclusively, to predispose to the generation of ventricular arrhythmias. These include such procedures as exposure to chloroform or barium chloride, anoxaemia, and ligation of the coronary arteries. Sometimes it is said that these "sensitize" the myocardium, in that injection of adrenaline or electrical stimulation may then more readily precipitate fatal ventricular fibrillation. This is perhaps an unhappy use of the term sensitization, which might be taken to imply that the natural functions of the heart are enhanced, whereas the bulk of the evidence points to the opposite conclusion.

1. *Anoxia*

Although Levy (111) had come to the conclusion that asphyxia only reduced the liability of the heart to ventricular fibrillation caused by the administration of chloroform and adrenaline, Resnik in 1925 (150) considered the possibility that anoxaemia might predispose to auricular fibrillation. In dogs, with both vagi cut and full doses of atropine, he found that when the auricles were stimulated by a faradic current, the early effect of anoxaemia was to predispose to auricular fibrillation. The effect of further anoxaemia was to prevent the development of fibrillation. He also observed that anoxaemia first decreased and later increased the refractory period of auricular tissue, and diminished the rate of fibrillation; but he was understandably cautious in the interpretation of these findings as applied to the genesis of auricular fibrillation. Smith and Wilson (183) used somewhat different conditions. They injected mecholyl into dogs with open chests, and observed that this procedure alone did not induce auricular fibrillation, whereas during anoxaemia caused by stopping the artificial

respiration pump the administration of mecholyl led to its development in 10 out of 19 animals, and that the arrhythmia disappeared when respiratory movements were restored. They made similar observations in heart-lung preparations in which the auricles were not allowed to become distended. And they showed that distension of the auricles also predisposed to auricular fibrillation induced by mecholyl. It would therefore appear that a rise of intra-auricular pressure sometimes has the same effect as a rise of intra-ventricular pressure in determining, under appropriate conditions, the development of arrhythmias. And in the instance cited, anoxaemia had a direct action on auricular muscle, independent of other changes which it causes in the cardiovascular system such as a rise of blood pressure, liberation of adrenaline or nor-adrenaline, or increased sensitivity of the heart to vagal stimulation (77) which also predispose to arrhythmias. There are other observations reported in the literature of the effect of anoxaemia, such as those of Horlick and Surtshin (85) who found that in dogs the production of auricular fibrillation by intravenous injection of large doses of acetylcholine was facilitated by the presence of anaemia due to phenylhydrazine, n-propyl disulphide or haemorrhage. Robbins and Baxter (151) also found that the ventricular arrhythmias developed by pushing cyclopropane anaesthesia in dogs to the point of respiratory arrest could be ascribed in part to anoxaemia, for when this was prevented by artificial respiration the blood cyclopropane concentration could be increased still further without cardiac irregularities. However, in these experiments other variables, such as those considered above, may have altered. This criticism cannot be levelled at the experiments of Wiggers, Wégria and Piñera (211) for they occluded one branch of the left coronary artery for only one or two minutes before testing the fibrillation threshold by rectilinear shocks applied to the ischaemic area of the ventricles during the vulnerable period. A substantial reduction in the strength of current required to induce fibrillation was observed, and this was regarded as one of the principal changes by which myocardial infarction initiates fatal ventricular fibrillation.

These observations, on both auricles and ventricles, taken together constitute a reasonably strong body of evidence to suggest that anoxia of cardiac muscle causes changes which predispose to the development of arrhythmias. They tell us little about the intimate nature of the mechanisms involved. Against the observation of Resnik (150) in the whole dog that anoxaemia initially decreases the refractory period, we have to set that of Wedd (200) that anoxia does not alter the refractory period of the turtle's heart. Nothing is known of the effect of minor degrees of anoxia on single cardiac muscle fibres; and its effect on nerve may or may not be relevant. Yet ischaemia of nerve-endings under certain circumstances may lead to increased excitability and spontaneous discharges (120), a phenomenon which is probably associated with an increase in the negative after-potential (57). There is insufficient evidence to show whether this analogy is too far-fetched.

2. *Chloroform, cyclopropane and allied substances*

Chloroform, benzol and cyclopropane, to instance three of the substances most widely used in the past to cause ventricular arrhythmias in conjunction

with adrenaline, have been spoken of as "sensitizing" the myocardium. Many investigators have come to the conclusion that these substances cause dilatation and weakening of the beat of the heart (64, 107, 124, 125, 131). In his review of the subject Meek ten years ago (125) concluded that it seemed "impossible to come to any analysis of the chloroform effect on the heart which predisposes it to fibrillation in terms of fundamental muscular physiology." There are still few indications of the type of hypothesis which would explain the surprising discrepancy that while, on the one hand, preliminary treatment with chloroform or cyclopropane is said to "sensitize" the myocardium to adrenaline, no completely convincing evidence has been adduced to show that these substances increase excitability, rhythmicity, the strength of contraction or conduction velocity. On the contrary, the weight of the evidence is strongly in favour of the view that they are "depressant" in all senses of the word.

There are some points of dissimilarity between the actions of chloroform and cyclopropane which may be mentioned:

i. There seems no doubt that dogs are very much more resistant to chloroform-adrenaline syncope than are cats (8, 125); yet they appear to be very susceptible to cyclopropane-adrenaline syncope, whereas cats are not so susceptible (6).

ii. As Levy first showed, adrenaline more readily produces fatal ventricular fibrillation in cats under light chloroform anaesthesia than when the anaesthesia is deeper. Similarly Tournade, Malméjac and Djourno (192) observed that faradic stimulation of the ventricles of the dog produced fibrillation in light but not in deep chloroform anaesthesia. On the other hand, Meek, Hathaway and Orth (126) showed that increasing depth of cyclopropane anaesthesia was accompanied by increasing susceptibility to the action of adrenaline in precipitating ventricular fibrillation. More recently Stutzman and Allen (186) found that *prolonged* administration of cyclopropane much reduced or even abolished the ability of large doses of adrenaline to produce ventricular tachycardia or fibrillation; however, it also reduced or reversed the pressor response.

These differences raise the question as to whether chloroform and cyclopropane really are working in precisely the same way, or whether perhaps one of them has some additional property which might account for the discrepancy. As Meek suggests, the effect of deep chloroform anaesthesia is not difficult to understand, and we are here dealing most probably with a simple toxic effect. In such deep anaesthesia all functions of the heart may be so far depressed that it is no longer susceptible to the peculiarly lethal effect of injected adrenaline; in fact, under such circumstances adrenaline is an effective restorative of a rapidly succumbing circulation (74, 192). Meek, Hathaway and Orth's experiments on cyclopropane quoted above included some observations under anaesthesia of a sufficient depth to arrest the intercostal muscles, and those of Robbins and Baxter (151) went still further; when the asphyxia was removed by artificial ventilation, even more cyclopropane had to be administered before spontaneous arrhythmias returned. Thienes, Greeley and Guedel (191) found that high concentrations of cyclopropane, during artificial respiration, abolish or minimize the incidence of spontaneous arrhythmias, though they did not then

examine the efficacy of adrenaline. On the other hand, Lee, Orth, Wangeman and Meek (107) found under similar conditions, using a larger series of dogs, that the incidence and severity of spontaneous arrhythmias increased as the concentration of cyclopropane was raised. Thus, bearing in mind the difficulty of interpreting many experiments in which the effect of systemic blood pressure changes cannot be assessed, there is as yet no convincing evidence that a high concentration of cyclopropane has any protective action in the intact animal against either spontaneous or adrenaline-induced arrhythmias.

There are many similarities in the actions of these anaesthetics. For instance in a preparation of the cat auricle at 30°C, Acierno and DiPalma (2) have recently shown that while ether, chloroform and cyclopropane depressed excitability and contractility, the refractory period was shortened by all three in direct relation to the concentration. This observation does not explain the greater incidence of ventricular irregularities under chloroform and cyclopropane as compared with ether, and if reduction in the refractory period is the crucial factor, this is difficult to reconcile with the observation of Greisheimer *et al.* (73) that simultaneous administration of ether reduces the incidence of arrhythmias under cyclopropane-adrenaline treatment. It is possible that in the whole animal changes in the refractory period produced by these anaesthetics may be of practical importance though it is certainly not the only determinant of their action.

There is another way in which chloroform, benzol or cyclopropane directly influence the heart. It has often been envisaged that they may cause local islands of damage, to a more severe degree than that suffered by adjacent tissue, and that local blocks may ensue under unfavourable conditions. An experimental example of this type of block and its effect on cardiac muscle has been provided by García Ramos (66). Garb and Chenoweth (65) have shown that benzol or chloroform decrease the electrical excitability of an isolated cat papillary muscle to a much greater extent than ether (compare 2) and this might explain the differences between their actions. There is a further possibility along the same lines of argument. The experiments of Hoff and Nahum (80) as already described led to the view that, for the production of ventricular rhythms, the ventricular rhythmicity (or automaticity) must be greater than that of the supraventricular (sinus node or auricular) mechanisms. If we were to suppose that the action of these anaesthetics, which we know depress certain cardiac functions, was greater on the auricles than upon the ventricles, one can readily visualize under the influence of adrenaline the origin of the simpler forms of ventricular arrhythmia. There is no direct evidence to support this hypothesis but it should not be too difficult to put to experimental test.

