The Croonian Lectures

ON

RADIO-ACTIVITY AND CARCINOMA: AN EXPERIMENTAL INQUIRY.

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By **W. S. LAZARUS-BARLOW, M.D., F.R.C.P.,**
DIRECTOR OF THE CANCER RESEARCH LABORATORIES, THE
MIDDLESEX HOSPITAL.

LECTURE III.

THE ELECTRICAL PROPERTIES OF RECOGNIZED RADIO-ACTIVE
SUBSTANCES; OF NON-MALIGNANT TISSUES; OF CAR-
CINOMATOUS MATERIAL; AND OF CERTAIN SUBSTANCES
COMMONLY SUPPOSED TO BEAR A CAUSAL RELATION TO
CARCINOMA.

THE researches to which I am now about to refer have been in progress for the past three and a half years nearly continuously. This length of time was necessitated partly by the importance of controlling certain of the results, but mainly by the fact that the differences between the control and the experimental conditions are so small that special care was necessary for their determination. The rate at which the electricity on charged gold leaves leaks from them is dependent upon so many factors that unless the extrinsic causes of leak are reduced to the lowest possible point small intrinsic differences are entirely lost sight of. Electroscopes in which the natural leak is greater than about 1 mm. per hour are quite useless for the purpose; in the majority of the cases the charged leaves approximated over a fixed distance at a rate of about 0.6 mm. per hour, and in a large number the rate was about 0.2 mm. per hour. It follows that the length of time necessary to obtain a single observation, whether control or experimental, is considerable; in no instance has it been possible to obtain more than one observation a day, and in certain of the experiments it took two days to obtain each observation. This difficulty was obviated to some extent by using several electroscopes. As a rule two control electroscopes (charged + and - respectively), and eight experimental electroscopes (four charged + and four charged -) were under observation.

It is unnecessary to enter here into a description of the apparatus or of the precautions taken; they are sufficiently described elsewhere.* Similarly, it is unnecessary, in the majority of cases, to refer to the actual experiments. It will suffice to state that the object of the research was to determine whether the leak of a fully earthed lead electroscope differed according as it did or did not contain one of the substances under investigation.

The substances examined were: Liver, kidney, lung, and spleen (four specimens of each) from non-malignant cases; four specimens of hepatic substance from livers the seat of carcinomatous metastasis; four specimens of the inorganic constituents of bones from non-malignant cases; four specimens of the inorganic constituents of bone from cases of carcinoma, in one of which the bone itself was the seat of secondary growth; twelve specimens of carcinoma. Of substances supposed to be causally related to carcinoma, the following have been examined electrically: Three samples of clay pipe, each sample consisting of portions of three distinct pipes from different sources,

powdered and mixed; two samples of soot; one sample of impure cholesterin gallstone from a case of columnar cell carcinoma of the gall bladder; one "pure" cholesterin gallstone; "pure" pigment gallstones; four samples of pitch from different localities; three samples of paraffin wax; three samples of betel nut; and one sample each of metallic arsenic, arsenious oxide, and coal.

In addition to the above, experiments have been carried out in connexion with the recognized radio-active substances—uranium, thorium, and pitchblende—in order to throw light, if possible, upon certain unexpected electrical phenomena.

In the case of the carcinomatous material diagnosis was always made microscopically. Four cases were primary (cervix, cervix, tongue, breast), and 8 metastatic. Of the latter, 6 came from the liver, the sites of the primary growth being rectum (3 cases), breast (2 cases), stomach (1 case); the remaining 2 were pulmonary metastases from cases of mammary carcinoma. The substances were introduced into the electroscopes in the dried powdered state to which they had been reduced for skotographic examination.

RESULTS OF EXPERIMENTS.

In the case of carcinoma material which has been extracted with water and subsequently with ether, or has been extracted once and for all with acetone, there is strong evidence that the leak of the electroscope is accelerated, whether the charge on the leaves be + or -. Similarly there is evidence that the inorganic constituents of bone, whether taken from non-malignant or from carcinomatous cases, accelerate electroscopic leak, whether the charge on the leaves be + or -. And, thirdly, clay-pipe, and possibly one sample of soot, acted in an identical manner.

So far, therefore, there is evidence to satisfy the physicist that the substances mentioned above are "radio-active" in the physico-chemical sense of the term. But already difficulties have arisen, for whereas the carcinomatous material produces skotographic effects when it has been extracted with water alone or with ether alone, it fails to do so when it has been extracted with both, or with acetone, while the inorganic constituents of bone and the clay pipe are equally non-skotographic.

The difficulty becomes much greater, however, when it is found that substances exist which, so far from accelerating the discharge of the electroscope or being without appreciable effect, actually retard the leak whether the charge on the leaves be + or -. I make this statement with a full sense of the responsibility I am incurring. I am aware that the physicist does not recognize such retardation or "antiradio-activity" as it may be termed. I am aware that it includes theoretical considerations of great magnitude, that if recognized radio-activity means the breaking up of large atoms into smaller ones antiradio-activity may mean the synthesis of elements with high atomic weight from elements with lower atomic weight. But I have carried out the experiments with the utmost care of which I am capable, and have found evidence of antiradio-activity a sufficient number of times to be convinced of the accuracy of my observations. Moreover, as the following experiments will show, I believe that evidence of antiradio-activity may be obtained by the use of recognized radio-active substances themselves.

