Physiology. — "*On Caesium-ions and Cardiac Action*". By Prof. H. ZWAARDEMAKER.

(Communicated in the meeting of October 27, 1917).

Years ago SIDNEY RINGER [1]), in his study of the composition of artificial circulating fluids, established that the isolated frog's heart can sustain its beats for some time, if to an isosmotic, faintly alkaline sodium-chloride solution, containing the necessary quantum of calcium, caesium chloride is added instead of potassium chloride. Caesium salt was substituted for potassium salt in an equivalent molecular amount. When we carried out the same experiment last winter we did not attain a definite result, but when we discovered this year that the heart of the summer frog responds to smaller doses of potassium chloride than the heart of winter frogs, we have undertaken again SIDNEY RINGER's caesium experiment [2]). After augmenting the usual calcium amount (200 mgr. $CaCl_2$ per Liter) to 250 mgr. dry calcium chloride (without water of crystallization) the summer hearts could be made to continue beating for an indefinite space of time by the aid of an appropriate quantity of caesium chloride. Broadly speaking, we can say that, for one heart, the dosis of caesium corresponds with that of potassium and rubidium. The minimum dosis, needed by a Kroneckered frog's heart in its RINGER's mixture, is smallest in weight for potassium chloride, then follows most probably rubidium, while the dosis of caesium chloride must be slightly larger. Molecularly, therefore, the dosages may be called fairly equal. The toxic dosis is a multiple; but we also found that, whilst (in summer) double the dosis of potassium is in most cases toxic, the caesium-dosis may be many times the minimum dosis that keeps the heart beating. A little beyond the minimum dosis lies the optimum quantity. In the months of September and October it amounted to about 40 mgr. C_8Cl per Liter of potassium-free RINGER's mixture.

1) SYDNEY RINGER, Journal of Physiology. Vol. 4, p. 370.

2) I was particularly prompted to do so, as the question was put to me by Dr. C. E BUCHNER, of Amsterdam whether it would be possible to demonstrate biologically the radio-activity of caesium, which had often been surmised on account of the relationship between this metal and potassium and rubidium.

When this had been established[1]) for a good many cases, I went into the question whether potassium-, rubidium-, caesium-chloride could be used promiscuously, which I found to be the case. The different substances may be alternated without any interval, provided the dosis be well chosen. It is quite unnecessary, therefore, to interpolate a perfusion of a solution of merely 7 grms of NaCl, 200 mgrs of $NaHCO_3$, 250 mgrs of $CaCl_2$ per Liter of pure water. If, however, we administer, instead of a caesium-containing fluid, a fluid containing uranium or thorium, we cannot maintain the cardiac action without an interpolation. If there is still some caesium left in the heart, it will come to a standstill when a uranium-, or thorium-fluid is sent through, which in other cases would answer the purpose, as illustrated by the subjoined figures.

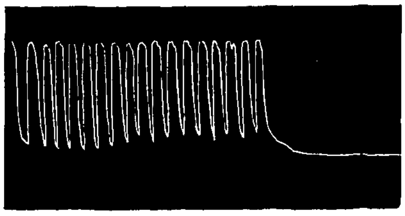

Fig 1.

A frog's heart, fed with a caesium-fluid (40 mgr. of CaCl per liter of potassium-free RINGER's mixture) and beating vigorously, is rapidly perfused with a fresh thorium-solution (20 mgrms of $Th(NO^3)^4$ per liter of potassium-free RINGER's mixture) the moment the curve in the figure commences. The heart will stop in complete relaxation after three minutes. After 25 minutes it will as suddenly recover its tonus and commence a series of rhythmical beats. This behaviour is easily accounted for. After the caesium-beats follows the caesium-thorium-equipoise, which causes a standstill, whilst in the end the thorium evokes new contractions.

It will be remembered[2]) no doubt that exactly the same phenomenon presented itself in a previous experiment in which potassium or rubidium was replaced by uranium or thorium. There also potassium- and rubidium-salts could be used promiscuously, nay could even be mixed. The same holds good for uranium- and thorium-salts. However, a potassium-, or rubidium-salt appeared to be antagonistic to uranium or thorium-salt. The favourable effect exerted by every one of these salts *per se* is neutralized by the coincident presence of a salt of the other group. The two actions counterbalance each other, so that it is as if they do not exist and as if the heart is in the same condition as it would be when left to itself without

[1]) Here I have much pleasure in thanking the assistant DE LIND VAN WIJNGAARDEN for his painstaking help.