The possibility that these anaesthetics may have a reflex effect upon the heart has been extensively explored. In 1912 Elliott (56) showed that anaesthesia with chloroform or ether was followed by reduction in the quantity of adrenaline stored in the suprarenal glands. Ether anaesthesia was shown to cause peripheral vasoconstriction and relaxation of the stomach and intestines (127), sweating in the innervated cat's fore-paw but not on the denervated side

(29), contraction of the spleen, inhibition of the virgin cat uterus and rise in heart rate (Bhatia and Burn, 19). The latter also found that these effects were not seen in a fully pithed animal, and that chloroform, which Miller (127) had shown also relaxed the intestines, acted in the same way as ether upon the spleen in their preparations. Samaan (161), by section of the nerve pathways involved, also came to the conclusion that ether increases the heart rate by reflex mechanisms involving both the augmentation of cardio-sympathetic impulses and the liberation of sympathomimetic substances via the splanchnics and abdominal sympathetic chains. Johnson (94) similarly found that ether anaesthesia no longer produced a rise in blood sugar in rabbits after bilateral adrenalectomy.

For cyclopropane, however, the evidence is more fragmentary. Barman (14) observed no increase in adrenaline secretion from the adrenals of dogs during cross-perfusion experiments. Youmans, Wangeman, Griswold and Karstens (214) showed that there was only a small rise in blood sugar, of up to 20 mg. per cent, under cyclopropane anaesthesia in dogs, and the cause of this rise was not determined. On the whole, the balance of evidence suggests that there is some increase in heart rate (125) though the mechanism has still not been adequately analysed.

On the other hand, there is a considerable body of evidence, though for various reasons not always conclusive, that suggests that some form of reflex mechanism may under particular conditions influence the outcome of chloroform- or cyclopropane-adrenaline treatment in the whole animal. Some of this has been discussed by Meek (125), who has made the good point that some of the earlier work may be misleading, since it was based on only a limited range of dosages, and that full account was rarely taken of the differences between species, or of the need for a rigorous control of the depth of anaesthesia and of the concentration and duration of adrenaline injections. The introduction by Meek, Hathaway and Orth (126) of a strictly standardised technique marks an important step forward in the analysis of this phenomenon, though the necessity for taking some account of the mean blood pressure obtaining at the time of the test was not then appreciated. These considerations complicate assessment of the available evidence.

Beattie, Brow and Long (16) showed that extrasystoles induced by chloroform anaesthesia in cats could be abolished by section of the hypothalamus, and that under chloroform anaesthesia stimulation of the posterior part of the lateral wall of the third ventricle produced extrasystoles. It seemed very reasonable to ascribe these observations to stimulation of the sympathetic outflow to the heart, since the arrhythmia disappeared after removal of the stellate ganglia or the sympathetic fibres supplying them, or to stimulation of other sympathetic pathways controlling the secretion of sympathetic amines which might be liberated in the blood. Such a conclusion concurs with Levy's original ideas (110, 111). But when we turn to the production of more serious forms of ventricular arrhythmia by chloroform or cyclopropane and adrenaline the position is confusing. On the one hand, there is no doubt that ventricular fibrillation may ensue in an

animal with a denervated heart (13, 110), or in a heart-lung preparation (62), yet various authors have reported that removal of the lumbar sympathetic chains (146), denervation of the carotid sinuses and section of the afferent nerve-fibres from the aorta (24), decerebration by a bloodless method or thoracic sympathectomy (7), partial abdominal evisceration, partial abdominal denervation or bilateral adrenalectomy (188), or removal of stellate ganglia (5) and adrenals (81) affords a measure of protection. On the other hand Rennick, Pardo, Gruhzit and Moe (149) concluded that the minor degree of protection afforded by thoracic sympathectomy was due to a reduction in the peak pressor response to adrenaline. When this was restored by infusion of blood the original sensitivity returned. The simplest explanation of this confusing wealth of scattered material, of which this is almost certainly not a complete summary, is that under the particular experimental conditions used, the removal of even a small part of the continuous secretion of sympathomimetic amines, or even the operative procedure alone is sufficient to upset the very delicate balance of the numerous factors which influence the outcome, so that the test dose of adrenaline is no longer effective in precipitating ventricular fibrillation. That this is the likeliest explanation is supported by those authors who have observed that, after their operative interference, adrenaline may yet be effective provided the dose administered is sufficiently increased. And this observation also agrees with Fawaz's comment (62) that ventricular fibrillation under cyclopropane or chloroform anaesthesia is more difficult to obtain in the dog heart-lung preparation than in the intact animal. There seems, then, some reason to believe that endogenous reflex secretion of adrenaline or noradrenaline may influence the outcome; and it is still possible that certain anaesthetics might accelerate this secretion in some way yet to be determined, perhaps by sensitization of afferent sensory pathways such as that which Whitteridge and Bülbring (207) described for the pulmonary stretch fibres.

This is not, however, the whole of the story. Ether anaesthesia has been very adequately demonstrated to cause just that effect in enhancing peripheral sympathetic discharges, which is now very tentatively postulated to play a part in the development of other anaesthetic-adrenaline ventricular arrhythmias. But ether is the least efficient of these anaesthetics in causing such disturbances; there is very reasonable doubt whether it ever does so. At most, therefore, this particular factor of increased sympathetic activity is a subsidiary one, to be placed on the same level perhaps as the rise of blood pressure in the mode of action of adrenaline in relation to this problem. Whether such substances as cyclopropane may also, reflexly or centrally, affect the parasympathomimetic control of the heart, there is only little evidence to suggest (152).

3. *Barium chloride and other substances*

The question of the mode of action of barium chloride in initiating ventricular arrhythmias has been reserved for separate consideration, because it raises in a particularly clear form certain ideas which might also have been discussed in relation to other substances which, alone or in combination, have this property.

Rothberger and Winterberg (159), Levy (111), and others (123) have shown it may cause ventricular extrasystoles, tachycardia or fibrillation. Barium chloride, injected into cats, dogs and rabbits has also been used to induce ventricular arrhythmias, with a view to studying their prevention by substances which might be expected to have an action like that of quinidine (20, 21, 25, 196, 198). Smith, Winkler and Hoff (184) showed that intravenous injection causes a sharp rise of blood pressure at the same time as extrasystoles occur. But this rise of blood pressure probably is not in itself responsible for the dramatic effect upon the heart. Rothberger and Sachs (157) confirmed the observations of earlier workers (105) that it initiated automatic activity in quiescent strips of mammalian left auricle and Deutsch and Lumdin (44) have shown that minute amounts of barium have the same action on small muscle bundles from the frog's ventricle. These observations are of particular interest in view of the well-documented ability of barium to initiate rhythmic activity in nerve. Feng (63) and Dun and Feng (52) showed that conduction of a volley of impulses may be followed by repetitive discharges in barium treated nerve. Occasionally spontaneous discharges also occurred. A detailed analysis of this action was carried out by Lorente de Nó and Feng (116) who found that barium caused depolarisation and a considerable increase in the after-potentials. No doubt these findings account for the observation that in intact cats barium in small doses excites, and in large doses inhibits, the discharge from the superior cervical ganglion (11).

To digress for a moment, Hazard & Quinquaud (76) have shown that the rise of blood pressure caused by intravenous injection of barium chloride is abolished by yohimbine, which is well known as a sympathicolytic. This observation, in conjunction with those detailed above, makes it seem possible that the blood pressure rise may well be due to enhanced sympathetic outflow, and liberation of adrenaline and noradrenaline in the heart from the adrenals and elsewhere. If this were so we have to envisage the possibility that in the whole animal the action of barium chloride upon the heart may be complicated by not only the rise of systemic arterial pressure, but also the liberation of other substances which may have in themselves an action predisposing to the development of arrhythmias. It is interesting that these considerations, which have arisen first in connection with substances such as chloroform and cyclopropane, should also apply to barium. There is little doubt that they are of very much more general application, and, for instance, must be borne in mind in any discussion of the mode of action of the veratrum alkaloids in precipitating cardiac arrhythmias in the intact animal (101).

Of more importance than this is the general proposition suggested by the somewhat analogous action of barium chloride upon nerve and heart muscle. It is pertinent to ask whether there are any other such substances which have properties of the same nature, and the example of the veratrum alkaloids immediately suggests itself. These alkaloids have been very widely used, usually in an impure form, for the study of changes produced in nerve, where they may cause under appropriate conditions repetitive discharges in response to a single stimulus, and, what was very striking when it was first discovered, a great increase in

the negative after-potential (71, 101), with a parallel increase in the supernormal period. These substances excite or sensitize repetitive discharges from peripheral sensory receptors in minute concentrations. In low concentrations they have a positive inotropic effect upon the heart similar to that of the digitalis glycosides and in higher concentrations cause arrhythmias of all types and finally ventricular fibrillation. This analogy between the actions of veratrine upon nerve and heart muscle in causing supernormality has been pointed out before (70). Recently Scherf and Chick (167) described in detail the arrhythmias generated by the topical application to the dog's ventricle of the crude alkaloidal mixture veratrine, or the pure alkaloids veratridine and cevadine in strong concentrations. They concluded that the mechanism of abnormal impulse formation from an ectopic centre was not closely related to the veratrine effect on nerve and muscle; but this distinction appears somewhat arbitrary in that it rests chiefly on the definition of where the first impulse which initiates the repetitive discharge comes from.