If an aluminium disc be kept in close proximity but not in contact with uranium or thorium or pitchblende for forty-eight hours under fully earthed conditions and its influence upon electroscopic leak after such exposure be compared with its influence before exposure, it will be found, I believe, that the rate of leak has become retarded. This retardation persists for many days, and is independent of the sign of the electricity with which the leaves are charged. Full details of the experiments are given elsewhere.† It will suffice to give here a summary of the results obtained in an experiment lasting over four months, and carried out in order to reinvestigate the question, owing to the adverse criticism to which the first set of experiments had been exposed. This second experiment completely confirmed the first.

* *Archives of the Middlesex Hospital*, vol. vii (Fifth Cancer Report), 1906, p. 190. In this article and in articles that have appeared in the Sixth and Eighth Cancer Reports (1907 and 1909) full details are given of the experiments upon which the conclusions referred to in this lecture are founded.

† See previous footnote.

Experiments showing that an aluminium disc which has been kept in proximity to a recognized radio-active substance has acquired retarding or antiradio-active properties on electroscopic leak. The values are the mean differences between the experimental and the control electroscopes (Cf. "Arch. Middlesex Hosp.," vol. xv, 8th Cancer Rep., 1909, p. 145).

Experiment.	Control Period.	Blank Experiment.	Actual Experiment.	Remarks.
I. Electroscope in which was examined the aluminium disc placed in proximity to uranium nitrate	Mm. -25	Mm. -25	Mm. -27	29 observations for retardation to 10 for acceleration.
II. Electroscope in which was examined the aluminium disc placed in proximity to uranium oxide	+86	+85.5	+82	36 observations for retardation to 9 for acceleration.
III. Electroscope in which was examined the aluminium disc placed in proximity to pitchblende	-18	-21.5	-26	44 observations for retardation to 2 for acceleration.
IV. Electroscope in which was examined the aluminium disc placed in proximity to thorium	-31	-34	-38.5	37 observations for retardation to 9 for acceleration.

NOTE.—In the case of thorium the observed acceleration occurred on the first four days of each of the two parts of which the actual experiment consisted and was evidence of the well-known "induced radio-activity" due to thorium.

The following experiment shows that a similar retarding property is conferred upon an aluminium disc that has been placed in proximity to a substance that itself has retarding influence upon electroscopic leak. This experiment was carried out at the same time and under the same conditions as those mentioned above.

Experiment.	Control Period.	Blank Experiment.	Actual Experiment.	Remarks.
V. Electroscope in which was examined the aluminium disc placed in proximity to a cholesterol gall stone	Mm. -3	Mm. -4	Mm. -8	41 observations for retardation to 5 for acceleration.

Returning now to a consideration of carcinomatous material itself, it appears that the electrical properties differ according as the substance has or has not been extracted before its influence upon electroscopic leak is determined. Moreover, the extract exerts a definite influence upon the leak, and that influence is in the opposite direction to that exerted by the extracted substance. This is shown by the following table, condensed from one given by me elsewhere¹:

Table showing the influence upon electroscopic leak of four specimens of carcinomatous material before and after extraction and of the extracts themselves.

	I.	II.	III.	IV.
Charge on gold leaves ...	- +	- +	- +	- +
Carcinoma, dried and powdered	A A	R? O	A O	A O
Above after extraction with ether	A A	R A	A A	A A
Above after extraction with ether and subsequent extraction with water	A A	A A	A A	A A
Ethereal extract of above...	R R	R R	R R	R R
Watery extract of above after its extraction with ether	R R	A? R	A R	R R

A is used to signify acceleration; R, retardation.

The manner in which the uncertain influence upon electroscopic leak exerted by the substance when simply dried and powdered gives place to an increasing evidence

for an accelerating power after each extraction, the powerfully retarding character of the first extract, and the less powerful but still distinctly retarding character of the second, afford a chain of evidence, not only for the existence of "antiradio-activity," but also for the presence of both forces in carcinoma tissue, that cannot lightly be dismissed. So far as concerns the accelerating influence of carcinoma material after extraction, the conclusion given above is supported by the results of examining electroscopically eight other specimens extracted with acetone.

While carcinoma tissue after extraction accelerates the leak, this is not the case with liver or lung from non-malignant cases. These extracted tissues were found uniformly to retard leak. The acetone extract of non-malignant liver, however, agreed with that from carcinoma tissue in retarding leak, and the unextracted tissue showed a less tendency to induce retardation than the extracted. Below are given the results obtained with four specimens of liver from non-malignant cases.

Table showing the influence upon electroscopic leak of four specimens of liver from non-malignant cases before and after extraction and of the extracts themselves.

	I.	II.	III.	IV.
Charge on gold leaves ...	- +	- +	- +	- +
Liver, dried and powdered..	A R	R? R	R R	R R
Above after extraction with acetone	R R	R R	R R	R R
Acetone extract ...	R R	R R	R R	A A?