[2]) H. ZWAARDEMAKER, Proceedings of 24 Febr. 1917, Vol. 25, p. 1096. (Proc. Vol. 19, p. 1048).

the usual diffusible potassium in the circulating fluid. It is then reduced to a standstill, from which it does not recover of itself, and after which it can initially resume its normal pulsations by adding in excess an appropriate amount of one of the radio-active salts, either of the one or of the other group. Now it appears that in the like equilibria caesium must be classed under the light metals. Potassium, rubidium, and caesium, therefore, constitute biologically one group; *uranium and thorium the other.*

In this connection it was expedient to ascertain whether the caesium-heart responded to electric stimuli, as is the case with the potassium- and the rubidium-heart. This proved to be the case. An appropriate induction stimulus produces an extrasystole. When, however, the ventricle was taken separately, the compensatory pause was absent.

Evidently the preparation acts merely upon ventricular automaticity, originating on the distal side of the atrioventricular boundary-line, and it consequently behaves like the sinus venosus as regards the rhythm after extrasystole.

It appears, then, that caesium resembles potassium also in its relation to the extrasystoles, and must be contrasted with uranium, which precludes extrasystoles [1]).

In a previous paper [2]) I have pointed out that the potassium- (resp. rubidium-)uranium-(resp. thorium-)equilibria can be largely shifted by the addition of fluorescein. This substance renders the heart more susceptible to the influence of uranium or thorium than to that of potassium or rubidium. This is why a heart, brought to a standstill by a precise counterbalancing of light and heavy metal, will resume its pulsations as soon as 100 mgrms of fluorescein per liter is added to the solution. The influence upon potassium (resp. rubidium), therefore, is inconsiderable, that of uranium is great. In this respect caesium is also to be classed with potassium. Fluorescein has next to no influence upon a heart, beating in groups under subminimal caesium-doses.

From the above we conclude that, biologically, caesium is doubtlessly to be bracketed with potassium and rubidium and that it is antagonistic to uranium and thorium, which was unknown heretofore. Suppose, therefore, that nature were to bring forth caesium-animals as it brings forth potassium-animals everywhere, they might be assumed to stand to radio-activity and electricity in the

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1) H. Zwaardemaker, Proceedings 1, May 26, 1917. Vol. 26.

2) H. Zwaardemaker, Proceedings Sept. 1917 Vol. 26, p. 255.

same way as the normal animal that we know. Such in reality is the case with regard to the caesium-heart. Mesothorium-radiation does not produce an appreciable influence. That a partial polonium-radiation should cause any alteration cannot be expected, the organ being enclosed in a pericardium, which largely obviates the penetration of the α-particles.

This withheld me from trying it. Meanwhile emanation-circulation may perhaps throw light upon this matter.

When applying it, the contrast between caesium-ions and niton-atoms, supplied by radium-emanation shows itself at once. When both ions and atoms are, in appropriate quantity, in successive perfusions without interval, brought to the surface of the cardiac muscle-cells, and perhaps penetrate into them, then the presence of ions or atoms alone will ensure pulsation, but when the same quantities occur concomitantly, a standstill will be brought about after a short wait.

If, for instance, first a circulation fluid, in which from 40 to 80 mgrs of caesium-chloride per liter, is allowed to pass and directly after it one with 150 Mache-units per liter, the vigorous caesium-beats will first gradually slow down to quiescence and subsequently be succeeded by emanation-pulsations.

The latter, however, are less broad, most likely because the calcium-dosis of the fluid is antagonised by the oligodynamic niton-dosis (absence of tonus-equilibrium).

