X-Rays and Living Matter.[1]

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THE possible importance of X-rays in the medical world was recognised so clearly by their discoverer, Röntgen, that the first communication on the subject was made by him to a medical society, and was published to the world in a medical journal. Nor were medical men slow to appreciate the potency of the weapon which had thus been placed in their hands. The medical profession, be it spoken to its praise, has been unremitting in its search for new weapons in the fight against disease. Dr. Gilbert, himself no mean physician, and author of the first treatise on magnetism, records, with perhaps undue scorn, how, in the days when magnetism was the latest scientific marvel, patients were dosed with decoctions of lodestone as a possible panacea for all ills. It was not likely that so startling a discovery as X-rays would be overlooked, and we find medical men among the pioneers of X-ray work in nearly all countries. Further, the economically effective demand of medical radiology for more power, and still more power, has persuaded engineers and manufacturers to produce the modern high-power X-ray plant which has made possible the recent advances in the subject.

It was discovered early, but unhappily not early enough, that whatever healing power the radiation might possess, its destructive power on human tissue was indubitable and great. Few of the pioneers of radiography and radiotherapy escaped the painful and intractable X-ray burn, which arises from too prolonged an exposure to the radiation, and not a few have died as a result of the injuries thus received. Their labours have not been fruitless, and X-ray treatment is now a standard part of the work of any properly equipped hospital. At the same time one can detect to-day a certain undercurrent of dissatisfaction among radiologists. The rays have not yet fulfilled all their expectations. In particular, in some grave diseases where remarkable cures have been effected by X-ray treatment, a repetition of the same treatment in other apparently similar cases does not invariably produce the hoped-for result. There are undiscovered factors remaining to be elucidated. We need to ask how X-rays act on living matter, and in particular upon the living cell from which all living matter is built. The biologist, the physicist, and the chemist must be called in to assist, and the investigations must take in a wider sweep, before these problems can ultimately be solved. In science, as in other walks of life, it sometimes happens that the longest way round is the shortest way home.

It must not be supposed that so promising a field of research has been hitherto left uncultivated. There is, on the contrary, an overwhelming accumulation of observations and experiments. The results of different observers are, however, so conflicting that most of the evidence cancels out and leaves only a small residuum which can be said to be known with any certainty. This is scarcely surprising when we consider the conditions under which much of the work has had to be done. It is only within quite recent years that apparatus has been designed which makes it possible to repeat a given exposure with even approximate certainty, even with the same apparatus. It is not possible, even now, to give identical exposures if the apparatus is changed; if, for example, a high-tension transformer is substituted for an induction coil, or a Coolidge tube for a gas tube. Each type of apparatus for producing X-rays, one might almost say each individual set, has its own peculiarities, which are reflected in the quality and quantity of the radiation it produces. Our present state of knowledge does not allow us to assume that any of these variations have a negligible effect on the results.

Nor is there, at the present moment, any standardised or completely satisfactory method of recording these varied exposures. The properties of a given X-radiation are determined, physically, by its wave-length or frequency and its intensity. The radiation from an X-ray tube is, however, not monochromatic. It consists of a band of radiation stretching over a considerable range of wave-lengths. In optical terms, our X-ray tube gives us a continuous spectrum, which, moreover, may be crossed by intensely bright lines due to the characteristic radiation of the target from which the rays come. The band of maximum intensity moves towards the short wave-length end of the spectrum as the potential on the tube is increased, but the radiation is always mixed. In fact, for a given current, we shall get a larger absolute output of radiation of long wave-length from a tube working at high potential than from one at low potential. The distribution of energy in this complex spectrum depends on the wave-form of the high-tension apparatus used to supply the X-ray tube, and on the tube itself. If, as seems quite possible (there is ample experimental evidence both for and against the supposition), the biological effect is a function of the wave-length, it becomes a matter of considerable importance to determine not only the extreme wave-lengths but also the distribution of energy between the different wave-lengths in the radiation used. The discoveries of Prof. Laue, and their ingenious applications by Sir Wm. Bragg, have rendered this possible, but in very few researches so far conducted on the action of X-rays on living matter has any attention been paid to this important factor.

The measurement of the intensity of the radiation is a still more difficult problem, and one which cannot yet be said to have been solved by the physicist. The ideal method would be to measure the energy in the beam by absorbing it completely in some heavy metal, such as lead, and measuring the heat produced. Unfortunately, the actual energy even in a powerful beam of rays is so minute that, although it has been detected, it would strain the resources of a well-equipped physical laboratory to measure it with any accuracy. It is necessary to fall back upon some secondary property of the rays. The only secondary property which is capable of being measured with the necessary accuracy is that of producing ionisation in any gas through which it passes. Gas through which X-rays are passing becomes feebly conducting to electricity

[1] Substance of a course of two lectures delivered by the author at the Royal Institution on January 19 and 26.

and the current which can be passed across the gas is a measure of the ionisation, and thus, indirectly, of the intensity of the radiation. Prof. Friedrich has proposed that the amount of X-radiation which will allow a charge of one electrostatic unit to pass across one cubic centimetre of air shall be taken as the unit quantity of X-radiation. This proposal has met with some opposition, but personally I do not see the possibility of finding a better unit, at any rate in the immediate future. At least it may be affirmed that until experimenters can agree upon some method of measuring their quantities, progress is not likely to be rapid.