Aconitine may prove to be a substance of the same nature. Its toxic properties have been appreciated, like those of veratrine, for centuries. In 1929 Scherf (163) gave a modern account of its action upon the heart, and emphasized its effect in increasing excitability; more recently he (164, 169) produced additional evidence by local application that its action upon cardiac muscle is a direct one. It has a similar effect upon isolated preparations (86, 157), as many earlier workers have shown (22), and like barium has been used quite extensively to induce ventricular arrhythmias, to prevent which ions such as magnesium (87) or drugs such as F1262 (25), α-fagarine or procaine (195) may be tested. The introduction by Scherf of a method of causing auricular arrhythmias by local application of aconitine has caused wider interest in this drug, which has therefore been investigated more thoroughly than for several decades. About the details of its action upon the fundamental properties of mammalian cardiac muscle remarkably little is known. It would be highly desirable to know how this remarkable substance affects not only excitability, power of contraction, and rhythmicity of cardiac muscle, but also what it does to conduction velocity and refractory period. There is a recent report by Charlier and Klutz (34) that two sympathomimetic amines are able to prevent the ventricular tachycardia caused by local application of aconitine. The implications of this observation on its mode of action have still to be examined. Segers (174, 175) observed that it had the same action on late negativity in the isolated frog's heart as did veratrine and barium. And Graham and Gasser (71) found that it also somewhat increased the height and duration of the negative after-potential in isolated nerve, though this action was much less dramatic than that of veratrine. There is also circumstantial evidence that aconitine may be able to provoke repetitive discharges from nerve. Like the veratrum alkaloids, application to the mouth or tongue, or indeed elsewhere in the body, first arouses a sensation of heat, tingling and then succeeding numbness. Strong concentrations similarly first stimulate and later paralyse peripheral motor nerves, the stimulation being manifested by fibrillary twitching. It would certainly be desirable to confirm this hypothesis by direct methods.

The effects of these three substances, barium chloride, veratrum and aconitine, upon nerve and cardiac muscle make one suspect that there may be a common factor in their actions. Since in isolated nerve the supernormal phase has been related to the negative after-potential, it seems worth while enquiring as to the existence of supernormality during the recovery phase of excitability in cardiac muscle.

SUPERNORMALITY AND MEMBRANE POTENTIALS

In 1919–20 Adrian (3, 4) demonstrated the existence of a supernormal phase of excitability during the recovery period in frog heart muscle and he related this to the presence of an acid environment. Wastl (199) made similar observations in fatigued preparations of the frog's heart. In 1934 Eccles and Hoff (54) showed that in some instances the recovery curve of excitability of the "pacemaker" of the cat's heart also passed the previous threshold and thus gave rise to "supernormality," though this was not related directly to the genesis of the next normal contraction. It would appear from the published accounts that a supernormal phase of excitability is not always nor very easily seen in cardiac muscle, unless it has been exposed to some noxious agent. In the untreated isolated auricle of the guinea pig at 37°C it has only been observed on three or four occasions, and then it appeared only for a few minutes, despite intensive search on a great number of preparations (41). Hoff and Nahum (82) showed that supernormality could be observed in the ventricle of cats under barbiturate anaesthesia, but not so readily after decerebration. They point out that this supernormal period fell during a period of continued electrical activity as shown by the electrocardiogram, and the cycle of excitability was determined at a number of different points on the surface of the ventricle. They suggested that these facts, considered in connection with the association of the supernormal period in nerve with the negative after-potential, imply a similar relationship in the mammalian ventricle. In 1941 Segers (174, 175) made a series of interesting observations on the isolated frog's heart, and produced evidence of the association of supernormality with the negative after-potential and of subnormality with an enhanced positive after-potential. He concluded that extrasystolic arrhythmias developed under the influence of all agents which augment the negative after-potential, such as an increase in the calcium concentration of the perfusion fluid, and the administration of aconitine, veratrine, adrenaline, strophanthin and digitalis; rhythmic stimulation of the cardiac muscle at frequent intervals also led to the successive accumulation of slow negative potential changes. This was also increased by distension of the heart and by appropriate polarisation. On the other hand agents which increased the positive after-potential, such as a rise in the potassium concentration of the perfusion fluid, acetylcholine, quinidine and cocaine, caused a diminution in excitability and inhibition of spontaneous activity. The method which Segers used for these measurements was to record the potential changes from two points on the surface of the ventricle, or from between a point on the ventricle and the perfusion fluid in the interior of the heart; in either instance one calomel half-cell attached to the ventricle was filled with saturated KCl, in order that

the responses should be unipolar. The recent publication of methods of obtaining membrane action potentials from single cardiac fibres of the frog heart *in situ* (212, 213), or from "false tendons" or Purkinje fibres of the dog and kid heart (50) makes it highly desirable that these observations of Segers should be repeated on such preparations, in order to obtain unequivocal records of these changes.

There does seem a real chance of unifying many of the factors which are concerned in the aetiology of arrhythmias into a common framework, by studying their actions on such isolated preparations. It is not to be supposed, however, that experiments of this type will alone solve all the problems with which we are concerned for there is little doubt that the syncytial nature of cardiac muscle in itself contributes greatly to the complexities of the problem. But without the evidence as to what drugs and other procedures do to single cardiac muscle fibres it is difficult to believe that much further progress will be made.

There is one further point which may now be made regarding the mode of action of chloroform and cyclopropane in predisposing to the development of cardiac arrhythmias under the influence of adrenaline. Apart from the various mechanisms which have already been discussed, there is the possibility of a direct action upon the myocardium, of a similar nature to that suggested by Segers to account for the action of barium chloride, aconitine etc., as explained above.

THE ECTOPIC FOCUS AND CIRCUS MOVEMENT THEORIES IN THEIR RELATION TO THE REFRACTORY PERIOD

In any general discussion of the initiation of cardiac arrhythmias, the relative merits of the ectopic focus and circus movement theories, in connection with both auricular and ventricular disorders, is bound to arise. This appears to be an appropriate point at which to consider them, because it must be obvious that the possibility of repetitive discharges originating from a single cell, by virtue of such changes as Segers described, implies an ectopic focus as the origin of the disturbance. The term ectopic focus, which has been so widely used in such discussions, does not necessarily mean that the discharge is arising from one single cell. There are several possibilities; an ectopic focus might consist of: i. a single cell; ii. a small group of cells, of which first one and then another becomes the pacemaker; iii. a small group of cells in which a circus movement is perpetuated. No comment is required on the first and second hypotheses; for the sake of simplicity the term unicellular ectopic focus will be used for either. To the third it may be objected that under the observed conditions of refractory period and conduction velocity obtaining in a living heart, the circuit would have to be so large that it would constitute an obvious circus movement, and not a small focus of irregularities located to a finite point in the cardiac muscle. This point of view might be taken to be substantiated by the calculations of Rosenblueth and Wiener (156) on the minimum size of the circuit required for maintenance of the disturbance in a dog's heart and the practical demonstration by Rosenblueth and García Ramos (155) that when the orifice in the auricles was

sufficiently enlarged by crush injury, a maintained circus movement could readily be established. In the normal heart this argument is undoubtedly valid, but in the heart treated with cyclopropane, barium chloride or aconitine, there are not sufficient data to judge. If in any region of damage conduction velocity is reduced, and if in particular transmission is very greatly or entirely impeded across the centre of that region, it is a theoretical possibility that, owing to the syncytial construction of cardiac muscle, a circus movement of very much smaller dimensions might be established. The difficulties of deciding between such possibilities in the living animal are so great that investigators have wisely been content not to enquire too closely into the meaning of the term "ectopic focus"; but from the point of view of the search for substances which may prevent the development of disorders of rhythm, this differentiation may well be of importance.

There is a further theoretical point to consider about the development of a rhythmic disturbance in a unicellular ectopic focus. It has been repeatedly observed that when a supernormal phase of excitability in cardiac muscle is encountered, it occurs early in diastole, just after the beginning of the relative refractory period, and therefore presumably close to that time at which repolarisation of the membrane is completed. If therefore a second discharge arises because of the existence of this supernormality, it must arise at this instant, and diastole will be cut short. This is what Segers (176) describes as "le battement auto-entretenu du coeur." If on the other hand a unicellular ectopic focus has become pacemaker to the heart, not because it fires off during the supernormal period of excitability, but because its normal automatic rhythm has been much enhanced, then the relative refractory period and diastole will not be curtailed. In the latter instance it is possible to conceive circumstances under which the frequency of the heart may rise smoothly from that which obtained under the normal influence of the sinus node to a higher value imposed by the ectopic focus. But if the activity of the ectopic focus is determined by the sudden appearance of supernormality, then one would expect a large stepwise increase in frequency as the ectopic focus became active. In the latter instance a decrease of the absolute refractory period, which would presumably be accompanied by an equivalent shift in the position of the supernormal period nearer to the spike, the point at which membrane depolarisation began, would then be accompanied by a substantial increase in discharge frequency. On the other hand, there is no reason to relate alterations in the refractory period to changes in the normal autogenous rhythm of the cardiac muscle. Perhaps an example will make the position clear. It has been known for very many years that acetylcholine causes a substantial decrease in the absolute refractory period, yet it slows the normal rhythm of the heart. The action of acetylcholine upon a unicellular ectopic focus beating by virtue of its inherent rhythm would therefore be to slow it, but if this ectopic focus were discharging according to a rhythm determined by a supernormal period occurring immediately following the absolute refractory period, then we should expect its discharge rate to be increased. This concept might well account for the ability of the vagus to increase the rate of auricular

flutter, while it stops stimulus formation during sinus rhythm or other auricular tachycardias, and Garrey in 1924 (68) considered this proposition.