A signifies acceleration; R, retardation.

In the first lecture evidence was given to show that the skotographic action of an organ which is the seat of carcinomatous metastasis differs from normal. Examination of four specimens of hepatic tissue from livers the seat of carcinomatous metastasis shows that the new growth also influences the electrical properties. Thus, in the table immediately preceding, the evidence for retardation exerted by the four specimens of acetone-extracted liver (each of which retarded the leak whether the sign on the leaves was - or +) consisted of 76 individual observations of retardation to 4 of acceleration. In the case of hepatic substance from livers the seat of carcinomatous metastasis, not only did two of the specimens show discordant results affording evidence of acceleration in the electroscope charged with one sign and retardation in the electroscope charged with the other, but the total number of individual observations in favour of retardation was only 52, against 28 in favour of acceleration.

Comparison of the results obtained with the inorganic constituents of bones from non-malignant and those from malignant cases affords confirmatory evidence of the influence of carcinoma upon the electrical properties of the tissues, but here the natural influence of the inorganic constituents appears to be accelerative and in carcinoma the tendency is increased. Thus two out of four samples of inorganic constituents of bone from non-malignant cases afforded discordant results, showing acceleration in the electroscope charged with one sign and retardation in the other, while the total number of individual observations in favour of acceleration was 41 (or 59 per cent.), against 29 for retardation, whereas when derived from cases of carcinoma the discordancy was somewhat less, and the total number of individual observations in favour of acceleration was 53 (or 66 per cent.), against 27 for retardation.

Leaving on one side the evidence afforded by electrical examination of kidney and spleen on the ground that the results are not sufficiently clear to allow of deductions being drawn, I pass to the consideration of substances commonly supposed to be causally related to carcinoma.

In this part of the subject the evidence that I have to offer is of different value in different cases. Electrical examination of clay pipe, of paraffin wax, and of cholesterol gall stone has been carried out on so many occasions that I have more confidence in the case of these substances than in that of others of which the electroscopic examinations are clearly too few. Here, I can only beg your

indulgence and plead the motto of our college as an excuse:

Ὁ βίος βραχύς ἢ δὲ τέχνη μακρή.

I have already stated that I find evidence that clay pipes exert an accelerating influence upon electroscopic leak whether the gold leaves be charged — or +. In the case of paraffin and cholesterolin gall stone the evidence is no less clear, but both substances exert a retarding influence, and again whether the electrical charge on the leaves be — or +. Experiments with different samples of pitch seem to show on the whole that this substance exerts a retarding influence, but there is no reason to suppose that a uniform effect would be produced by all samples of this or of any other substance of an impure or complex nature. The same criticism holds good in the case of soot, one sample of which yielded me evidence of retardation, while the other gave uncertain results. Metallic arsenic, arsenious oxide, and betel nut appeared to be without effect upon electroscopic leak, but too few experiments were made with them to allow me to speak with confidence.

In my experiments with the substances mentioned above—some of the earliest made in the entire research—I sought to show that the accelerating or retarding property was manifested, even though the substance under examination were covered with an aluminium cap. In numerous instances this appeared to be the case, and undoubtedly, if true, it would afford convincing proof of the similarity of the action of the substances with that of recognized radio-active substances. But owing to the fact that I have found an aluminium disc to become electrically modified by the proximity of a recognized radio-active substance or of a pure cholesterolin gall stone, my conclusions on this point require reconsideration. It may be added, however, that even if the influence from the substances did not traverse the aluminium, it would not disprove the possibility of their being essentially "radio-active," since conceivably they might only give off alpha particles, or alpha particles and beta radiations of so low penetrating power that they failed to traverse the aluminium screen.

Having described in brief the electrical effects of the various substances that particularly interest us from a medical point of view, it is now necessary to revert to the recognized radio-active substances.

I have already said that I have reason to believe that recognized radio-active substances induce "antiradio-activity" in an aluminium disc with which they have been placed in proximity, though not in contact, for a certain length of time. This change, I believe, is indicated by the acquisition of a retarding power by the disc on electroscopic leak. But there is no doubt that a metallic surface that has been bombarded by radio-active rays manifests physical change of a gross kind. Thus, the anticathode of an x-ray tube not infrequently becomes perforated in course of time, an aluminium disc which has been exposed to radium for four months shows actual pits on its surface, while an aluminium disc exposed to the relatively feeble radio-activity of uranium for four months shows a loss of polish of its surface over an area corresponding to that which had been in proximity to the uranium. In the last lecture it will be shown that animal cells, in like manner, afford evidence of altered behaviour as the result of proximity to recognized radio-active substances.

This brings us to a consideration of extreme importance. There is no doubt that the facts and the conclusions of the chemist and physicist cannot be applied to biological problems in a crude manner. It is unnecessary to labour this point. It is supported by the whole of chemical physiology and pathology, from so simple an example as the fact that iron in combination with globulin in the form of haemoglobin fails to give the ordinary chemical tests for inorganic iron to the complicated problems of immunity which have shown repeatedly that the animal body is not a mere test tube in which a simple chemical process is taking place. In a word, for the biologist, a necessary preliminary to consideration of radio-activity as understood by the chemist and physicist is a determination whether the radio-active element when in combination with protein behaves in the same way as it does when in combination with other elements to form an "inorganic" compound. It is in the latter form alone that it has been examined by chemist and physicist.

