children born in recent years, as essentially all calcium available in the biosphere is, and will be, contaminated with Sr^{90} from weapon tests.

If in the first instance considered above a uniform contamination is assumed, 7000 g of bone will receive an average dose of 7.25 mrem/day. This dose rate is maximal to red bone marrow, which on the average receives 1.5 mrem/day. The degree of mineralization varies, however, and it is found, on comparing regions of the same dimensions as the average beta range ($\sim$ 2 mm), that there may be calcium concentrations which differ from the average by a factor of 2 to 3. This implies that certain parts of the bone and bone marrow may receive doses of around 15 mrem/day.

It is apparent, however, that a constant intake of Sr^{90} will not give a nonuniform contamination of the skeleton in the sense described above. The mechanism of remodeling and exchange gives rise to a biological half-life for Sr^{90} in the skeleton, and the radioactive decay has some influence, as well, on the equilibrium state. If we assume an effective half-life of 2700 days (7.4 years), the Sr^{90} concentration may be expected to vary from the average by a factor of about 2 for a 15-year period and by successively larger factors for longer periods. To some extent this fact is accounted for by the differences in mineralization. Therefore in the case of chronic poisoning with Sr^{90} a higher figure than 0.1 μc is tolerable as total body burden; tentatively, the 1 μc level may be considered to be tolerable.

Today the Sr^{90} contamination of the geosphere and the biosphere is steadily increasing. This corresponds to a situation with aspects that lie somewhere between those of acute and chronic Sr^{90} poisoning. Children in the 0- to 5-year age group are examples of individuals with chronic poisoning conditions. Adults above 20 years of age are more likely to be examples of acute poisoning.

It should finally be pointed out that the conditions described here in relation to Sr^{90} have their counterpart for other isotopes. For instance, it seems that the evaluation of the hazards from radium poisoning should take into account the difference between acute and chronic poisoning. This is the more advisable since the short range of Ra alpha particles will cause greater differences in the local dose rates than is the case with Sr^{90}.

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Notes

1. An extensive bibliography is to be found in A. Engström *et al.*, *Bone and Radiostrontium* (Almqvist and Wiksell, Stockholm, 1958).
2. This article is part 3 of a series on health hazards from fission products and fallout; for part 1, see K. Low and R. Björnerstedt, *Arkiv Fysik* 13, 85 (1957); part 2, by R. Björnerstedt, is in preparation.

27 October 1958

Release of Autonomic Mediators in Cardiac Tissue by Suprathreshold Stimulation

Abstract. Pharmacological evidence is presented supporting the theory that the increase in contractile strength of isolated cardiac muscle under suprathreshold stimulation is due to the release of an adrenergic mediator (norepinephrine). However, release of this material does not account for changes in contractile strength associated with changes in frequency of stimulation at threshold levels.

Whelan *et al.* have reported that during periods of suprathreshold stimulation (stimulation at voltages well above threshold) contractile force of isolated cat papillary muscle gradually increases, while that of the cat atrial strip gradually decreases, or first decreases and then increases (*1*). They tentatively attributed these alterations in force to release of autonomic mediators by the suprathreshold stimuli, release of acetylcholine mediating a decrease, and release of "one of the epinephrine compounds" mediating an increase. A similar postulate had been made previously by Nelemans (*2*) and by Ursillo (*3*) to explain force changes following short periods of tetanic stimulation of spontaneously beating frog heart and mammalian atria, respectively.

Several years ago, while working with isolated left atria, we encountered the same phenomena reported by Whelan (*4*). With guinea-pig atria at both 27° and 37°C, suprathreshold stimulation increased contractile strength (Fig. 1*B*), whereas with rat atria at 27°C, it produced either a decrease or a decrease followed by an increase. Since the decrease in contractile strength produced in rat atria could be blocked by atropine and potentiated by physostigmine, we concluded that it was mediated by released acetylcholine. However, we were unsuccessful in our early attempts to obtain convincing pharmacological evidence that the increase in contractile strength produced in guinea-pig atria was due to release of adrenergic mediator, since none of several adrenergic blocking agents, including dibenamine, available to us at the time produced a clear-cut blockade of the increases in strength elicited by epinephrine and norepinephrine.

During the past year we have returned to the problem of identifying the potentiating material released by suprathreshold stimulation of guinea-pig left atria, making use of two newer pharmacological agents. One of these agents is 1-(3′,4′-dichlorophenyl)-2-isopropylaminoethanol hydrochloride (DCI), which recently has been reported to be an effective blocking agent against both the inhibitory effect of sympathomimetic amines on certain smooth muscles and the stimulating effects of these amines on the heart (*5*). The second agent is reserpine, which causes a rapid and drastic depletion of the endogenous catechol amines (chiefly norepinephrine) of cardiac tissue when it is administered to animals at high dose levels (*6*).