An agent which reduces the absolute refractory period would also be expected to increase the frequency of a circus movement, and that was Lewis, Drury and Bulger's explanation of their observation that vagal stimulation increases the frequency of the oscillations in auricular fibrillation (112, 113). There are very many references in the literature to the ability of vagal stimulation, acetylcholine or substances closely related to it to provoke disorders of rhythm. Both in animals (41, 83, 91, 144, 153, 183) and in man (15, 36, 141) these have caused auricular fibrillation. Scherf *et al.* (169) observed that vagal stimulation increased the rate of auricular flutter induced by local application of aconitine to the auricle. And in the isolated auricle in which repetitive discharges have been initiated by appropriate stimulation early in the relative refractory period (40), acetylcholine greatly increases the frequency of discharge. When the refractory period is reduced by the presence of acetylcholine, repetitive discharges are also very much easier to initiate, and last for very much longer. Similarly Brown and Acheson (27) observed that stimulation of the vagus or injection of acetylcholine increased the rate of auricular flutter in the dog, in which an auricular circus movement had become established according to the technique of Rosenblueth and García Ramos (155). Indeed with adequate doses of acetylcholine auricular fibrillation occurred. It is difficult to believe that all these observations on the effect of vagal stimulation or the injection of cholinergic substances on the initiation, maintenance and increase of frequency of auricular arrhythmias can be explained other than by a reduction of refractory period. For such procedures all decrease the automatic rhythm of the heart. However, as explained above, a reduction of refractory period might increase the rate of discharge both of a circus movement, or of a unicellular ectopic focus *dependent for its rhythm on supernormality and the refractory period.* These observations then cannot help us to decide between these two alternative mechanisms.

To digress, Scherf *et al.* (169) did consider the possibility that vagal stimulation might have a sympathomimetic action upon the heart, by way of the accelerator fibres which run in the vagus. Indeed it has been shown that an adrenaline-like substance is liberated on injection of acetylcholine (84). This however, appears to be due to a nicotine-like action of acetylcholine and is not paralysed by atropine, whereas the effect of acetylcholine in provoking auricular fibrillation is abolished by atropine (83, 166).

The next type of experiment in which we might hope to obtain information about the nature of the arrhythmia is that in which electrical stimulation of various kinds is used to start the disturbance, and this is a subject which deserves separate consideration.

ELECTRICAL STIMULATION IN THE INITIATION OF ARRHYTHMIAS

Faradisation of the auricles or ventricles has been known for many years to start flutter or fibrillation. According to the species and condition of the animal, faradisation of the auricles may cause a transient or continuing arrhythmia.

Rectangular stimuli of constant form are just as effective as the unpredictable output of an induction coil, but no systematic analysis appears to have been made of the relationship between frequency and strength of the threshold stimulus required to start flutter on the one hand, and the refractory period prevailing in the muscle on the other hand.

A single shock delivered at an appropriate instant in the cardiac cycle will also initiate arrhythmias, and this type of excitation is more readily analysed. In 1921 de Boer (23) showed that fibrillation of the ventricle of the frog's heart could be induced by a single induction shock applied directly after the end of the refractory period; he also believed that a bad metabolic condition of the heart favoured fibrillation. In 1930 Andrus and Carter (12) showed that during vagal stimulation, a single induction shock applied to the dog's auricle *in vivo*, soon after the end of the refractory period, frequently produced auricular fibrillation. It was later shown that a single D.C. shock of 10–30 msecs. duration applied to the dog's ventricle during the T wave induced ventricular fibrillation, and the work of Wiggers and Wégria (205, 209, 210) put this method on a sound foundation as a technique for determining the "fibrillation threshold" of ventricular muscle and the action of various substances on it.

Wiggers and his colleagues state that in order to elicit multiple extrasystoles or fibrillation, current strengths are necessary (10–20 ma) several hundred-fold stronger than that required for threshold shocks during diastole (129). Ventricular fibrillation initiated in this way starts with a series of three to six large bizarre electrical complexes which recur at progressively decreasing intervals and change their form in successive beats (208). It was clear that the effective stimulus fell near the end of the absolute refractory phase, and it was suggested that this gave rise to a "rhythmic centre from which several impulses are discharged at an accelerating rate." And again, "the progressive decrease in refractory periods associated with the accelerating rate of responses, combined with delay in conduction, furnish ideal conditions for re-entry of impulses, *but only after the second, third or fourth truly premature beats have run their course*" (129). The conclusion that the initial accelerating discharges originated from a single rhythmic centre was supported by the observation that the order of excitation on the surface and interior of the ventricle (as measured by three electrodes close to the point of stimulation) during these initial responses remained the same, and that there was a period between beats when no area was excited. Various reservations must be made before agreeing with this conclusion; it is not clear to what extent the strong and presumably widespread tissue polarisation which results in the neighbourhood of the stimulating electrode, as a result of the enormous shock applied, may subsequently alter conduction velocity and refractory period below that electrode. If these variables were substantially modified, a very much smaller circus movement might have been generated than that which the authors designed their experiment to detect. It is also arguable whether three electrodes distributed according to their pictures across the ventricle were sufficient. To determine the sequence of events in the isolated auricle very many more test points were required (41). And it is pertinent to suggest that the application of

so large a current pulse when effective, may well depolarize simultaneously a considerable area of muscle, and thus create conditions in which a small local circus movement may arise. However, since the authors have been at pains to exclude a small circus movement, within the limits of their experimental methods, the possibility that a "unicellular ectopic focus" is responsible must be considered. And since to be effective the stimulus must be applied during the "vulnerable period," which appears to be very early in the relative refractory period, it seems at first sight that a unicellular ectopic focus might be discharging during supernormality. But before reaching this conclusion there is another feature of this procedure which deserves close attention, that is, the necessity for using a current strength several hundred-fold greater than that necessary for threshold excitation during diastole, after the end of the relative refractory period. It hardly seems likely that such an excessive current strength would be required if supernormality were a regular feature of the dog's ventricle. Harris and Moe (75) could indeed find no evidence of supernormality. Moe, Harris and Wiggers (129) concluded that the tissue polarisation of such a strong brief shock is so great that it persists until early diastole, and is therefore effective even if delivered at a time before this, before the end of the T wave and therefore presumably before repolarisation is complete. These calculations were based on measurements taken from the external surface of the heart, and the value of the tissue polarisation is therefore likely to be much underestimated because of the shunt afforded by surrounding tissue. It would be interesting to know what effect stimuli of this magnitude have on the membrane potential of a single fibre; observations such as those of Weidman (206) seem likely to illuminate this aspect of the subject. It is possible that the residual polarisation which these workers have postulated as the effective stimulus for the first beat of the "rhythmic centre" is also responsible in part for the initiation of subsequent beats. Harris and Moe (75) have examined the effects of anodal and cathodal polarisation in causing arrhythmias in the dog's heart. Segers (176) also has shown that appropriate polarisation is in itself sufficient to initiate automatic discharges from an otherwise quiescent piece of cardiac muscle, and he relates their origin to the appearance of supernormality. It is certainly true that the crucial initial discharges, which recur at progressively decreasing intervals after the application of an effective D.C. shock to a dog's ventricle, and which precede the development of fibrillation, are of a frequency very much greater than that of the natural rhythm of the untreated heart, and the intervals between these discharges very roughly approximate to the expected value of the refractory period. The phenomenon of the acceleration of these discharges might be related to the well-known observation that increasing the frequency of stimulation of cardiac muscle reduces the refractory period (75, 128). As has been pointed out above, evidence of this type associates the mechanism responsible for the repetitive discharges with the refractory period but it does not distinguish between a unicellular ectopic focus hypothesis and a small circus movement hypothesis.

In isolated preparations the opportunity for accurate measurement of the time relations between the arrival of the excitatory process at various points in

the tissue is greatly increased. It was observed by Segers (176) that rhythmic stimulation of a quiescent auricle needed to exceed a certain critical frequency in order that the auricle should continue to show repetitive discharges after the stimulation was stopped. These repetitive discharges continued for a short length of time and then abruptly ceased. They were related by Segers to the presence of supernormality. During investigations on the refractory period of isolated auricle Dawes and Vane (40) made somewhat analogous observations. It was found that a single shock applied very early in the relative refractory period is sufficient to cause a burst of repetitive discharges, at a frequency much greater than the normal rate of auricular beat; the intervals between these discharges were approximately constant and slightly greater than the value of the absolute refractory period just determined. When first observed it was only possible to obtain a few such discharges, but since that time the phenomenon has been found to continue for an hour or more under favourable conditions. These include any change, such as increase of temperature or addition of acetylcholine, which decreases the refractory period (Cf. 47). It was also found that rhythmic stimulation of a quiescent auricle would initiate the repetitive discharges, provided that the frequency of stimulation approximated to or somewhat exceeded that at which the interval between stimuli equalled the absolute refractory period. This then is probably the explanation of Segers' observation referred to above, and agrees with recognition by Wiggers and others of the necessity for an effective stimulus to fall during the "vulnerable period" in order to produce ventricular fibrillation, whether it be a single D.C. shock or alternating current.