Even if a series of inorganic compounds of a radio-

active element be examined it will be found that the radio-activity as measured by the rate of leak of an electroscope is not identical for all of them. Thus, Colwell and I have shown that the rate of leak of an electroscope in which are examined a number of uranates of the alkalis and alkaline earths as well as the nitrate and sulphates of uranium varies inversely as the atomic weight and the valency of the elements with which the uranium is linked. From this we argued that uranium in combination with the huge protein molecule would show a correspondingly enormous diminution of its influence on electroscopic leak.² This proved to be the case. We showed, further, that the radio-activity of the uranium is not lost, but only masked, for the ash of an incinerated albuminous compound of uranium or of such inorganic compounds as the nitrate and sulphates of uranium or ammonium uranate (which are more or less completely disintegrated on incineration with the formation of an ash consisting chiefly or entirely of an oxide of uranium) produces a profound acceleration of leak. Similar results were obtained with the nitrate and sulphate of thorium and a thorium albuminous compound. Full details will be found in the original paper. Below are given examples in illustration of the statements made above:

Mean values of electroscopic leak in the presence of certain uranium and thorium compounds in the natural state and after incineration.

	Mean Rate of Leak per Hour in Mm.	
	Natural State.	Incinerated.
Black uranium oxide	175	177
Ammonium uranate	125	171
Thallium uranate	101	114
Uranyl sulphate	91	177
Uranyl nitrate	80	187
Uranous sulphate	62	159
Uranium Witte-peptone	22.4	126
Uranium serum (pleural fluid) ...	13.5	85
Uranium egg-white	13	95
Uranium spleen-pulp	10.9	53.6
Thorium sulphate	62	124
Thorium nitrate	55	142
Thorium egg-white	7.5	41.4

Natural leak of empty electroscope 3.6 mm. per hour.

Now the uranium and thorium albuminous compounds contained about 10 per cent. of the radio-active element by weight, and it has already been said that their photographic effect is small and may be completely wanting, even though they be allowed to act on the film through a thin layer of air, while at least the thorium compound fails to affect the film through a screen so thin as that formed by brushing egg-white over tissue paper. Evidence of radio-activity in the physical sense is therefore reduced to a very low point, and it is easily conceivable that with smaller percentages of the radio-active element, or in combination with still larger molecules or combinations of molecules, all evidence of "radio-activity" should be lost, although the fact that the substance in question contains the recognized radio-active element would be immediately demonstrable on removing the impeding constituents of the compound by incineration.

Proceeding on these lines I have incinerated animal substances of all kinds, in the hopes of setting free a radio-active substance that would be recognized by physicists and chemists, but without success. Clearly the tissues contain no radio-active substance which can survive exposure to a white heat. Whether they contain a radio-active substance that can withstand a temperature of 300°, after which skotographic action disappears, but is dissipated or disintegrated between 300° C. and the temperature of white heat, it is impossible to say. In any case experiments with albuminous compounds of recognized radio-

active substances, such as uranium and thorium, indicate that small evidence of radio-activity manifested by an animal tissue does not necessarily mean that that tissue contains only a small amount of a radio-active element. The smallness of the evidence may simply depend upon the relative completeness with which the radio-activity is masked by the albuminous molecules with which the radio-active element is in combination.

By comparing the rates of electroscopic leak when the substance is directly exposed to the charged leaves, and when it is separated from them by a screen of thin aluminium foil, it is possible to separate that portion of the leak which is due to the impact of alpha particles from that portion due to beta and gamma rays. As is shown by the following table, the masked radio-activity consists chiefly, if not entirely, of alpha particles. In the case of thorium compounds, the table is of particular importance, inasmuch as it not only shows the great increase of leak due to alpha particles after incineration, but also an enormous disappearance of some radio-active element producing beta and gamma rays during incineration. It is necessary to add that the amount of radio-activity that is removed from thorium compounds by incineration varies considerably under a number of circumstances that need not be mentioned here, but that all the thorium compounds given in the table were prepared from a single sample of thorium, and are comparable amongst themselves, though not with those given in the preceding table.

Portions of the rate of leak per hour occasioned by certain uranium and thorium compounds due to alpha particles and to beta + gamma radiations.

	Natural State.		Incinerated.	
	α Particles.	$\beta + \gamma$ Rays.	α Particles.	$\beta + \gamma$ Rays.
Black uranium oxide	145.8	29.2	144.0	33.0
Ammonium uranate	101.2	23.8	145.5	25.5
Thallium uranate ...	79.4	21.6	82.6	21.4
Uranyl sulphate ...	57.0	35.0	142.8	37.2
Uranyl nitrate ...	52.4	27.6	151.9	35.1
Uranous sulphate ...	52.8	11.2	127.0	11.0
Uranium egg-white	4.8*	0.6*	124.0	1.8*
Thorium sulphate...	24.1	77.9	78.4	27.6
Thorium nitrate ...	21.7	70.6	127.8	16.2
Thorium hydroxide	104.0	496.0	123.0	22.0
Thorium egg-white	3.1*	1.4*	46.5	7.8*

* In the case of these low values the ascertained leak has been corrected by the natural leak of the electroscopes determined specifically for the purpose on each occasion; elsewhere it is neglected.

