ON PHYSIOLOGICAL RADIO-ACTIVITY.

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The heavy radio-active elements belong to three groups: the radium-, the thorium-, the actinium-groups. No representative is normally found in the animal organism, except perhaps a trace of emanation. On the other hand a specimen of the light radio-active elements of Campbell and Wood is a permanent constituent of the body. Potassium is found to a quantum of 40 grams.

The potassium has been stored for a great part in the muscle-cells and in the red blood-corpuscles. Besides in this fixed condition potassium also occurs in our blood as a free, diffusible ion, of which the amount is usually estimated at rather more than 1 gm. Now the radio-active radiation of 1 gm. of potassium is readily demonstrable in an ionization-chamber. Campbell and Wood (1) have suggested a very simple method of doing this. W. E. Ringer and myself tried the method and without difficulty confirmed the fact. When spreading on the bottom of an ionization-chamber, of a capacity of two litres, a perfectly dry potassium-salt, we found the air ionized twice as strongly as when only the penetrating field of radiation of the earth and the secondary activity of the wall would have affected it. On the other hand perfectly dry sodium-, or lithium-chloride is altogether inactive. Such a potassium-radiation passes easily through several films of stannum, and reaches half of its original strength through aluminium of 0·4 mm. thickness. If, instead of aluminium we had taken an animal tissue, the reduction to half its strength would have been observed with a passage through a layer of 1 mm. The radiation of 1 gm. of potassium, distributed over all the blood is not perceptible with our present means. Only when this amount is enclosed in a small space does it become physically measurable. From this it does not however follow that when diffused it is biologically without influence. Night and day the potassium-atoms force their way in all directions. Every atom, wherever it may be, is surrounded by a miniature field of radiation. β-particles are dispersing on all sides at irregular intervals. Materially this is of little significance, for the magnitude of every particle is of the order of one-thousandth of a hydrogen-atom. But energetically the radiation is of importance, since the mobile, electrically charged electron (1) in flying past acts by induction; (2) transfers kinetic energy; and (3) imparts its charge where it comes to rest. A positively charged atom remains behind.

The activity induced while the particle is shooting along, will detach everywhere electrons from their atoms, and is, therefore, of itself of some importance. It is difficult to form an estimate of the consequences. However, we can state *a priori* what will happen in case such a β-particle sticks fast. Let it be assumed that this takes place in a colloidal complex, then the transferred negative electric charge will be able to leave the complex only by loosening one of the ions absorbed to the surface, say, an OH-ion, and sending it adrift. We see, then, that an exchange of ions will have begun which would have been wanting without radiation. Considering the immediate effect of corpuscular radiation, the γ-rays, emitted along with it, may I think be provisionally left out of account. In 1915 I asked myself what might be the physiological significance of the radiation, which, owing to the potassium, pervades almost the whole human body. The answer was not difficult to find in the case of the free potassium occurring in the plasma sanguinis, since we possess in the isolated frog's heart an organ, the muscle-cells of which are on all sides in almost immediate contact with the circulating fluid. As moreover these muscle cells show their vital functions spontaneously by pulsations, we are enabled to remove from them the influence of the free potassium, respectively to expose them to it, and so to establish the results immediately. When such a heart is supplied in all its lacunæ with ordinary Ringer's mixture (NaCl ·67 p.c., $NaHCO_3$ ·02 p.c., $CaCl_2$ ·02 p.c., KCl ·01 p.c.), it will keep beating for hours. When, however, the potassium is left out, it is reduced on an average in 30 min. to a standstill. Sometimes the standstill will come abruptly, at other times the beats slow down gradually, while alternate groups of systoles and quiescence are noted, or sometimes the arrest of the heart's action is introduced by a decrease of the magnitude of the contractions. In all such cases the heart may resume its beats by adding again the potassium to the circulating fluid.

This shows that the potassium-ion is indispensable to the cardiac action. Various attributes of potassium-ion may be responsible. Its velocity of migration, its colloidal importance as a univalent ion, its position in the lyotrope series, its specific chemical affinity, its radio-activity—all these properties might be regarded when looking for the real cause of this indispensability. We purpose to ascertain whether the last-mentioned property, *i.e.* radio-activity, is answerable for it. This will be the case if it can be proved that the potassium can be replaced by other radio-active elements.