If any apology should appear to be needed for devoting so large a portion of our space to the question of measurement, it is certainly provided, not merely by the large mass of painstaking observations which have been rendered almost nugatory for want of it, but also by the records of recent work in the subject. Everything, in fact, seems to indicate that the biological effect of the rays may vary in a perfectly astounding manner with quite trifling variations in the magnitude of the exposure and the wave-length of the radiation. Only within the last few months a paper has come through from Australia, in which the author, Dr. Moppett, claims to have demonstrated a selective effect of the radiation of surprising sharpness. Dr. Moppett spread out his beam of X-rays into a spectrum, by means of a Bragg spectrometer, and exposed one of the important membranes of an ordinary chicken embryo in turn in various parts of the spectrum. He found that at certain definite positions in the spectrum, that is to say for certain definite wave-lengths of the radiation, the cells in the membrane were rapidly killed by the action of the rays, while much longer exposures to neighbouring wave-lengths produced no effect. The effective radiations had wave-lengths of 0·11, 0·53, and 0·79 Ångström units. Wave-lengths differing by only a few per cent. from these values were quite inoperative.

The paper, it must be confessed, is sadly lacking in the details which a physicist requires to assess its accuracy, and in many particulars it is by no means clear. One would certainly not have expected to obtain a selective effect with radiation of so short a wave-length as 0·11 Å.U., and if this result is verified we may have to revise some of our physical ideas as to the absorption of X-rays by matter. It is desirable that Dr. Moppett's work should be repeated. If, however, for the moment we accept these results, it is not difficult to point the moral. The wave-length 0·11 Å.U. is somewhere near the limit of the spectrum for a hard X-ray tube. It requires for its excitation a voltage across the tube of about 120,000 volts. Suppose the experimenter to be working his tube somewhere about this voltage. A slight rise in the voltage will produce a copious supply of the deadly radiation. On the other hand, if the voltage falls by but a small amount this radiation may be absent altogether. A trifling change in the supply voltage, to which few of us would, in practice, pay any attention, may thus completely alter the nature of the results obtained.

Experiments indicate that the margin in the case of the dosage given is equally narrow. Although the effect of a prolonged exposure to X-rays is invariably lethal, small doses often produce a healthy stimulation. This has been proved, by Prof. Russ among others, in the case of rats. It is also very evident in the case of Protozoa. I have found that an old culture of *Colpidium Colpoda*, for example, may be stimulated to new growth and active division by a suitable dose of radiation. The margin between stimulation and death is a very narrow one. In fact it is possible, by a careful adjustment of the dose, to have as the result of a single exposure individual colpidia, showing every sign of stimulation, swimming about vigorously among the corpses of those which have been killed by the same dose. A slight increase in the dose, say an extra ten per cent., will kill off the whole culture. A decrease of ten per cent. produces only stimulation. It is clear, in this instance at any rate, how narrow is the margin which separates these diametrically opposite effects. In radio-biology—if we may be permitted to coin the word—as in other sciences, exact measurement is the key which unlocks the door of knowledge.

It is no part of the purpose of this article (the attempt would be impossible in any case) to give a résumé of the vast amount of observations made on the action of X-rays on living matter. It is doubtful whether most of them can throw much light on the fundamental problem which underlies them all. In irradiating an animal, or even a tumour growing on an animal, we are dealing with a part of a highly organised and closely interrelated structure, and any effects which are observed may be merely secondary and only indirectly due to the irradiation. So true is this that it applies even to the parasites on the body. Bacteria, for example, are notoriously resistant to the action of the rays when exposed in a pure culture. On the other hand, the same bacteria infecting a wound will often be killed by quite small exposures to the radiation, and such exposures are now frequently used as a means of clearing and healing a wound. The problem, difficult enough in any case, only becomes manageable if reduced to its simplest form, and the simplest form in biology is the individual cell.

We are fortunate in possessing at least a preliminary study of the effect of X-rays on the individual cell. Methods have now been perfected by which it is possible to remove a number of cells from the tissues of a live animal and to cultivate them for long periods in glass vessels, where they continue to thrive and multiply, quite independently of the fate of the animal of which they were once a part. Dr. Strangeways has studied the action of X-rays on these isolated cells, and a preliminary account of his work was communicated a year or so ago to the Royal Society. One of the striking facts which emerges from his work is that it is extremely difficult to destroy a resting cell by the action of the rays. Doses far heavier than could be safely applied to the human skin leave them apparently unaffected. Further observation, however, showed that this absence of effect was only apparent. The cells had been very vitally affected, but the effects of the rays only became visible when the cells began to divide.