As to the work done and the changes produced within the molecule by the imprisoned alpha particles, it is only possible, as yet, to speculate. Evidence has been given that carcinoma material, with its tendency to accelerate electroscopic leak, modifies the electrical conditions of the tissue in which it lies; it is not impossible that the bombardment with alpha particles undergone by an aluminium disc in proximity with a recognized radio-active substance may lead to that "antiradio-activity" of the disc which I have described.

LECTURE IV.

INFLUENCE OF RECOGNIZED RADIO-ACTIVITY AND OF CERTAIN SKOTOGRAPHIC NON-MALIGNANT MATERIALS UPON THE DIVISION OF ANIMAL CELLS.

HITHERTO the experiments I have described have been of a chemical or a physical nature; the next step, and the last I am at the present time in a position to make, will be into the animal kingdom. Whatever the results we may have obtained, their sole importance to us as biologists, and even more as medical men, lies in any application they may have to the processes going on in the animal cell. If radio-activity, if the peculiar skotographic and electrical properties we have now found, to be associated with a number of substances some of which are

derived from the animal body, influence cell nutrition, cell growth, cell multiplication, they are of interest to us; if not, we may leave them on one side.

The cell which I have chosen for this part of the research is the ovum of *Ascaris megalocephala*, an intestinal entozoon of the horse. When removed from the oviduct the ovum shows a thick cell membrane, a single undivided cell, and a general absence of pigment or foodstuffs. Since it is obtainable in enormous numbers, is clearly visible with a half-inch objective, and passes through the changes up to the formation of a complete living and moving embryo worm within a few days or a few weeks, according to the temperature at which development is allowed to proceed, it is very suitable to our purpose.

Examination of the development of the ovum when it has been exposed to the influence of recognized radio-activity, has been carried out in the case of α rays, radium, thorium, and uranium.³ The results agree remarkably, not only in their general direction, but also in the fact that certain special effects are produced by the two most potent members of the group—radium and α rays.

The experiments consisted in determining the rates of division of the cells under conditions that differed only in respect of their exposure or non-exposure to radio-activity. In the case of α rays, exposure lasted varying times, from two minutes to twenty minutes, and the ova were exposed to the rays at the commencement of the experiment when they were all in the one-cell stage. In the case of radium, thorium, and uranium the ova were exposed to the action of the substance during the whole time of their development. Inasmuch as α rays are gamma rays alone, while radium, thorium, and uranium give off alpha particles as well as beta and gamma rays, the experiments differed in this respect. Moreover, since the radium, thorium, and uranium were exposed to the ova without any intervening substance except a thin layer of air, the cells were acted on by all three constituents of radio-activity in the case of these substances.

Below are given the results of an experiment using α rays.

Characters of Cell Division in 200 Ova after Exposure to X Rays for Varying Periods.

Immediately after exposure:
All cells in 1-cell stage.

24 hours after exposure (room temperature):

	Control	1-cell stage.	2-cell stage.
Control ...	...	158	43
2 min. exposure ...	...	140	60
4 " " ...	...	151	49
6 " " ...	...	164	36
9 " " ...	...	175	25
12 " " ...	...	184	16
15 " " ...	...	187	13
20 " " ...	...	194	6

48 hours after exposure (room temperature):

	Control	1-cell stage.	2-cell stage.	3-cell stage.	4-cell stage.
Control ...	...	74	65	26	35
2 min. exposure ...	...	71	52	22	55
4 " " ...	...	81	42	21	56
6 " " ...	...	90	46	20	44
9 " " ...	...	107	53	21	19
12 " " ...	...	104	60	15	21
15 " " ...	...	128	43	14	15
20 " " ...	...	126	57	13	14

This experiment, which has been repeated on many occasions with similar results, shows conclusively that α rays have a dual effect. Short exposures accelerate, long exposures retard, cell division.

Since the ovum does not increase in size during development it becomes impossible to conduct the experiment satisfactorily during the period between the four-cell stage and the early embryo, but with the formation of the embryo the accelerating and the retarding influences of the α rays again become manifest. Thus the ova, concerning which details have been given above, were transferred to the incubator at 37° C. during the third and fourth days after exposure to α rays, and it was then found that the control specimen showed immature embryos and 1 living and moving worm; the two-minute and four-minute specimens were indistinguishable from the control, and also showed 1 living and moving worm apiece.

But in the six-minute specimen there were 3 living worms; in the nine-minute specimen, 6; in the twelve-minute, 1; in the fifteen-minute, 2; and in the twenty-minute specimen there were 21 living and moving worms. Here we have evidence of accelerated development. Evidence of the antagonistic influence of the rays on the same specimens of ova was obtained by keeping them in the incubator for a further period of three days, by which time development has proceeded to its furthest extent within the egg case.

The Final Results.