This phenomenon of repetitive discharges at high frequency from auricular muscle was found to occur in small strips of muscle free, so far as was ascertainable, from a central orifice or area of damaged tissue, so small that it was thought hardly possible for a circus movement to exist (40). But since that time, on more than one occasion, sufficient evidence has been accumulated by recording from a large number of places on a single auricular strip during one unchanging repetitive discharge lasting half an hour or more, to convince the observers that a circus movement existed in a small section of the muscle. This does not exclude the possibility that in other experiments the disturbance may have originated from a point focus, but it does suggest that under favourable conditions a circus movement may exist in smaller pieces of tissue than had been supposed. And incidentally, in conformity with the observations of Mines (128) and Garrey (67, 68), it was found that the discharge could be stopped by a single properly-timed stimulus.

THE UNICELLULAR ECTOPIC FOCUS THEORY

This seems an appropriate point at which to discuss the direct experimental evidence for the existence of what has been called a unicellular ectopic focus. That thought to be produced by a single D.C. shock in the mammalian ventricle has already been considered above.

In the dog's auricle Scherf found that topical application of aconitine as a

subepicardial injection of a dilute solution, or by the use of a few crystals on the exposed surface, caused auricular tachycardia or fibrillation (164, 168); cooling this small area stopped the arrhythmia, though it reappeared almost at once on warming. He and his colleagues found it difficult to believe that a small circus movement could be involved because the flutter or fibrillation returned so readily. Later they also observed that stretching the wall of the auricle increased the rate of discharge, and converted tachycardia to transient fibrillation (170). They drew analogies between their observation of the effect of stretch on impulse formation in the mammalian auricle and in other tissues, sensory and motor nerves and skeletal muscle. They believed that the mechanical devices which they used for causing stretch influenced only the formation of stimuli and not conduction velocity (162), but no measurements were made on refractory period. For that reason it is impossible to offer an opinion on the relevance of this very stimulating observation. Their further point, that auricular extrasystoles caused by intravenous injection of minute doses of aconitine disappear during vagal stimulation whereas the repetitive discharges which follow topical application of aconitine are accelerated, may be explained by the dual action of vagal stimulation or of cholinergic substances described above, if we suppose that stronger concentrations of aconitine also reduce the refractory period (172). In the latter paper Scherf and Terranova held that the following observations spoke against a circus movement as the underlying mechanism: i. the reappearance of the arrhythmia after cooling; ii. the slow evolution of the reappearing flutter without any change in the form of the P wave after cooling; iii. the production of auricular pauses during the flutter by means of vagal stimulation.

In the opinion of the reviewer none of these arguments alone is absolutely decisive, though together they are formidable. In the first place it seems impossible that only a single point on the surface of the heart should be cooled; the effective cooling must spread over an area surrounding the thermode. We have no information about the limits of this area. Nor indeed have we the necessary basic information about the action of this drug on the fundamental properties of cardiac muscle. Any stimulus, for instance one arising from the normal pacemaker, entering an area recovering from cooling and already damaged by aconitine might restart a small circus movement. The slow evolution of the reappearing flutter might be due to the gradual recovery in conduction velocity and concomitant reduction in refractory period. And finally the observation of auricular pauses might be due either to occasional blocks developing around the periphery of the circuit, or to inconstant changes in the circuit path. In a single isolated auricle showing repetitive discharges, varying degrees of block have often been observed, and sudden changes of discharge frequency have also been seen, which sometimes proved to be due to an alteration of the circuit path (41). These considerations make it desirable to suspend judgment on the question of whether the aconitine discharge really does arise from a unicellular type of ectopic focus. The analogies drawn with other tissues, particularly with nerve, are very powerful, but they do not constitute scientifically decisive arguments.

It is strange that, while so much attention has been concentrated on the effect

of topical applications of aconitine, until recently relatively little work has been done on the very similar action of cholinergic derivatives. In 1940 Nahum and Hoff (83) found that the application of strips of filter paper (0.2 x 1.0 cm.) soaked in acetyl-β-methylcholine 1:500 to 1:2,000 led in some instances to auricular fibrillation without any further procedures. Local application of atropine prevented this action of the drug. Hirschfelder and Tamcales (79) used this method for testing the ability of some local anaesthetics to stop auricular fibrillation, and Gertler and Karp (69) used it to test atabrine. If it be objected that sufficient of the drug were thereby absorbed or spread over the surface of the auricle, surely the same argument can be applied to experiments using aconitine? And one is tempted to enquire whether the action of the two substances is fundamentally the same. That appears at first sight the inference to be drawn from Scherf and Chick's (166) more recent study of the arrhythmias caused by topical application of acetylcholine to the auricles or ventricles; they concluded that, as with aconitine, their results could not be explained on the basis of circus movements alone. In a later paper (167) they came to somewhat similar conclusions after experiments with topical applications of veratrine. It is a notable feature of all these experiments that strong concentrations of the substance used are required, whether it be aconitine, acetylcholine or veratrine. From the available literature it is not certain whether this will cause a local area of depolarization. This is a possibility, and, when one considers the very strong shocks required to produce ventricular fibrillation by electrical means, suggests that the explanation for all these phenomena may be of a similar nature. The production of an area of myocardial damage, greater in the centre than at the periphery, and of very roughly circular shape is necessarily a common feature of these methods of producing arrhythmias.

Finally there are the experiments of Prinzmetal *et al.* (147, 148) using high-speed cinematography as well as other methods, on flutter and fibrillation induced in the dog by aconitine and electrical stimulation. Observations have also been reported on the naturally-occurring disease in man. The authors have come to the conclusion that the same basic mechanism, a single ectopic focus, is responsible for auricular premature systoles, paroxysmal tachycardia, flutter and fibrillation. The evidence is hard to assess, particularly in respect of the high-speed films. The movement of the wall of the auricle is of a rather gross character, contraction in one part is accompanied by movement in another, and this causes some difficulty in interpretation. While these experiments provide evidence that under the particular conditions used there is no circus movement of a gross character, the intimate nature of the ectopic focus is still undetermined. And we have to set against this general conclusion that large circus movements were not observed the more recent observations of Rosenblueth and García Ramos (155) of just such circus movements in dogs, as well as the very careful and now classical experiments of Sir Thomas Lewis and his colleagues. It is not possible to come to a final conclusion on the present evidence.

It is indeed difficult to believe that evidence *of a quite unequivocal nature*, on the question of whether a unicellular ectopic focus will discharge repetitively in

the manner suggested, will ever be obtained by the application of drugs to the intact, or even perhaps the isolated auricle alone. The spread of the drug following its application by the methods used hitherto is quite beyond the control of the experimenter, who must then rely upon his recording apparatus to determine the size and nature of the centre emitting the consequent rhythmic discharges. Only when the drug is limited to a single cell, perhaps by injection within that cell, or when records are obtained from a single cell, which alone is discharging repetitively, uninfluenced by its neighbours, will a sound experimental foundation be laid for this hypothesis. It should also be acknowledged that the two mechanisms envisaged as determining the rhythm of an ectopic focus, unicellular or small circus movement, are not mutually exclusive. Both may exist and due account must be taken of this possibility.

THE ACTION OF SUBSTANCES WHICH PREVENT OR STOP ARRHYTHMIAS

Prevention or arrest of experimental or human cardiac arrhythmias has been reported with a depressingly wide variety of chemical substances. But before considering the implications of these findings, it is pertinent to enquire what properties they might be expected to possess. This may be considered either from the point of view of a circus movement, or of a unicellular ectopic focus. As to the former it has been recognized ever since the work of Mines (128) and Garrey (67) that prolongation of the refractory period might reasonably be expected to arrest circus movement. But, as Sir Thomas Lewis pointed out, a simultaneous decrease in the conduction velocity will act in the opposite direction. Indeed, since quinidine was found not only to prolong the refractory period but also to slow conduction, these two actions would well explain both the invariable slowing of the auricle which follows the use of quinidine in flutter or fibrillation and the frequent failure to restore a normal rhythm (112). The practical problem of stopping a circus movement is possibly more complicated still, since as the refractory period is prolonged a time will be reached when the excitatory state is travelling in the relative refractory period of the preceding cycle. In such circumstances conduction velocity may be reduced still further. It follows from what has been said of the hitherto widely accepted theory of the action of quinidine in auricular arrhythmias that to be effective a therapeutic agent should prolong the refractory period without unduly reducing conduction velocity. Here we arrive at a virtual impasse. It is certainly possible to measure accurately under standardized conditions the action of drugs, or of alterations in the environment on both refractory period and conduction velocity in heart muscle. But unfortunately no systematic study on both variables has yet been conducted, in spite of the very strong theoretical reasons for supposing that measurements of either alone will not give a reliable indication of the behaviour of a substance on circus movements. There is a further defect in our knowledge of the basic facts about this subject. It is clear that, provided a drug effects a very considerable prolongation in refractory period, some reduction in conduction velocity may be tolerated, as in quinidine; but we know virtually nothing of the quantitative aspect of this relationship. Finally, there is a case for believing that the

ability of quinidine, in sufficient concentration, to reduce excitability, also may play a part in its therapeutic effect on a circus movement. For if we consider the means by which the excitatory state is propagated from one cardiac muscle fibre to the next, then how does the syncytial bridge between the cells operate in practice? It is almost certain that, as in nerve, the size of the action potential, or of the current produced by the activity of one unit will determine whether the next unit is excited. Thus an over-all reduction in excitability may be the crucial factor in determining that the passage of a circus wave, travelling already within the relative refractory period of the preceding cycle, shall fail to excite the next element in the ring, and hence die out.