Among the light metals there is besides potassium another radio-active element, viz. rubidium. This element can serve as a substitute for potassium in every respect as was pointed out by Sidney Ringer(2); it can be explained by chemical affinity. But outside the *Mendelejeff*-group (to which potassium and rubidium belong) we cannot appeal to chemical affinity. At the same time the technical difficulty presents itself to hit upon the right dose, for on the one hand no effect can be expected from too small a dose, and on the other hand too large a one might produce a toxic effect. These considerations compelled me to look for dosages that might be called to some degree æquiradio-active to potassium. Happily Rutherford's *Manual*(3) gives the relative intensity of radio-active effects, both of the heavy and the light metals.

Potassium, he states, is 1000 times weaker than the β-radio-activity of uranium, uranium again is, 1,000,000 times weaker than the β-radio-activity of radium. If, moreover, we reflect that the β-radio-activity of radium amounts to only 1 p.c. of the total radio-activity of that element, it follows that the potassium in Ringer's mixture is about 100 milliard times weaker than its quantum of radium.

On the basis of Rutherford's data we are in a position to compute for every radio-active element one wishes to substitute for potassium, the dose which, when diffused in a litre of circulating fluid, will sustain the amount of radiation produced by potassium in physiological conditions. For these calculations and a correction made I refer to previous publications(4). In collaboration with Mr T. P. Feenstra I succeeded in detecting that not only rubidium, but also uranium, thorium and radium can replace potassium(5). When long afterwards I had at my disposal some ionium I compared a commercial preparation with a uranium-unit (which may be done as both emit α-rays) and readily found an effectual dosage. A similar result was achieved with lanthanum-, and cerium-preparations, which through the admixture of some actinium appeared to possess a trace of radio-activity. When an æquiradio-active quantum of them is added to a potassium-free Ringer's mixture, they can sustain the beats of a frog's heart for an indefinite time.

In experimenting with ionium, lanthanum and cerium an impediment is met with in the impossibility of maintaining the salts used in solution in an alkaline fluid. Yet it is essential to sustain the weak alkalinity of the circulating fluid. In order to ensure this we added some neutral red in a Mariotte's flask, from which the modified Ringer's mixture was sent through the heart *via* a Kronecker cannula under a constant pressure (8 cm. water-pressure). When the ionium-, lanthanum-, or cerium-salts are added and neutralized with sodium carbonate, a precipitate is produced which removes the active constituents from the fluid. (In the long run this is also the case with thorium-nitrate, which was used in the thorium-experiments, but with this substance I could continue the experiments for at least a few hours without precipitation.)

All these impediments are obviated by transforming the thorium, the ionium, the lanthanum, and the cerium to a colloidal state, and by adding them to the potassium-free Ringer's mixture. Both in the real and in the colloidal solution exactly the same dose of thorium is required (6).

Thus a radio-active element, whichsoever it may be, added in a dosage æquiradio-active to potassium, to a potassium-free Ringer's mixture, renders such a solution as effectual a circulating fluid for the heart of a cold-blooded animal as the original fluid. It may be that for weak hearts, and for hearts in a morbid condition K is somewhat better than Rb, U, Th, Ra, To, or Ac, but there is not much difference, and it is certain that strong hearts continue beating for hours. We also made a counter-experiment by trying to add non-radio-active elements. In this endeavour it is a question of mere good luck, when the right dose is hit upon, as there is no guiding principle whatever. But neither my co-workers, nor myself, have ever encountered a non-radio-active element that could replace potassium in Ringer's mixture. There is only one exception, viz. cæsium (7), to which, however, radio-activity has repeatedly been ascribed. A cæsium-preparation that was not capable of ionizing our ionization-chamber, was subsequently found to be physiologically active. We can attempt to solve this question only by assuming beforehand that the cæsium atoms radiate indeed, but that their penetrating power is too low to drive their electrons out of the cæsium-layer that covers the floor of the ionization-chamber. Upon the basis of this working-hypothesis, in itself not quite rejectable, we are led to suppose that cæsium contains β-particles with a velocity even less than that of the α-particles (which largely ionize the air) and also less than that of the electrons which are detached through photo-electricity. Perhaps they have the velocity of δ-particles. The logic of facts urges us, until more light is thrown upon this problem, to ascribe to cæsium a radio-activity which reveals itself physiologically, but not physically so far as can be made out with the present means of experimentation.