	Complete Development.	Failure of Development.
Control	193	7
2 minutes' exposure	193	7
4 " " " " " " " " " " " "	169	31
6 " " " " " " " " " " " "	166	34
9 " " " " " " " " " " " "	165	35
12 " " " " " " " " " " " "	174	26
15 " " " " " " " " " " " "	157	43
20 " " " " " " " " " " " "	133	67

Movement and Absence of Movement in Fifty Completely Developed Embryos.

	Living and Moving.	Motionless.
Control	45	5
20 minutes' exposure	30	20

This antagonistic influence of α rays upon the development of the ova of *Ascaris megalocephala* has already been described by Perthes,⁴ and Bonney and I fully confirm his results, both with regard to the main position and with regard to the observation that, though division of the cells may go on for a certain length of time, exposure to α rays in large doses leads to the formation of monstrosities and abortive embryos. Perthes, however, failed to recognize an accelerating influence.

Working with the root-tips of plants, Cattley⁵ has obtained results similar to those of Bonney and myself, both as regards acceleration and as regards retardation of cell division, but he found no evidences of gross pathological change at any time.

Exposure of ova to radium leads to results practically identical with those following exposure to α rays. For the first twenty-four hours of the experiment division occurs more rapidly in the cells exposed to radium than in the control, but from that time forward division in the control comes to the front, and at the conclusion of the experiment the control contains a larger number of living and moving worms than the sample exposed to radium. Nevertheless, as in the α -ray experiment, the first fully-developed and living worms are met with, not in the control, but in the irradiated specimen. Finally, the specimen exposed to radium shows ova in all stages of development, in some of which the division appears to have proceeded on normal lines previous to its arrest, while in many it has been irregular, as shown by abnor-

malities of the number of cells to which division has given rise, and a wide irregularity in size of the daughter cells (Fig. 14).

As might be expected, exposure of ova to uranium or thorium leads to less marked results than exposure to α rays or radium. In particular, there is no evidence of the production of monstrosities, nor is there any recognizable difference in the number of ova that arrive at the formation of living worms. On the other hand, acceleration of division in the early stages and retardation in the later are shown with clearness. The following experiment illustrates these points.

Experiment showing the Influence of Exposure to Thorium or Uranium Oxide upon Cell Division in the Ova of *Ascaris megalocephala*.

September 29th, 1908.—All ova in 1-cell stage.

	1-cell stage.	2-cell stage.
September 30th.—		
Control	157	43
Thorium-exposed	136	64
Uranium-exposed	141	59

	1-cell stage.	2-cell stage.	4-cell stage (and over).
October 1st.—			
Control	0	17	183
Thorium-exposed	4	21	175
Uranium-exposed	3	10	187

October 2nd.—Control. All cells in morula stage.

Thorium-exposed { All cells in morula stage, but the morula
Uranium-exposed { appears to be composed of fewer cells than in the control.

October 3rd to 7th.—No perceptible changes in any of the specimens.

	Living Embryos.	Incomplete Embryos.
October 8th.—		
Control	115	85
Thorium-exposed	42	158
Uranium-exposed	81	119

October 11th.—All specimens consisted of fully developed living worms.

Examination into the effect upon cell division of exposure of the ova to other substances (a layer of air intervening) is being carried out at the present time in my laboratory by Somerville Hastings and myself.

In a preliminary communication⁶ we record the results of experiments with materials of importance in connexion with the subject now under discussion. Thus we have examined the effect of exposing ova to various extracts of tissues having skotographic power, and find marked evidence that the rate of development is influenced by the character of the extract in proximity with which they are dividing. Thus the proximity of a protein-free watery extract of sheep's liver or of ovary of herring causes the ova to pass from the one-cell stage to the two-cell stage more slowly than in the control—that is, retards development—while a similar extract of the testis of the herring accelerates division. Quite apart from the results to which this remarkable observation may possibly give rise in the

future, it is clear that the effects of these extracts, acting on the cell as they do, through the egg case, and producing results similar to those which follow exposure of the ova to the action of α rays and radio-active substances in general, suggest that there resides in animal tissues a force unrecognized hitherto, and resembling radio-activity in certain respects.

SUMMARY OF RESULTS.

I have now laid before you the results I have so far obtained in this research. I have not hesitated to occupy

Fig. 14.—The development of the ova of *Ascaris megalocephala* under the influence of radium. Note the great variability in the stages of division, all stages from a single undivided cell to a complete worm being recognizable.

the greater part of the time at my disposal in this way, partly because in cancer research there is at present more need for practical experiment than for theoretical disquisition, and partly because the Croonian Lectures afford a rare opportunity for presenting the results of a prolonged research in an orderly manner. It is right, however, that in the time remaining to me I should summarize my results, and, as far as may be, consider established facts in connexion with carcinoma under the light that they afford.