A similar analysis may be made of the factors likely to influence an arrhythmia controlled by a unicellular ectopic focus, discharging at a frequency inversely related to the refractory period, of the type considered above. In this instance it is obvious that a prolongation of refractory period will reduce the frequency of discharge, and that a reduction of excitability may cause the discharge to cease. Alterations in conduction velocity would here be irrelevant.

On both theories then, a reduction of excitability, accompanied by a prolongation of refractory period, is desirable on theoretical grounds. If the disturbance is due to a circus movement, due account will also have to be taken of the conduction velocity. As DiPalma and Schultz (48) have pointed out, the ideal "anti-fibrillatory" drug should also have other properties, more in the nature of omitting unpleasant potentialities than in possessing desirable ones. For instance it should not reduce the contractility of cardiac muscle, it should not itself lead to cardiac irregularities, it should not cause unpleasant side-reactions, it should be readily assimilable, and its blood concentration should be easily maintained for an effective period of time.

Perhaps the most extraordinary feature of the substances which have been used in the treatment of cardiac arrhythmias is that quite a number of them appear on occasion to have precipitated yet more serious or even fatal arrhythmias. That this is true of quinidine is widely known, and DiPalma and Schultz (48) have pointed out once again the particular hazard of using quinidine in the presence of myocardial damage or a conduction defect. Perhaps it is unwise to argue from experience in man, however alarming it may be, since in such instances myocardial damage is almost certainly present and it is by no means certain to what extent this may have contributed to the outcome. But what are we to make of the observation that α-fagarine, a drug which has been submitted to extensive experimental and clinical trial as a substitute for quinidine, may also produce ventricular tachycardia and fibrillation on intravenous administration to presumably normal animals (48)? It would be valuable to be assured that this action of α-fagarine is not simply a terminal event brought about by a severe cardiovascular disturbance, and that it really is due to direct myocardial action. There is good evidence that α-fagarine prolongs the refractory period, reduces excitability and slows conduction velocity (10, 43, 132–134). Scherf (165) found that it stopped auricular fibrillation produced in dogs by local application of aconitine, and Tacquini (189) found a similar therapeutic effect in man. Yet

though it may be used successfully clinically, multifocal ventricular extrasystoles may also result, even though a normal sinus rhythm has been restored (171). Recently DiPalma and his colleagues (46, 49) have had a very similar experience with another compound, a synthetic analogue of α-fagarine. On the other hand, there appear to be no records of similar accidents with substances like procaine, possibly because its toxic effect on systems other than the cardiovascular are of predominant importance.

While there is not sufficient evidence to suggest how these substances themselves cause ventricular tachycardia or fibrillation, one point may be made. In considering the effects of various forms of damage to the myocardium, in particular that due to ether and chloroform, it was observed that deep chloroform (111, 192) and ether anaesthesia (73) reduced the liability to arrhythmias. It is therefore unlikely that all types of severe myocardial damage by drug action predispose to ventricular fibrillation.

Consideration of the other properties shown by substances which have been used successfully in the treatment of experimental or clinical arrhythmias does not throw much further light on the nature of these arrhythmias. They all prolong the refractory period, and reduce excitability and conduction velocity, in so far as these have been measured by reliable methods. It is also interesting that these substances are local anaesthetics (37, 38, 48) (data on this point appear to be lacking for α-fagarine), and so may be presumed to have similar actions upon nerve. Here is a further analogy, similar to that drawn in preceding sections of this review on the ability of the same substances to elicit repetitive discharges both in nerve and cardiac muscle. It is difficult to disregard the implication that the fundamental mechanism which determines excitability is the same in both tissues, even though the time course of the action potential shows such differences.

METHODS

There are only a limited number of methods for investigating the quinidine-like action of drugs, on which sufficient work has been done to assess their reliability. Whether even these are likely to pick out the right therapeutic compound is still a matter of opinion. There is no doubt that the basis of all these methods is empirical, for there are but two alternatives. Either you select a method of producing a cardiac arrhythmia experimentally and see if one substance is better than another at preventing or arresting it, or you measure the change caused by the drug in some property of cardiac muscle which on theoretical grounds is thought to be of crucial importance in the development or maintenance of that arrhythmia. The assumption involved in the latter method is far from being a matter of scientific certainty.

1. *Levy's method*

By this is meant all those methods in which chloroform, benzol or cyclopropane are used in combination with adrenaline to produce ventricular arrhythmias. This method has already been discussed in considerable detail above, and

reference has been made to the standardization of technique introduced by Meek, Hathaway and Orth (126), and to the necessity of considering the role played by the blood pressure in this procedure. (There is evidence that quinine (96) and quinidine (39) may reduce the pressor action of adrenaline while small doses of procaine (117), may actually increase it.) Wégria and Nickerson (203) have also introduced a modification of the method, in which the use of benzol is preferred as being more reliable in the production of arrhythmias, and in which ventricular fibrillation is stopped by "A.C. counter-shock." A number of trials are therefore possible before and after the administration of the substance to be tested. This method obviously has much to recommend it, as adequate control observations are possible on the same animal, and it is not necessary to rely so much on statistical treatment of the fate of groups of animals.

There is one further critical consideration which must be borne in mind, that is the effect which a compound of potential therapeutic use may have in decreasing or increasing the release of endogenous sympathomimetic substances, or in modifying directly the cardiac action of adrenaline or of the anaesthetic used. Perhaps an example of this potential fallacy may be given. It is conceivable that a substance may prevent adrenaline having its myocardial action by competing for the same receptors in the heart; such a substance would be expected to prevent adrenaline-cyclopropane induced arrhythmias, but would not necessarily prevent or cure the human disease. According to Stutzman and Allen (186), as mentioned above, prolonged exposure to cyclopropane itself has an "adrenolytic" action. It is interesting that recently Krayer and his collaborators (97–99, 102–104) have found a number of substances that antagonized the cardio-accelerator action of adrenaline; quinidine also possessed the same property (100). It is highly unlikely that this is a specific action of quinidine in the sense used above; it is probably one manifestation of the direct myocardial action of quinidine, yet the precise implications of this antagonism are intriguing. Another example of the possible difficulties in interpretation using this method is to be found in experiments with local anaesthetics like procaine. Since all methods suggest that procaine prevents arrhythmias, and its use in surgical practice is satisfactory, there seems little doubt of its efficacy. This does not mean to say that successful experiments with the cyclopropane-adrenaline method alone have established its efficacy *with scientific accuracy*, for procaine is a sufficiently potent local anaesthetic to block both afferent and efferent nervous pathways (27, 117, 182). One group of workers at least have come to the conclusion that even procaine affords no practical protection (89), though the methods they used differed in some details from those of other workers (31, 187). It appears that the effect of procaine in such tests is very shortlived, as is only to be expected by its rapid breakdown and removal from the bloodstream (28, 115, 178, 180), and this may well explain the discrepancy. It is a little surprising that since this substance (like many others) is administered by slow intravenous infusion during anaesthesia pharmacologists have not made wider use of this method of administration. No doubt this will be necessary in the future. The multitude of variables involved also explains why there are discrepancies in the literature as to the efficacy of

ergotamine (8, 143, 145) and of procaine amide (119, 135). Nickerson and Smith (143) have even remarked on a seasonal variation in sensitivity to cyclopropane-adrenaline induced arrhythmias.

Much useful information has been gained with this method, but it is quite clearly incapable of giving a quantitative answer, and it is even doubtful whether substances possessing a small degree of activity can be distinguished from those possessing none at all. There does not seem to be any fundamental reason for using cyclopropane rather than chloroform or benzol, though there is perhaps the practical reason that more recent (American) work has been carried out with the former, and so the results from different laboratories may be more readily compared.

2. *Barium and aconitine methods*

These include methods based either on the intravenous injection or the topical administration of barium chloride, aconitine, acetylcholine, acetyl-β-methylcholine and other substances. It seems likely that more such compounds will come to hand in the future, as in the recent report of ventricular arrhythmias caused by 2489F (93) and of auricular fibrillation caused by some propylene glycol derivatives (181). All such methods are bound to be of qualitative value only, and some of the considerations discussed in relation to the "Levy methods" also apply, since these experiments are usually performed in whole animals, and not all the variables have yet been investigated. Mention should also be made of the use by Tripod (195) of perfusion of the Langendorff (106) preparation of the cat or rabbit heart with varying concentrations of aconitine to produce arrhythmias. In conjunction with some other quantitative test, these methods give greater assurance before proceeding to clinical trial, and they appear to have been used in this way occasionally (25).