A striking result, achieved in our substitution-experiments is—premising æquiradio-activity—the equivalence of substances emitting

α- and β-rays. In order to observe this more closely the commercial uranium was deprived of uranium X after Soddy and Russell's method (8). This renders the uranium a true α-emitting substance. It is the same with radium, which when diffused in very weak dilution in Ringer's mixture, can, of course, not be expected in this highly diffused state, to be in equipoise with it decomposition products. In that case every one of the radium-ions exerts its influence quite independently. Ionium in colloidal state in the circulating fluid is also a true α-emitting substance. So is thorium applied either in the form of thorium-nitrate, first precipitated with ammonia and subsequently dissolved again in nitric acid, or as a colloidal thorium-hydroxide.

All these α-emitting bodies, taken up in potassium-free Ringer's solution in the proper doses, proved, as already stated, excellent potassium-substitutes, which when duly administered enabled the isolated frog's heart to continue beating for hours. In similar experiments Kronecker's method may be adopted, viz. a double perfusion cannula is slipped from the sinus venosus into the ventricle (9), or another method may be used by inserting a cannula both into the venæ and into the aorta, in which case the circulation is maintained with the natural valve-mechanism. The recent method of Amsler (10) also proves effectual. Under all these circumstances the elimination of potassium from Ringer's mixture finally leads to arrest of the cardiac action, whereas replacement of potassium by every one of the other radio-active elements restores it again.

In the latter case the result is the same whether an α- or a β-ray is applied. The systoles return when the other conditions are well chosen, such as: (1) an appropriate osmotic pressure, so that the concentration of the sodium chloride cannot fall below 0·4 p.c., nor rise above 0·8 p.c.; (2) an internal pressure of about 8 cm. of water; (3) a proper saturation of Ringer's mixture with oxygen, which is guaranteed by the very construction of Mariotte's bottle; (4) a weak alkalinity, which is shown by the yellow coloration of the added neutral red; (5) a precise amount of calcium, ranging from 200 to 400 mgms. of calcium chloride (without water of crystallization). In summer, we may encounter hearts falling short of vitality, as is also the case with the hearts of animals that have long been pent up, but an adept experimentalist will avoid all these self-evident difficulties, so that it is needless to point them out here[1].

[1] The temperature should not deviate too much from the mean temperature. Severe cold has an unfavourable influence, causing an excessive tonus, so that the perfusion of the heart is disturbed. Excessive heat is also fatal, as it lowers the spontaneous automaticity.

The facts I wish to accentuate are: (*a*) that substances emitting α- and β-rays serve our purpose equally well; (*b*) that about the same absolute radio-activity should be assigned to the doses used (in other words that the total kinetic energy of the emitted particles should be the same for every element); (*c*) that the modus of solution of the elements does not alter the result, provided precipitation is avoided.

At the very outset of my inquiry I purposed to ascertain whether there might be some substances that modify the action of our element or its substitutes. Though it is impossible to alter in any way the radio-active radiation of the atoms themselves, it might yet be possible to render the heart more responsive to radio-active influence or that it could be guarded more or less against that influence. We were so fortunate as to detect a favourable substance, a sensitizer[1], viz. fluorescein (11, 12). The addition of a little of this aniline-dye (as sodium-salt) to the circulating fluid afforded an opportunity of diminishing the potassium dose considerably and the uranium- and thorium-dose much more. Afterwards another sensitizer was found in eosin, but its use is dangerous, because in order to ensure effect we must apply an almost toxic dose.

An inhibitory influence on the access of radio-active atoms to the muscle-cells is exerted by another substance, viz. calcium. This might be expected from Loeb's equilibrium-tests (13). Now, when there is much calcium in the circulating fluid, also much K, U or Th must be added and the reverse (14). Strontium and barium work similarly to calcium; magnesium, however, does not (15).