The original question with which I started—namely, Do the physical agents which are commonly supposed to give rise to cancer (clay pipes, soot, etc.), and do samples of carcinomatous material afford evidence of the possession of radio-active properties?—is not conclusively answered. In certain respects they behave like the radio-active materials of the chemist or physicist, but in no single instance do they respond to all the criteria of recognized radio-activity. Thus, I have shown that many of the substances affect a photographic plate in the dark; but, on the other hand, few can act on the plate if a screen be interposed, and even in those instances in which a positive result is obtained under these circumstances, it is doubtful whether the interposed celloidin screen is fairly so called. Nevertheless, it is doubtful whether the power of acting through a screen is a necessary criterion of radio-activity, since I have shown that albuminous compounds of recognized radio-active substances may possess a power of acting on the photographic plate which will not traverse an extremely thin screen, and, indeed, may be devoid of photographic powers altogether. In the latter respect they are comparable with clay pipe, inasmuch as neither type of substance acts on a photographic plate and both accelerate the discharge of an electroscope. In the same category comes carcinoma material which has been extracted with acetone or with water and subsequently with ether. Possibly, too, some specimens of spleen and of the inorganic constituents of bone are to be reckoned in the same class.

Even a greater difficulty arises in connexion with those substances which I have found to retard electroscopic leak. Such a property is entirely repugnant to present ideas of radio-activity. If I am correct in asserting that evidence of retardation can be obtained by the use of recognized radio-active substances, as in the case of aluminium discs which have been placed in proximity to uranium, thorium, or pitchblende, this difficulty is overcome. It may be that the dual accelerative and retarding influence which I have found all forms of radio-activity to exert upon the development of the ova of *Ascaris megalocephala* will help in determining this important question. Already this line of research is indicating that certain animal extracts having skotographic powers resembling those of radio-active substances up to a certain point are able to influence the rate of development of animal cells when acting on them from a distance, and through the screen of their own egg case. It is not impossible that we shall find that the laws of radio-activity as determined by the physicist require some modification when adopted into biology owing to the presence of the protein molecule, just as the laws of filtration and osmosis have required adjusting to the special circumstances of the case. I showed some years ago that the presence of even a minute trace of protein profoundly modifies the rate of osmosis,⁷ and I showed in the last lecture that combination of a radio-active element with a protein molecule profoundly modifies the rate with which it induces electroscopic leak, and its photographic powers.

Table showing Principal Skotographic and Electroscopic Results hitherto Obtained.

Type of properties:	The substance acts on a photographic plate directly and also through a screen. It accelerates electroscopic leak whether the charge on the gold leaves be — or +.
Recognized radio-active substances	Radium, uranium, thorium, uranium albuminate some weeks after its preparation.
Other substances of research	No member found.

Type of properties: The substance acts on a photographic plate directly but not through a screen. It accelerates electroscopic leak whether the charge on the gold leaves be + or —.

Recognized radio-active substances Uranium albuminate directly after its preparation, thorium albuminate weeks after its preparation, doubtfully, directly after preparation.

Other substances of research Carcinoma material after extraction with either water or ether but not both.

Type of properties: The substance acts on a photographic plate directly and also through a screen. It retards electroscopic leak whether the charge on the gold leaves be + or —.

Recognized radio-active substances No member of the group found.

Other substances of research Solid mass of hepatic material.

Type of properties: The substance acts on a photographic plate directly but not through a screen. It retards electroscopic leak, whether the charge on the gold leaves be + or —.

Recognized radio-active substances No member of the group found.

Other substances of research Carcinoma extract, watery or ethereal, non-malignant liver, before and after extraction with acetone, acetone extract of liver, cholesterin gall stone.

Type of properties: The substance has no photographic action whatever. It accelerates electroscopic leak whether the charge on the leaves be + or —.

Recognized radio-active substances Thorium (?) and certain specimens of uranium albuminates directly after preparation.

Other substances of research Carcinoma material after extraction with acetone, clay pipe, possibly some others.

Type of properties: The substance has no photographic action whatever. It retards electroscopic leak, whether the charge on the leaves be + or —.

Substances prepared by means of recognized radio-active substance Aluminium discs after proximity to uranium or thorium or pitchblende.

Other substances of research Aluminium disc after proximity to cholesterin gall stone, paraffin wax, liver substance after extraction with acetone.

The Relation of Radio-activity to Carcinoma.

Leaving now the question whether the substances commonly supposed to be causally related to cancer and certain animal tissues, including carcinomatous material, are radio-active as unanswered—and, in our present state of knowledge, as unanswerable—we may pass to consider recognized facts in connexion with carcinoma as a disease in the light of the experimental evidence I have adduced. It is impossible for me to traverse the whole field, partly from lack of time, partly because I should thereby introduce too much contentious matter. I shall therefore confine myself to a few salient points, offering you something in the nature of an impressionist picture.