3. *Arrhythmias produced in the whole animal by electrical stimulation*

This includes the oldest experimental method of producing auricular or ventricular arrhythmias by direct faradization. Wiggers and Wégria (210) in a very lucid and critical exposition of these methods came to the conclusion that the common feature of them all was the interposition of a *single* effective shock during the vulnerable period. Rhythmic stimulation by an induction coil, or by more reliable methods such as rectangular pulses of predetermined duration or sine-wave pulses, was therefore a more elaborate and less satisfactory procedure. Evidence was adduced to show that prolonged oscillating currents give erratic responses (204, 205) and that the duration of fibrillation thus excited in cats, or the number of times spontaneous recovery occurs (58), are not reliable indications of a therapeutic action. On these grounds they based their conclusion that the "fibrillation threshold" in dogs as measured by a single shock delivered during the vulnerable period was to be preferred. However, Wégria and Nickerson (203) later came to the conclusion that this method was rather difficult and tedious. The current strength required was very large, and it is interesting to observe that in a recent paper DiPalma, Lambert, Reiss and Schultz (46, 49),

reverting to the use of rhythmic pulses (wave-form and duration not recorded) at a fixed frequency of 600 per minute also had to use very strong stimuli (threshold between 2 and 8 ma.) in order to produce ventricular fibrillation in cats. For comparison it is worth recording the fact that the threshold current required to excite the isolated mammalian auricle is less than 0.1 ma. (rectangular pulse form, duration 2–5 m.sec.), and that repetitive discharges can be initiated by an interpolated pulse very little stronger, usually not more than 0.2 to 0.3 ma., and sometimes even less. DiPalma and his colleagues (46) found their method satisfactory for quantitative evaluation of the relative activity of a number of synthetic compounds, though they do not appear to have checked it by using substances whose activity has been tested by other methods, and the criticisms offered by Wiggers and Wégria (210) still apply. Only the latter appear to have had practical experience of both types of method, though admittedly they did not use cats. It may well be that the use of cats, in which the fibrillation is evanescent, is better than that of dogs, in which ventricular fibrillation is usually fatal, and has to be stopped by strong electrical stimulation ("serial defibrillation" or A.C. countershock).

Whether the form of electrical stimulation is by a single pulse delivered during the vulnerable period, or by rhythmic pulses from an induction coil or less variable form of stimulator, and whatever the view held as to the mechanism whereby the arrhythmia is thus started, there can surely be no doubt as to one general conclusion. If a substance reduces the excitability of the myocardium a greater current strength will have to be used either to excite a single response or to cause flutter or fibrillation. In that case the ability of a substance to raise the "fibrillation threshold" the expression used by Wiggers and Wégria, is not necessarily an indication of a specific ability to prevent arrhythmias; it may be due to reduced myocardial excitability. Of course it is very likely that reduced myocardial excitability is one of the fundamental properties required in an effective therapeutic agent for treating cardiac arrhythmias, but there are certainly more direct, more reliable and less drastic methods of measuring excitability than by measuring the "fibrillation threshold" in any of the ways described. Wiggers and Wégria have considered this proposition, and took the view that it still remains to be demonstrated that there is a relationship between the strength of the diastolic stimulus necessary to evoke a premature contraction and the stimulus necessary to cause fibrillation. This is indeed the essence of the problem, but in view of the very well established fact that quinidine and procaine (to take two specific examples), both substances which raise the fibrillation threshold (202, 210), also reduce myocardial excitability (17, 51, 121), it is really up to those who use these methods to show that they are measuring the specific ability of a substance to prevent fibrillation rather than reduce myocardial excitability. Indeed, in the summary to their paper, Wiggers and Wégria (210) also state their belief that the "fibrillation threshold" of the dog's ventricle as measured by their method "takes into account the irritability of non-refractory myocardial fractions during the vulnerable phase of systole, and also any local state that may be necessary for the initiation of ventricular

fibrillation." To the reviewer this statement seems to be a virtual abandonment of the whole position, for if the method takes into account myocardial irritability or excitability, what grounds have we for supposing that any active substance affects the local state necessary for the initiation of fibrillation? Until it can be conclusively demonstrated that these methods do more than measure (somewhat indirectly) the effect of a substance on myocardial excitability, it is illogical to attach to this measurement a greater significance.

4. *The ability to stop an established arrhythmia*

The ability of a substance to stop an established arrhythmia in an experimental animal is clearly an excellent demonstration of therapeutic action before proceeding to clinical trial. By its very nature however it is not a test that can conveniently be put on a quantitative basis. There are isolated examples in the literature of substances which are claimed to have been effective in arresting ventricular fibrillation (17), but some doubt is attached to this interpretation because of the cardiac massage and other procedures which are necessary at the same time. Of more practical interest is the development by Rosenblueth and García Ramos (155) of a method, already referred to above, of ensuring that auricular flutter once established by electrical stimulation in the dog shall continue without spontaneous arrest. Brown and Acheson (27) have demonstrated the ability of procaine and two related compounds to cause reversion to a sinus rhythm in this preparation. Auricular fibrillation induced by the administration of drugs could presumably be used in the same fashion, if it were certain that spontaneous reversion did not occur during the course of the experimental period.

5. *Isolated preparations*

Isolated preparations of the auricle or ventricle have been used very extensively for the investigation of the fundamental properties of cardiac muscle. The papillary muscle of the cat's heart has the particular advantage of being readily isolated and containing mainly parallel bundles of fibres (33, 72). Auricular muscle preparations are more complex in nature. One of the latter was used for the determination of the "maximal rate" at which the muscle would follow electrical stimuli, as a readily determined index of the refractory period (37, 38). This method has been used by a number of workers to determine quinidine-like activity (1, 10, 45, 53, 55, 59, 122) and the observation that the percentage decrease in maximal rate is linearly related to the logarithm of the drug concentration has been confirmed. However a number of radical modifications in the procedure adopted is desirable. It should be explained that this method was developed towards the end of World War II because of the sudden scarcity of quinidine. Time could not then be spent in constructing the apparatus for direct measurement of the refractory period, and an approximation which was easy to measure (but less easy to interpret) was adopted instead. Now that the urgency no longer exists the method should be superseded by one in which the refractory period is measured directly, and not merely the refractory period but excitability and conduction velocity at the same time. The isolated guinea-pig or rabbit

auricle can be used at 37°C for this purpose, with action potentials recorded from one or more points as an index of activity. Apart from other considerations, the slope of the curve relating refractory period and temperature is much less steep at 37°C. The auricle is driven by a just supra-threshold stimulus at a frequency just greater than its natural sinus rhythm, and a second stimulus interpolated to test the return of excitability. It has been found desirable to pay attention to the following points (40, 41); the refractory period must be measured by plotting the whole of the excitability curve, so that the limits of both absolute and relative refractory period are delineated; the refractory period so measured varies with the frequency of the driving stimulus (as is well-known), and with the relative frequency at which the test stimulus is applied and with the strength of the driving stimulus. A little consideration of these observations shows that it is most unlikely that the "maximal rate" as previously determined is simply related to refractory period as usually defined. And it is doubtful whether many of the figures recorded for refractory period in the literature are quantitatively reliable, since the influence of all these variables has not always been recognized. It may be argued that the "maximal rate" is a useful approximation, and that in practice it appears to give an index of activity which is roughly justified by experience. Nevertheless its future use cannot be regarded as anything but a retrograde step, when the alternative is presented of direct measurement of properties which are defined so as to be as unambiguous as possible and which are generally regarded as fundamental to the nature of cardiac muscle. Similar measurements on comparable preparations of ventricular muscle are also desirable, and DiPalma and Mascatello (47) have evidently made a beginning in this direction. Finally, it is perhaps appropriate to emphasize once again the importance of gaining some information about the action of potential anti-fibrillatory drugs on the membrane potentials of single cardiac muscle fibres.

6. *General considerations*

The danger of relying too much on results obtained by bioassay on isolated tissues is well recognized; in the intact animal there are so many other variables which play a part. In this particular field concerned with the search for drugs which will arrest or prevent cardiac arrhythmias many, but possibly not all, of these variables have been recognized. It would be most unwise to proceed without tests in the whole animal as well as on isolated tissues, and some combination of these techniques may prove to be the best. On the isolated auricle or ventricle it is practicable to devise a routine method of comparing the quantitative effects of drugs on the fundamental properties of the heart. A selection of those which seem most promising might then be tested on one or more of the qualitative whole animal techniques, of which Wégria and Nickerson's benzol-adrenaline technique with A.C. countershock to stop ventricular fibrillation (203), Scherf's aconitine method (169) or Brown and Acheson's use (27) of Rosenblueth and García Ramos' auricular flutter method have much to commend them.

Finally it must be borne in mind that drugs of this type are required for dif-

ferent therapeutic purposes, for arresting established auricular flutter or fibrillation, for preventing ventricular fibrillation during intra-thoracic operations and for preventing paroxysmal tachycardia. For some of these purposes it is clearly desirable that an effective drug should be assimilated readily by mouth, and that the blood concentration should not fall too rapidly; quinidine fills this particular requirement moderately well. For other purposes, as during surgery, a long duration of action is not so essential, and procaine, which is more rapidly eliminated, may be given by slow infusion intravenously; the blood concentration is in this instance more directly under the control of the anaesthetist. In setting up a systematic investigation of these drugs, therefore, some consideration of the duration of a drug's therapeutic effect is necessary, as well as of its undesirable toxic properties. The fact that the therapeutic action is transient does not preclude it from being very useful in particular clinical applications, and reduces the danger of prolonged excessive dosage.