The physical conditions under which the experiment is carried out (temperature, pressure, thermodynamic potential) are fairly easy of control. Not, however, the vital conditions. There always remain animals, whose hearts react perfectly, others whose hearts do so quite unsatisfactorily, which sometimes renders it extremely difficult to fix upon the appropriate dose, above all in the months between winter and summer and between summer and winter. This is the more difficult as the summer and winter dosages must not be equal. Dr S. De Boer (16) found in the summer doses of potassium, uranium and thorium to be considerably smaller than the corresponding winter doses. This was also the case when the calcium content was increased intentionally[2].

[1] Methylene-blue, neutral red, hematoporphyrin, chlorophyllin do not appear to be sensitizers. In a certain dose they are toxic.

[2] In summer the calcium content of the frog's blood is twice as large as in winter (D. J. de Waard, Meeting of Physiologists, Amsterdam, 20 Dec. 1917).

	Salt thrown into solution per litre in mgms.	
	in winter to 200 mg. $CaCl_2$	in summer to 250 mg. $CaCl_2$
Potassium chloride	100	20–50
Rubidium chloride	150	30–80
Uranyl nitrate	25	0·6–6
Thorium nitrate	50	2–10
Radium salt	0·000005	0·000003

In winter the uranyl nitrate doses may be raised to twice the original quantum, when the calcium chloride content is doubled. Evidently calcium exerts antitoxic influence not only on potassium but also on uranium. The immediate toxic effects reveal themselves much sooner in the radio-active substitutes of potassium than in potassium itself. Whereas in winter the dose of potassium-chloride may, even with a small calcium dosage, be raised to four times the normal dose and even higher, the uranyl nitrate dosage must not be raised higher than double the normal quantity. Likewise, with a low calcium dosage, the colloidal thorium hydrogen must not be raised higher than to about double the minimum dose. Also with regard to radium salt we are restricted to a narrow latitude for variation. This involves a great difficulty in assigning the appropriate dosage necessary to evoke the pulsations, especially in summer. This effort may be considerably facilitated by administering alternately a potassium-free Ringer's mixture and the circulating fluid on trial. In case one happens to have too much, the heart will resume its systoles as soon as the excess is washed out by a potassium-free fluid. This, however, produces only a temporary effect, because in the long run there will be a deficit of the indispensable radio-active element, whereas on the other hand a permanent pulsation will ensue when the right solution has been hit upon.

The cause of this anti-toxic action of calcium on potassium and on its radio-active substitutes, can be looked for in two directions. First of all it may be associated with a certain degree of tonus in the heart muscle, necessary for automaticity to show itself. The radio-active elements, in large doses, lower the tonus, calcium reinforces it. A proper equilibrium between these two is, therefore, one of the conditions to be fulfilled for a heart to be capable of contracting. I lay the stress on the capability of contracting, as omission of the calcium-ion from Ringer's mixture does not interfere with the electrocardiogram, that remains intact (17). The other conception is an immediate anti-toxic action between the radio-active elements and the earth alkalis. The hypothesis would be only possible by assuming that the toxic action of calcium (also strontium and barium) is neutralized by radio-activity, but in that case this toxic action should be itself of a radio-active nature, which is not the case.

Among the potassium substitutes are light metals as potassium itself and rubidium, and heavy metals (all the other radio-active elements). They all are, when considered separately, sustainers of automaticity. However, when supplied collectively, so that in the circulating fluid a light metal occurs side by side with a heavy one, they counterbalance each other's beneficial influences as well as their toxic effects. The reaction is reversible, for a little more or a little less of the light or of the heavy metal, makes the heart resume contractility (18). It also appears that there are certain doses which, when counterbalanced, give rise to a standstill. Whole series of such sets of two antagonistic metal doses may be found. The higher antagonisms are by no means multiples of the lower ones, for when in a graph the quanta are represented by their logarithms, straight lines will be obtained (19).

In such a graph the points above and below these lines represent regular beats, provided we do not go too far from the equilibria. A frog's heart (*e.g.*) can be safeguarded against potassium toxication by adding the harmless thorium to the circulating fluid. In order to avoid an extreme relaxation of tonus, which might be unfavourable for the result, the calcium content must also be augmented. This experiment fails with the mammalian heart, because the distance between the circulating blood and heart cells is too great. The rapidly migrating potassium-ion will very soon reach the muscle cells but the thorium-ion fails to do so within the time of experimentation.