The first effect of the rays, produced by quite short exposures, was to lessen very materially the number of cells passing through the process of cell division, or mitosis. Dr. Strangeways records that an exposure of only 5 of Prof. Friedrich's units produces an appreciable diminution in the number of cells passing into mitosis. With a dose of 10 units the number was still less. After 15 units only a few cells in mitosis were visible, but the phenomenon was seen occasionally until the exposure reached as much as 85 units. Thus while a small dose of X-rays is sufficient to prevent the majority of the cells from dividing, a much larger dose is required before the whole of the cells are affected.

Dr. Strangeways has not yet provided us with a numerical estimate of this effect, but we hope that he and his collaborators may be able to do so before long. In the meantime, if we attempt to express his descriptions graphically, the curve which we shall have to draw relating the number of cells in mitosis with the exposure to the rays will be one which, plunging rapidly downwards at first, approaches zero asymptotically for prolonged exposures; it will, in fact, resemble closely an exponential curve. Now a curve of this type suggests strongly that the effect we are considering is a probability effect—in other words, that whether a cell will or will not go into mitosis after a given dose of X-rays is a matter of chance, the probability of its not doing so becoming greater as the dose is increased. This variability may, of course, be in the cell. Some may be more susceptible to the action of the rays than others. It is always legitimate, though not very helpful, to invoke the biological factor. I have ventured to suggest the possibility that it has nothing to do with the cell, but lies in the nature of the agent which we are using against the cell, that is, in the X-rays themselves.

An analogy, which is in fact a very close one, may help to make the matter clear. Suppose that we were firing at a swarm of midges with a machine gun. The number we should hit per second would be proportional to the number present in the swarm. At first we should claim a large number of victims, but, as the swarm gradually melted under our fire, the chance of hitting a midge would become smaller and smaller. To hit the last two or three would entail the expenditure of much ammunition and considerable patience. The survivors, however, would not owe their prolonged existence to any biological factor, or to any immunity either inherent or acquired, but simply and solely to their good luck. The number of survivors would, in fact, decrease exponentially as the number of bullets fired into the swarm increased.

Now, as Prof. C. T. R. Wilson's photographs show us very graphically, a beam of X-rays is very much like a swarm of bullets—only a negligible proportion of the atoms in the path of a beam of X-rays are affected in the least by the passage of the beam. It is quite easy to show that if the rays are conveying a dose of one unit per minute, as was the case in Dr. Strangeways' experiments, an individual atom would be effectively hit by the radiation on an average only once in a million years. The probability of a hit increases with the size of the particle, and a tissue cell would receive on an average about 14 hits per second, but as a hit is a matter of pure chance some would clearly receive more and others less than the average. This variation becomes more important as the size of the particles becomes smaller, and some of the important structures in the cell are much smaller than the cell itself.

It is not difficult to calculate what size the structure must have to fit in with the curve which we have constructed from Dr. Strangeways' description, on the assumption that a single hit registered by the rays on this particle suffices to put the cell out of action. Its diameter, assuming it to be spherical, would have to be about 1/2500 m.m. This is of the order of magnitude of the centrosome, a body which is considered by many biologists to play an important part in the process of cell division. With a target of this size, half the cells would be put out of action with an exposure of 12 units, 25 per cent. would survive a dose of 24 units, while 6 per cent. would still be capable of mitosis even if the dose were increased to 48 units. It will be seen how closely these numbers fit the phenomena we have described. It seems possible, to say the least, that the quantum theory must be taken into account in biology as well as in physics, and that a single cell may have a much more direct and painful appreciation of the existence of quanta than is possible to our grosser senses.

The scanty data which we possess on the action of X-rays on living cells indicate that the simple exponential relation which we have suggested is rather exceptional. The curve relating the number of survivors to the dose of X-radiation is generally sigmoid in shape. Practically no effect is produced until the dose exceeds a certain value. After this point is reached the number of cells affected increases rapidly, but there are always a few which survive much larger doses than the average. Curves of this kind are given by Dr. F. C. Wood, as expressing the result of his recent experiments on the effect of X-rays on cancer cells *in vitro*. Theoretically, we get a relation of this kind if we assume that a definite succession of hits is required to produce the result we are aiming at—say, for example, the destruction of the cell. I have given a calculation of the form of the curve on this assumption in a recent paper before the Cambridge Philosophical Society. A very considerable amount of rather tedious work will be necessary before sufficiently experimental results can be obtained to afford a real test of the theory, but the results so far accumulated are distinctly promising.

It need not be emphasised that these attempts to drag the biological action of X-rays into the domain of physics are extremely tentative. It is possible, even probable, that in the ultimate issue we shall find in the living cell something which transcends all physics and chemistry, but this is no legitimate excuse for failing to push our sciences to their extreme limits. Whatever the ultimate result may be, we are sure to find much of interest by the way. The primary effect of the absorption of X-rays by an atom, in fact the only effect of which physicists are aware, is the expulsion of a high-speed electron from the atom. That, it would appear, must be the starting point of any purely physico-chemical theory of the action of X-rays on living matter. What subtle series of changes is thus initiated in the complex chemical compounds which make up the cell is a problem, like that of the song the syrens sang, the answer to which no man knows, but which may not be beyond the wit of man to conceive. Nature, as usual, leaves us guessing. That is precisely why we find her so fascinating.