RESULTS

From what has been said on the critique of the various methods, it will be appreciated that it is far from easy to reach any conclusions, on a firm scientific basis, about the quantitative activities of substances tested. Where an author has measured the activity of a number of substances, using the same method, he is naturally entitled to draw conclusions within the limits of reliability of that method; the applicability of these conclusions to the problem of naturally occurring arrhythmias in man is another matter. All this is so obvious that it is perhaps impertinent to restate it. Strict quantitative comparison of results obtained by one technique with those obtained by a method based on a fundamentally different concept is not logically justifiable. Such comparisons are useful in suggesting the lines which new work shall follow, but they cannot be regarded as providing firm evidence of relative activity. This is of course a principle which is generally acknowledged in any scientific enquiry, but it applies with particular force to this field in which so many methods have been used, and in which the relevance of any method to the therapeutic object rests on insecure foundations.

In only a few papers have the activity of any substantial number of compounds been compared by the same worker in the same laboratory over a short period of time (38, 46, 72, 122, 134) and it is not possible to compare the activities recorded in all these series for the reasons discussed above. Apart from these papers a heterogeneous collection of compounds have been studied by widely differing methods, of a variety which it is hardly possible to classify. A general description of some of the more interesting of these classes of compounds and their therapeutic use has been given in a recent review by DiPalma and Schults (48) to which reference may be made. There are only a few selected topics on which further comment seems desirable.

The appended table gives a list of results obtained by a number of authors with different methods, using quinidine and procaine. The wide variation in what is regarded as an effective dosage does not engender very great confidence

in the quantitative value of these methods considered as a whole. It is interesting to observe that among the lowest effective doses recorded for either substance is that needed to restore a normal rhythm in continuing auricular flutter in the dog (Rosenblueth and García Ramos' technique). And this once again makes one wonder what the other methods are really measuring. It is interesting to calculate what the approximate blood levels in some of these experiments

TABLE 1

Results obtained with quinidine and procaine by various methods

DOSE REQUIRED TO PROTECT AGAINST:	SPECIES	QUINIDINE	PROCAINE	REF.
Cyclopropane-adrenaline arrhythmias	Dog	Slight 5 mg./kg. Clearcut 10–15 mg./kg.	Just significant 10 mg./kg.	(143)
	Dog	15 mg./kg.	12–16 mg./kg.	(8)
	Dog		5 mg./kg.	(30) (31)
	Dog	1–20 mg./kg.*		(88)
Chloroform-adrenaline arrhythmias	Dog		4–5 mg./kg.	(180)
Benzol-adrenaline arrhythmias	Dog		8–10 mg./kg.	(178)
	Dog	5–15 mg./kg.		(203)
Electrically induced auricular arrhythmias	Cat and Rabbit		2.5 mg./kg.	(197)
	Dog		10–20 mg./kg.	(79)
	Rabbit	1 mg./kg.		(134)
Electrically induced ventricular arrhythmias	Dog	2.4 mg./kg.	8–10 mg./kg.	(202) (210)
	Cat	3.5 mg./kg.		(173)
	Rabbit	1 mg./kg.		(134)
Auricular fibrillation induced by acetyl-β-methyl choline	Dog		1–6 mg./kg.	(79)
Dose required to arrest continuing auricular flutter	Dog	1–2 mg./kg.	1–2 mg./kg.	(1) (27)

* All doses effective 10 min. after injection; thereafter duration of protection varied with the size of dose.

may have been. After a rapid intravenous injection of procaine into a dog, in a dose of 10 mg./kg., the blood procaine level rose in 10 seconds to 70 mg./L and after 5 minutes was only 5–10% of this (3.5–7.0 mg./L) (115). Similar observations have been made on cats (28). Since different workers have tested the protection given by procaine at different times after its injection it is difficult to draw any firm conclusions about the therapeutic blood level required in these experimental procedures. The comparable data on man are more informative.

In clinical use procaine may be infused at rates of 10–60 mg./min. (190), or given in single intravenous injections of 100 mg. (32), sometimes repeated. Blood procaine levels of less than 1 mg./L (26) up to as much as 8 mg./L (90) have been recorded. The blood concentration of quinidine following single oral doses of 0.6–1.0 Gm. in man has also received much attention recently (42, 78, 95, 114, 201). The concentration of quinidine in the plasma at the time of conversion from auricular fibrillation to a normal sinus rhythm has been recorded as varying from 3.3 to over 20 mg./L, though few patients required more than 10 mg./L (95, 185). A concentration of 10 mg./L of either procaine or quinidine would be expected to cause a considerable decrease in the maximal rate of the isolated auricle when it had reached equilibrium (10, 38, 122), and has also been shown to prevent the arrhythmias caused by aconitine in the perfused heart (195). There is therefore a reasonable measure of agreement as to the effective concentrations.

STRUCTURE AND ACTION

As DiPalma and Schults (48) have pointed out, the ability of atropine to prevent or to arrest arrhythmias has often been considered, and there is evidence to suggest that under particularly favourable conditions it may sometimes be effective. The implications of this conclusion are less easy to analyse. Atropine is often regarded as the type-substance of a particular class of compounds which antagonize the muscarinic actions of acetylcholine, but it has other properties in addition. It is believed to possess a feeble local anaesthetic action and when used in high concentration reduces the "maximal rate" of the isolated auricle (38). This no doubt is a partial explanation of why it is sometimes effective in preventing cardiac arrhythmias. It also abolishes the effect of acetylcholine in reducing the refractory period, which may be another reason for its efficacy. The use of atropine as a type-substance can therefore be misleading. There are good grounds for preferring the quaternary metho-salt of atropine, or some other quaternary ammonium salt of similar structure and activity for this purpose (92) as such substances do not possess local anaesthetic activity. And it is interesting to recall that quaternary salts of local anaesthetics which have a quinidine-like action are themselves inactive. This raises once again the theoretical consideration as to which constituent, the base or cation, of a solution of a local anaesthetic (or indeed atropine) is the active one, and indicates the desirability of repeating Trevan and Boock's (194) experiments, using cardiac muscle instead of the cornea, and measuring excitability and refractory period instead of local anaesthetic activity.

Since quantitative data on the relation between structure and action in this field are so limited it is unprofitable to discuss the details of this aspect of the problem further than has already been done (38, 46); yet there are certain general considerations which may be worth mentioning. It has already been pointed out that saligenin, a moderately powerful local anaesthetic of very different structure than procaine, possesses no basic group and has no action on the auricle in high concentrations (38). But Diethyl-amino-ethanol and some of its

derivatives (27, 118, 154) are active, and it is evident from this work that the aromatic group is not essential for activity, though its presence very greatly increases activity. Whether this is accompanied by a yet greater increase of toxicity may depend on the nature of the aromatic group. Another transformation of the parent molecule has yielded procaine amide (119) which is more stable than procaine in plasma, though less active. It can be taken by mouth and has been used therapeutically in man (18), where it is said to be more effective and less toxic than quinidine for the treatment of ventricular arrhythmias.

Although all these substances which have proved effective in preventing cardiac arrhythmias possess a more or less distant structural relationship to the well-known local anaesthetics, and so far as they have been examined are themselves local anaesthetics, it should not therefore be concluded that "quinidine-like activity" is necessarily confined to this broad structure type. The possibility that dibenamine may have a direct myocardial action as well as an adrenolytic effect has been debated (1, 142). The general anaesthetics certainly possess rather similar attributes. They block conduction in nerve, and there is good reason to suppose that chloroform and ether will if given in sufficient concentration prevent the development of cardiac arrhythmias (73, 111, 192). These general anaesthetics have a very considerable action on the central nervous system, quinidine and procaine a much less considerable effect, and procaine amide and diethyl-amino-ethanol less still according to early reports. There is a reasonable chance of yet further improvement.

In conclusion, it seems that because of our lack of certainty about the basic physiological mechanisms responsible for the various forms of cardiac arrhythmias in man, and because of the unreliability of methods for testing appropriate therapeutic agents in animals, we are bound to proceed for some time to come on an empirical basis. This is occasioned by the multitudinous factors involved in investigations of activity and toxicity in the whole animal. Nevertheless it is felt that systematic experiments on isolated tissues, combined with greater realisation of the factors which may influence the outcome of experiments in the whole animal, are likely to improve the position in the future, and lead to a more rational appreciation of the fundamental properties desired in an effective therapeutic agent.

SUMMARY

1. The methods of producing cardiac arrhythmias in experimental animals have been surveyed from the point of view of the variables which determine whether an arrhythmia results. These include the level of the blood pressure, the oxygen saturation of the blood, myocardial damage and perhaps the endogenous secretion of sympathomimetic amines.

2. Some of the methods for producing cardiac arrhythmias, such as the use of barium chloride, the veratrum alkaloids and aconitine, suggest an analogy with nervous tissue, in which these substances cause repetitive discharges, super-

normality and an increase in the negative after-potential. This is only part of the evidence which suggests that many of the variables which influence the outcome of these and other procedures in the intact animal may have a common basis in their effect on the membrane potentials of individual cardiac muscle fibres.

3. The meaning of the term "ectopic focus" has been examined. Two hypotheses which may explain the origin of discharges from an ectopic focus were considered in relation to the experimental evidence.

4. In the light of the evidence outlined above, the prerequisites for a therapeutic agent to prevent or arrest arrhythmias have been discussed, and the methods used for measuring "quinidine-like" activity criticised. There seems little likelihood of removing these methods from their present empirical foundation without further knowledge of the behaviour of single myocardial cells. In the meantime it is desirable to recognize the tacit assumptions on which these methods are based.

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