The season, fluorescein and the calcium content, determine to a certain extent the dosage of the radio-active elements taken separately. It may be expected, therefore, that the lines of antagonism will be influenced likewise. This is really the case, but the factors in question do not interfere with the straightness of the logarithmic lines. When taking calcium in orderly quantities of 100, 200, 300, 400, 500 mgms. of chloride, without water of crystallization, these straight lines will even be found to run parallel *inter se*. I think this to be quite in character with the above exposition that the radio-active effects are influenced only indirectly by the coincident calcium amounts (20).

After establishing the favourable effect of potassium and its substitutes, as well as the antagonism between light and heavy radio-active atoms for the frog's heart, the question arose whether something of this kind would hold for other organs also. The organs which in the first place are naturally suggested are those which are almost immediately encircled by the blood flow. Dr J. Gunzburg(21) encountered such a case in his study of the function of the vascular endothelium. If a newly killed winter frog is perfused from the aorta with normal Ringer's fluid, which, because air-bubbles pass through it, is sufficiently saturated with oxygen[1], even after 24 hours no œdema will be observed of the subcutaneous lymphatic follicles, nor of the internal organs. No sooner, however, is the potassium omitted from the circulating fluid than a violent œdema is developed, which may cause an increase of body-weight of from 20 p.c. to 40 p.c. This œdema can be prevented by replacing potassium by its substitutes (Rb, U, Th). The effectual dose is smaller than is required for the recovery of the cardiac automaticity. Excess is deleterious and gives rise to an œdema, which is hardly to be differentiated from that which is evolved through the lack of a radio-active constituent. The antagonism of the light and the heavy metals also made its appearance again, just as the mutual support of atoms of one and the same category.

A third organ was detected by Hamburger and Brinkman(22). They had previously discovered that the glomerulus-epithelium of the frog's kidney completely checks the glucose of the circulating fluid, when a well chosen Ringer's mixture is used, but that glucose appears in the urine directly the potassium is left out. Instead of potassium, uranium or radium may be taken in such a dosage as is required to prevent the œdema; nay, what is more, also the antagonism of potassium for uranium was found, when Hamburger and Brinkman were so kind as to comply with my request to trace it out.

Also organs whose cells are separated from the blood, may be put to the test, if some contrivances are resorted to, many of which are suggested by the antagonism we discovered(23). One of them consists in adding per litre of potassium-free circulation fluid a few mgms. of uranyl salt (nitrate, acetate or sulphate) and after this, neutralizing the potassium that passes from the tissues into the circulating fluid, when it is sent, not through a lacuna system, as in the heart of the frog, but through a capillary system, which is environed on all sides by a potassium-containing tissue. After neutralizing the fixed potassium we are enabled to study the synapsis between vasomotor nerves and vascular muscles, the synapsis between vagus and heart muscle cells(24) and the myoneural transition between the motor nerve and the voluntary muscle(25).

[1] **Supersaturation, *e.g.* by allowing pure oxygen to pass through, prevents œdema; a complete removal of calcium produces the same effect. Similarly the simple physiological common salt solution of former times does not generate œdema.**

Further the movements of the œsophagus and the intestine can be observed from the new view-point. In all these cases both the recovering effect and the antagonism can be proved. Whether there are still more organs, I shall leave for the present undecided. The new facts induced us to examine also emanation. Emanation is, as known, a chemically indifferent gas, Ramsay's niton, which escapes from radium when this is kept in an aqueous solution. This niton also emits a corpuscular radiation of the nature of α-rays. When we put the appropriate amount of emanation in a potassium-free Ringer's mixture (about 100 Mache units), a frog's heart (brought to a standstill, through removal of potassium) will recover its pulsations, and also an emanation heart (treated similarly) will be under the influence of the antagonism. A sudden perfusion of potassium-containing fluid causes an abrupt standstill, which will disappear at once on the inflow of potassium-free fluid[1]. It is again the niton-atoms that give the oligo-dynamic effect; but their number is so small that the quantum taken up in a litre of circulating fluid cannot be weighed. Nor do they exert any chemical action, for niton is an indifferent gas of the argon-type. Emanation manifests itself only through its radio-active properties, and it is through these very properties that it partakes in the antagonism.