So far as we are aware, the typical feature of the nitonatoms is the charge they emit. This, at any rate, must be the immediate agent, as the transformation-products, which the adsorbed atoms of the dissolved emanation will produce during the first four days and later on in an ever lessening amount, can hardly play a part in the short experiments described by us. This warrants the conclusion, that caesium will likewise produce a charge, but of the opposite sign, and that the detected antagonism between caesium and emanation rests on this difference of sign. [1]) It appears, then, that here also caesium must be classed among its homologues rubidium and potassium, which like caesium send out charged ions of a sign

[1]) Also a mutual adsorption extrusion by which one metal repels the other from the surface of the cardiac muscle-cells, may perhaps account for the antagonism in the immediate proximity of the threshold of the two actions, premising that both elements then are subliminal. But we took intentionally more than the threshold of emanation (and later on of radium). Then, however, the adsorption-interpretation falls through, as, indeed it also fails before the antagonism radiation-uranium, with which our phenomenon is quite analogous.

opposite to that of the niton-atoms. Rutherford [1]) has also observed that probably potassium emits few but highly penetrable β-rays, in contradistinction to the more numerous but less penetrating ones of rubidium. One is thus led to suppose caesium to throw out still more numerous, but extremely absorbable β-rays. This is why in the circulating fluids the required caesium-dosis and the rubidium-dosis are about equal, and on the other hand why this radiation has not yet been demonstrated physically. Only the atoms from a caesium-preparation, lying very near the surface, will be capable of exerting any effect. (Chemical? or ionising?).

The emanation-experiment naturally led us to investigate with a radium-solution. Owing to their being completely absorbed the α-rays of radium exert an enormous effect in the immediate proximity. That is why only few are required to obtain the restoring effect upon the perfused frog's heart: 3 microgr. of radium per liter of circulating fluid will do. So, if this oligodynamic radium-dosis (or double this dosis) is rapidly sent through the lacunae of a frog's heart that pulsates with 80 mgrms of caesium-chloride, a standstill will commence after a short wait, just as with emanation. Afterwards rhythmical beats will reappear, this time — after the caesium has been extruded — in consequence of the radium-action. By allowing caesium to flow through again at this moment we again succeeded in evoking a fresh standstill and — after extrusion of the radium — finally again vigorous caesium-beats.

The subjoined figures illustrate the phenomenon. Fig. 2 shows the arrest of caesium-beats by radium, and the subsequent recurrence of normal radium-pulsation after the standstill, when the caesium in the heart is completely substituted by radium. 1 cm. of the abscissa corresponds with the time of 1 minute. The curve is taken from a continuous graph, in which by interchanging the feeding flasks,

Fig. 2.

Fig. 3.

[1]) RUTHERFORD in MARX's Hdb. der Radiologie, Vol. 2, S. 530.

caesium- and radium-pulsations have been registered, every time with an interval of equilibria without pulsations.

The second curve originates from another experiment. The registering leaf moved along at the rate of $\frac{1}{6}$ cm. per minute. The piece cut from the graph relates to a caesium-standstill after radium, succeeded by caesium beats. The transitions in either case, illustrated here, took place per crisin.

Conclusions

1. The light radio-active metals and the allied caesium, as well as the heavy radio-active metals uranium, thorium, niton and radium, sustain the contractility of the isolated frog's heart (ventricle pulsating on its own automaticity).

Effectual doses for summer frogs are:

of potassiumchloride	from 30 to 50	mgr. per L.	(min. 20—25 mgr.)
" rubidiumchloride	from 40 to 80	" " "	(" ± 30 ")
" caesiumchloride	from 40 to 80	" " "	(" ± 30 ")
" uranylnitrate or acetate	from 1 to 6	" " "	(" ± 0,7 ")
" thoriumnitrate	from 2 to 10	" " "	

" emanation less than 100 Mache-units

" radiumsalt less than 3 millionths of a mgr. per Liter.

2. A biological antagonism exists between:

$$\left\{\begin{array}{l}\text{Potassium}\\ \text{Rubidium}\\ \text{Caesium}\end{array}\right\} \begin{array}{c}\rightarrow\\ \leftarrow\end{array} \left\{\begin{array}{l}\text{Uranium}\\ \text{Thorium}\\ \text{Emanation}\\ \text{Radium}\end{array}\right\}$$

3. In all probability caesium emits β-rays of very low penetrating power, upon which depends its similar effect to that of potassium and rubidium.