Exposure of guinea-pig left atria to about 10^{-4} g of DCI per milliliter for 10 to 20 min effectively antagonized the positive inotropic action of epinephrine and norepinephrine (Fig. 1, *A* and *C*). The antagonism persisted for long periods after washout of the DCI, whereas certain undesirable side effects of DCI at the concentration used—such as de-

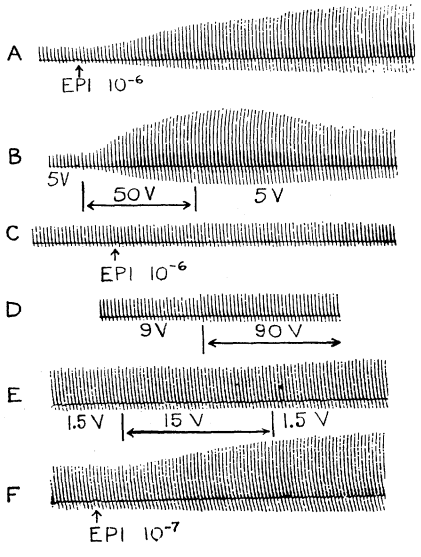

Fig. 1. Effects of suprathreshold stimulation and of epinephrine on contraction amplitude of isolated left atria of guinea pig under various conditions. Recordings were made with an ink-writing isotonic lever, exerting 1*g* tension on the atrium, which was suspended in 20 ml of oxygenated Krebs bicarbonate solution (*p*H 7.4) at 27°C. The stimulus was provided by a Grass 4C stimulator (biphasic pulse, 1 to 2 msec duration) at a frequency of 1 per second through Ag-AgCl electrodes. *A*, Effect of epinephrine on atrium from a normal guinea pig; *B*, effect of suprathreshold stimulation on the same atrium; *C*, effect of epinephrine on the same atrium after treatment with 10^{-4} DCI for 10 min; *D*, effect of suprathreshold stimulation on the same atrium after DCI treatment; *E* and *F*, effects of suprathreshold stimulation and of epinephrine on atrium from a reserpinized guinea pig.

pressed contractile strength, increased refractory period and threshold, and partial conduction block—largely disappeared within about 30 min after washout (7). Therefore, quantitative testing for adrenergic blockade was usually carried out about 30 min after washout of DCI. Despite its persistence, the blockade appeared to be of the reversible competitive type, susceptible to "breakthrough" by very high concentrations ($\sim 10^{-5}$ g/ml) of epinephrine and norepinephrine. That the blockade was relatively specific was indicated by the fact that DCI did not significantly antagonize the positive inotropic effects of added Ca^{++} or strophanthin. On the other hand, the increase in strength with suprathreshold stimulation was antagonized by DCI as effectively as was that due to added epinephrine or norepinephrine (Fig. 1, *B* and *D*). This finding strongly supports the hypothesis that the increase with suprathreshold stimulation is mediated through release of some adrenergic substance (probably norepinephrine).

Additional strong evidence for the hypothesis was obtained with atria from guinea pigs which had been pretreated with reserpine (approximately 1 to 5 mg/g day intraperitoneally for 1 to 2 days) in order to deplete cardiac catechol amines. Such atria still responded well to added epinephrine or norepinephrine, but with suprathreshold stimulation they now gave either no significant increase in strength or a slight decrease (occasionally followed by a slight delayed increase) (Fig. 1, *E* and *F*). It should be noted that Burn has similarly used reserpine to show that the stimulating effect of nicotine on isolated rabbit atria is actually due to adrenergic mediator released by this agent (8). We have confirmed Burn's results with nicotine, using normal and reserpinized guinea-pig atria, and in addition have found that DCI can block the positive inotropic action of nicotine.

In preliminary experiments on cat papillary muscle, DCI and reserpine have yielded results completely analogous to those reported above for left atria of guinea pigs. Thus, we directly support Whelan's hypothesis that the increase in contractile force of papillary muscle with suprathreshold stimulation is due to the release of "one of the epinephrine compounds." However, we must disagree strongly with Whelan's suggestion that "epinephrines" and acetylcholine, released at each spontaneous beat or electrically driven beat at threshold voltages, are responsible for such phenomena as positive treppe and poststimulation potentiation. Such phenomena are still strikingly demonstrable in both guinea-pig atria and cat papillary muscles when potentiation due to suprathreshold stimulation has been eliminated by DCI or reserpine (9). Also, negative treppe in isolated rat atria is not altered by atropine blockade of the depression due to suprathreshold stimulation.