The radio-active antagonisms, therefore, prompt us to divide all the radio-active atoms into two groups (27):

Group I. Emitting β-rays	Group II. Emitting α-rays
Potassium	Uranium
Rubidium	Thorium
(Caesium?)	Colloidal thorium
	Radium
	Colloidal ionium
	Colloidal lanthanum
	Colloidal cerium
	Niton (emanation)

In their physical properties the two groups show but one contrast, viz., when alighting, the corpuscular radiation of the first group imparts a negative charge, those of the second one of the opposite sign[2]. So, when counterbalanced cautiously, their actions can be mutually neutralized. Here, then, we have virtually to look for the origin of radio-active antagonism.

[1] Amsler's method cannot be adopted for emanation tests, unless the fluid in which the heart is beating is shut up in a closed reservoir.

[2] The kinetic effect, the inductive effect by their movement, the colloidal (lyotrope) effect, are of the same sign for either group.

In the foregoing two important principles have presented themselves:

(1) the property of radio-active atoms to restore and to excite the heart's function, provided they are freely diffusible and in æquiradio-active dosage;

(2) the radio-active antagonism of these atoms, by which they are divided into two groups, which are characterised by the opposite signs of their corpuscular radiation.

In this way radio-activity becomes a power in the functions of a great number of organs, a power that seems to exist apart from matter (28). This leads us to a far-reaching problem, viz. whether corpuscular radiation, as such, and apart from the atom, can also restore or excite the heart's function.

In the autumn of 1916 I obtained from St Antonius' Hospital in Utrecht, a preparation of 6 mgms. (?) of mesothorium, enclosed in a glass bulb, and with my co-workers C. E. Benjamins and T. P. Feenstra (29) I began to radiate a series of hearts that had been brought to a standstill by removal of potassium. When placing the preparation at 1 cm. from an isolated heart, and permanently perfused with a potassium-free fluid, the pulsations returned invariably. This sometimes happened very soon (after 3 min.), sometimes after a considerable time (1 hour); the average time was 28 min. Removal of the mesothorium caused a standstill, while pulsation recommenced when the mesothorium was added again. After such repetitions the reaction follows sooner than after the primary restoration of the systoles. Once we succeeded five times running[1].

When mesothorium is allowed to remain in the proximity of the potassium-free perfused heart that has recovered its beats through radiation, the systoles will cease on an average after half-an-hour (reversible, for removal of the preparation restores the cardiac action). It appears, then, that there are two kinds of standstill; the one caused by a deficiency, the other by an excess. By a simple method it can be made out which of the two threatens the faintly beating heart. The experimentator only has to break off the uninterrupted flow of potassium-free fluid in the previously radiated heart and to perfuse the organ with the complete fluid. If an excess of radio-activity is already present in the organ, the heart will stop abruptly after Ringer's mixture has been introduced, whereas in case of a deficiency the pulsations, which are

[1] Only in summer, when the vitality of organs is weakened, it may occur that systoles fail to reappear.

perhaps slackening or being interrupted at short intervals, will increase in rhythm and magnitude through the addition of Ringer's mixture, and will persist for an indefinite time.

Afterward we obtained two somewhat weaker preparations. With these approximately the same results were achieved, especially when we started not from a condition of potassium-free perfusion but from the condition of equilibria previously described. We generally used a solution of 40 mgms. of potassium chloride and 10 mgms. uranyl nitrate in a litre of potassium-free Ringer's mixture. A weak radiation of β-rays causes the heart to beat on an average after 13 minutes. In such a case the organ may again be brought to a standstill (reversible) by adding an extra quantum of uranium to the circulating fluid. This quantum varies with the distance of the raying preparation. When plotting a graph with the logarithms of these quanta along the axis of the ordinates and the distances between the heart and the preparation along the axis of abscissæ, a straight line will be obtained, of which the production will cut the axis of the ordinates somewhere. This point of intersection corresponds for a preparation of about 5 mgms., covered up with mica, to 40 mgms. of uranium; for a preparation of about 3 mgms., also covered up with mica, to 19 mgms. of uranium (30).

From the description of the preceding experiments the reader will have concluded that our radio-active antagonism previously met with between light and heavy metals, applies both to β-radiation on the one side and to perfusion with heavy metal on the other. Indeed, when taking a thorium salt instead of uranium the experiment also succeeded. We may safely range the corpuscular radiation of a β nature under the radio-active antagonism on the side of the light metals. That the normal frog's heart *in situ* shows no effect whatever of a weak radiation is quite in keeping with this.

When at the beginning of our inquiry the problem of potassium replacement was raised, it appeared that both light and heavy radio-active atoms, added in an appropriate dosage to the circulation fluid, are competent to restore the lost automaticity. It was reasonable, therefore, to ascertain whether besides β-radiation also α-radiation could recover the systoles arrested through renewal of potassium. My co-worker G. Grijns (31) found that polonium (precipitated by galvanoplasty on copperplate and bent round an isolated heart) restored pulsation in 33 experiments four times unequivocally and ten times doubtfully. Obviously the much less rapid α-rays penetrate only with difficulty through the pericardium and consequently do not always reach the points of the atrioventricular region[1] which are most sensitive for automaticity.

Our radium-experiment with the heart induced my colleague H. J. Hamburger in the autumn of 1917 to carry out some radiation experiments on the kidney, with the assistance of D. J. de Waard (32). The abnormal permeability for glucose, mentioned before, which occurs when the potassium is removed from the circulating fluid returns when the organ is radiated from a short distance with 5 mgms. of mesothorium (in a glass bulb). At the same time an œdema arose in the kidney, which could be established by weighing.

In the early summer of 1917 I observed with Dr J. W. Lely (33) the influence of mesothorium radiation on the excitability of the heart for the inhibitory action of the n. vagus. The result was positive. The action of the vagus was reinforced by it.

These experiments with free radiation lend support to the above supposition that the radiation fields of the diffusible radio-active atoms promote the function of the organ. The question, however, is whether this favourable effect is direct or indirect. A direct effect would seem to be proved by the perfect analogy between the consequences of internal vagrant radiation and those of the radiation of the preparations arranged by the side of the heart, while an indirect effect would seem to be confirmed by a continual liberation of a little potassium from the potassium depôts of the cells. In the heart 1 mgm. is loosened per litre of circulating fluid, a quantum in itself insufficient to sustain automaticity; nevertheless it is set free continually, and, therefore, when the perfusion is discontinued, it will sometimes generate a short series of contractions. The internal radiation causes no appreciable increment of the liberated potassium, but the chemical method by which we tried to ascertain this, is little sensitive. True, external radiation causes in the red blood corpuscles of the horse a loosening of potassium, also when hæmolysis is avoided (unpublished experiments), and it may be that the result achieved here, applies to all cases, but the question as yet is by no means set at rest.

Meanwhile the hypothesis of an indirect effect of external radiation furnishes the advantage of removing the discrepancy between the inactivity of the permanent fields of radiation of the depôt potassium on the one side and the remarkable activity of internal fields of radiation

[1] The frog's heart in Kronecker's method derives its automaticity sometimes from the auricles (then it yields after an extra systole a compensatory pause); at other times from the ventricle (then there is no compensatory pause after the extra systole).

on the other. This discrepancy is, therefore, reduced to a quantitative difference which is easy of explanation. Incessantly the permanent corpuscular radiation liberates some potassium atoms from the composite complexes of molecules of the gels of the muscle-cells and of the blood-corpuscles. This is easy to understand, for by the β-, as well as by the α-radiation a continual ionic movement is brought about in the sols and the gels of the tissues, which is sure to exert catalytic activity. But the permanent radiation of the fixed tissue-potassium is extremely weak, that of 3–6 mgms. of mesothorium or of radium, arranged by the side of an organ, is much stronger. This renders the hypothesis highly plausible.

An experimentum crucis, by which the validity of this supposition may be tested, is the following. When a frog's heart, after having come to a standstill through removal of circulating potassium, is made to pulsate again through polonium radiation the sudden supply of normal Ringer's mixture must cause an abrupt standstill, if the action is direct; no change, however, will take place, if the automaticity is based on liberation of potassium. I have recently performed this experiment[1] and obtained the positive result (direct antagonism).