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References and Notes

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2. F. A. Nelemans, *Acta Physiol. et Pharmacol. Neerl.* 2, 51 (1951).
3. R. C. Ursillo, *J. Pharmacol. Exptl. Therap.* 122, 78A (1958).
4. The first part of the work discussed in this report was carried out at Washington University in 1953 by the senior author and Mrs. de Gubareff, with support from the American Heart Association. The second part, involving DCI and reserpine, was carried out at the State University of New York during the past year by the senior author and Mr. Grossman, with support from the New York Heart Association. We are indebted to Dr. I. H. Slater of Eli Lilly and Co. for the DCI and to Dr. A. J. Plummer of Ciba Pharmaceutical Products, Inc., for the reserpine used in this study.
5. C. E. Powell and I. H. Slater, *J. Pharmacol. Exptl. Therap.* 122, 480 (1958); N. C. Moran and M. E. Perkins, *ibid.* 122, 55A (1958).
6. A. Bertler, A. Carlsson, E. Rosengren, *Naturwissenschaften* 43, 521 (1956); M. K. Paasonen and O. Krayer, *J. Pharmacol. Exptl. Therap.* 123, 153 (1958).
7. Lower concentrations of DCI (10^{-6} to 10^{-5} g/ml) produced insignificant side effects of the types mentioned and usually strengthened contractions somewhat but did not produce a sufficient degree of blockade for our purposes.
8. J. H. Burn and M. J. Rand, *Brit. Med. J.* 1958I, 137 (1958).
9. W. Sleator and T. de Gubareff [*The Physiologist* 1, 4, 73 (1958)] have recently used reserpine to show that treppe in guinea-pig atria is not due to release of adrenergic mediator.

12 September 1958

Earth Oblateness in Terms of Satellite Orbital Periods

Abstract. A theoretical equation relating the earth's oblateness to the anomalistic and nodical periods and orbit parameters of an earth satellite is presented. In the absence of exact data on nodical periods, Vanguard prediction data are utilized to obtain a check calculation for the oblateness and to establish the validity of the method.

The utility of artificial earth satellites for independent determination of the earth's oblateness by means of observations of the secular perturbations of the orbit [precession of the node and of perigee (1)] is well recognized. In the course of studies of such orbit perturbations, I have derived an equation for the difference between the anomalistic period T_A (perigee to perigee) and nodical period T_N (node to node) which should provide an additional independent means for determining the oblateness. Specifically,

$$T_A - T_N = \frac{JR^2 r_o^2 T_o}{a^4(1-e^2)^{5/2}}\left(2-\frac{5}{2}\sin^2 i\right) = \frac{2\pi JR^2 r_o^2}{(GM)^{1/2}a^{5/2}(1-e^2)^{5/2}} \times \left(2-\frac{5}{2}\sin^2 i\right) \quad (1)$$

where J is the coupling constant in the oblate earth's potential (2), R is the equatorial radius of the earth, r_o is the distance from the center of the earth to the satellite at the node, T_o is the satellite period for an assumed spherical earth, G is the constant of gravitation, M is the mass of the earth, a is the semimajor axis of the orbit, e is the orbital eccentricity, and i is the angle of inclination of the orbit to the plane of the equator.

Because of the precession of the line of apsides (3) r_o will range in magnitude from a perigee distance of $(1-e)a$ to an apogee distance of $(1+e)a$; and we come to the interesting conclusion that the difference between the anomalistic and nodical periods will exhibit a cyclic variation whose period is equal to that of the precessional motion of the line of apsides. The extremes of $(T_A - T_N)$ are then

$$(T_A - T_N)_{\substack{\text{min.}\\ \text{max.}}} = \frac{JR^2 T_o (1 \mp e)^2}{a^2(1-e^2)^{5/2}} \times \left(2-\frac{5}{2}\sin^2 i\right) = \frac{2\pi JR^2(1\mp e)^2}{(GM)^{1/2}a^{1/2}(1-e^2)^{5/2}} \times \left(2-\frac{5}{2}\sin^2 i\right) \quad (2)$$

which can differ by as much as 20 seconds for orbits of low inclination. Note that for $\sin^2 i = 4/5$ the difference in periods vanishes, which is in accord with the fact that at this inclination, 63.5°, the line of apsides neither advances nor regresses (3). For i less than 63.5°, the anomalistic period will be greater than the nodical period; and, conversely, at larger inclinations the nodical period will be the greater. In any case, the difference in periods increases with orbit eccentricity, and only for near-circular orbits ($e=0$) will there be no cyclic variations in $(T_A - T_N)$. Unlike the motions of the node and perigee, which fall off rapidly with distance, $(T_A - T_N)$ falls off very slowly with increasing orbit size; and hence the effect should be detectable even for orbits at great distance.

Equation 1 has been developed to first-order in the oblateness parameter J on the presumption of no drag or other perturbing factors. For satellites with perigees above the region of sensible atmospheric drag the orbit parameters should be measurable to great accuracy, which