In whatever way the effect of external radiation may be brought about, it is certain that radio-activity is a mighty biological factor, capable of restoring a lost function. Such a factor can act either as a c a u s e, or as a c o n d i t i o n.

In physiology the term "cause" conveys a special idea, when the factor, which—under certain conditions—is considered as such, is extremely small relative to the effect it produces. In such a case the cause is called a stimulus, which is conceived to be equipped with a number of properties which experience has shown belong to many stimuli.

First of all there is a threshold value, below which no effect is seen, as is the case in our experiment. The quantum of potassium liberated incessantly from the potassium depôts of the tissues, is too small to be operative. This will happen only when the quantum is augmented by the migrating potassium-ions by which the stimulus rises beyond the threshold.

A second property is the existence of an optimum beyond which an action does not increase any more. This peculiarity of stimuli in general also affected our experiment. As soon as the potassium dose is raised to from four to six times the quantum, or the uranium or thorium dose is

[1] Academy in Amsterdam, 1 Oct. 1919.

doubled, toxic effects are noticeable which at the beginning are still reversible.

A third property is the inactivity of permanent equable stimuli, and activity as soon as a certain difference of intensity manifests itself. We encounter this peculiarity in the inactivity of the penetrating radiation of the potassium depôt of the muscular tissue, but we do not know whether the immediate cause is to be found only in the equable nature of the permanent radiation, or also in that the cells adapt themselves in their threshold to the intensity of this radiation, for the very reason that this intensity is permanent.

A fourth property is that which is called in many systems the "all-or-none" principle. We encounter it in many of our cases in a sudden and vigorous recovery of the function, when the supply of the radio-active atoms or of the internal corpuscular radiation has continued long enough.

Finally, that the causative agent is really small compared with its effect follows from the oligodynamic character it assumes in a number of cases. In virtue of the circulation experiments, in which to the initially inactive circulating fluid a trace of radium was added, I have estimated the intensity of the stimulus at about 10^{-7} erg. This is of the same order as that which must be assigned to the small adequate stimulus, which provokes a just perceptible action of the higher senses (34).

This marked resemblance between the radio-active physiological action and the properties of a stimulus justifies us to consider the radio-active influence on the organism as a stimulation. "Condition" has hardly any effect upon the facts as they present themselves to us. For, if it had, a perfectly equable radiation would then be competent to fulfil the conditions in the end, as *e.g.* that of the potassium depôt, which has such a penetrable power that its half-value is reached only at 1 mm. from the source.

Without this difficulty the action would be quite easy to explain, because a permanent radiation as Hardy (35), Fernan and Pauli (36) and Collwell and Russ (37) have taught us, may modify the fluidity of protein solutions. Meanwhile, there is always a possibility that the influence upon the fluidity alluded to, could be acting as a permanent in conjunction with a stimulating action exerted by the fluctuating ions. But an investigation into the realization of this possibility would be an encroachment on the territory of tonus-actions, which is not on our programme. Nor do I wish to discuss another point, that might perhaps elucidate the direct inactivity of the permanent radiation of the potassium depôt. I mean "screen-action," which might be exerted by the iron atoms in certain parts of the cell[1], by which these parts in contradistinction to others, are isolated from the influence of corpuscular radiations.

Conclusions.

1. In a large number of systems the potassium atom may, as regards function, be replaced by all the other radio-active elements, the heavy ones as well as the light ones, provided the dosages are æquiradio-active.
2. When applied simultaneously the substances emitting α-rays and those emitting β-rays are reciprocally antagonistic.
3. Potassium is (as bearer of the physiological radio-activity) for many cells a stimulus, which can restore and sustain function when it is brought in contact with the surface of the cells, as a free, diffusible ion in the circulating fluid.
4. A free radio-active radiation can take the place of potassium, when previously the potassium is omitted from the circulation.

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[1] Basing on the occurrence of a circular deviation in the path of the migrating particle, as soon as it approaches an iron atom (which will certainly happen qualitatively, less certainly quantatively).

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