One of the most certain features of carcinoma (at all events, as we meet with it in this country) is that it occurs more commonly in women than in men, and that the case-incidence, corrected by the number of persons of the sex living at various ages, in both sexes runs on parallel ascending lines up to the age of about 55 years, while after that age the lines diverge, liability to the disease continuing to increase in males but undergoing a sharp diminution in females. It is certainly remarkable that the degree of skotographic power of the liver in the two sexes and at different age-periods affords a pair of curves agreeing absolutely in these points with the curves of cancer liability (Fig. 15). It is possible that the identity of the two pairs of curves is a coincidence, and that both cancerous and skotographic conditions may depend upon some common underlying cause—for example, senility. Thus, curves made for the incidence of fibrotic kidney and greyness of hair would probably run parallel courses, but no one would infer that the one bears a causal relation to the other. But when one finds that the liability of liver, kidney, lung, and spleen to primary, and in the main to secondary, growth varies directly with their skotographic power, that the liability of gall bladder, urinary bladder, and kidney to carcinoma varies directly with the skotographic value of the calculi by which severally they are affected, that carcinomatous

material possesses this skotographic power, practically without exception, and that the normal skotographic power of a tissue is modified by the presence in it of a carcinomatous mass, the idea that the two are in some way interdependent is strengthened. And when one further finds that these tissues, or their extracts, are capable of influencing the rate of division of animal cells, the suggestion that in them lies the key of a disease which is, after all, nothing more than a disorderly overgrowth of a particular variety of cell, becomes alluring. Nor is the fact that certain of the extracts have been found to possess accelerative, while others possess retarding, powers on development a difficulty, for it is clear that for the occurrence of a carcinoma it is as necessary for the subjacent tissues to undergo a diminution of their normal resisting powers to the encroachment of the epithelial cells as for these latter to undergo an increase in their normal rate of reproduction.

This brings us to the question of metastases. I have long felt that the metastases in carcinoma are not regarded in their proper light. Stripped of non-essentials, the occurrence of a metastasis simply means that a cell which is capable of growth is lodged in a situation at which it is not killed. That is to say, the tissues into which a carcinomatous cell is carried by embolism, tissue permeation or other means plays as considerable a part in determining the occurrence or non-occurrence

Nevertheless, the fact that the existence of carcinoma in a body affects the skotographic power of the liver of the patient, even though the liver itself be devoid of metastasis, indicates that an influence is exerted by the carcinoma, or the initial cause of the carcinoma, upon distant parts. And in this connexion one may ask whether it is not possible that those rare cases may be thus explained in which

death in carcinoma cannot be attributed with fairness either to the mass of growth, septic absorption, mechanical interference with vital parts, or other similar cause. One of the most noteworthy points in connexion with carcinoma is that a mass will kill, being carcinoma, which would probably not kill if (*caeteris paribus*) it were inflammatory. It is only necessary to compare the certain death from so small a mass of disease as is often a carcinoma of the body of the uterus, with the relatively good prognosis of a far more extensive tuberculosis, actinomycosis, or tertiary syphilitic condition.

If the general liability to carcinoma in males and females be split up into its component parts and the liability to carcinoma at different sites be considered individually, certain interest-

ing points are disclosed. This has been done for 6,421 cases of cancer at the Middlesex Hospital of which details as to age are available. The cases are distributed as follows: Uterus, 2,205 cases; breast, 2,128 cases; alimentary tract from stomach to rectum, 470 female and 586 male cases; tongue and rest of mouth, 783 cases (male); lip, 251 cases (male). The total

number of cases of each kind in each quinquennial age-period has been corrected for the number of persons (male or female, as the case may be) surviving at that age-period from 100,000 persons born. The curves thus formed are given in Fig. 16.

The most striking point in the curves is that whereas all of them show a rising liability with increasing age, this increasing liability only persists to the end of life in the case of cancer of the lip. In every other instance a maximum is reached, after which the liability to cancer diminishes with more or less suddenness. And, further, the maximum liability to cancer of a special organ does not occur at the same age as

the maximum liability to cancer of another organ, nor are the ascents and descents of the different curves equally rapid or high in all cases.

There is thus a great contrast between cancer of the lip and cancer of the uterus, for example, so far as the liability of individuals to the two types of disease is concerned. This difference may clearly depend upon either a difference in the incidence of the cause of cancer or

Fig. 15.—F.L., Female liver skotographic value; M.L., male liver skotographic value; F.C., female liability to cancer; M.C., male liability to cancer.

Fig. 16.—Liability to carcinoma at different age periods. (Middlesex Hospital.)

disseminated through the body in all cases, but in half of them they are destroyed at the seat of their lodgement.

In what the difference between a tissue which allows a transported carcinoma cell to grow and multiply and a tissue which destroys it consists it is impossible to say, but the different properties of tissue extracts upon the division of the ova of *Ascaris megalocephala* are such that in them may perhaps lie the solution of the question.

upon a difference in the tissue upon which the cause is acting. So far as a difference in the tissue is concerned, there is no doubt that the maximal liability to cancer of the uterus occurs about the menopause, and that it diminishes with great rapidity immediately after. But the uterine, and particularly the cervical, changes following the menopause are amongst the least marked of climacteric changes, and in any case are minute compared with the uterine modification following a pregnancy. If, however, we consider the question from the point of view of a difference in the incidence of the exciting cause of the disease the matter becomes simpler.

The cervix uteri is particularly suitable for an inquiry into the etiology of carcinoma. It is a limited region, it is in the majority of cases affected by the simplest form of carcinoma, the squamous cell variety, it is placed out of reach of an infinitude of accidents and forces which act upon other parts covered with squamous epithelium, and it is liable to three conditions, two of which, namely, bathing with menstrual blood and bathing with seminal fluid, are peculiar to it, while the third—laceration during childbirth—is merely a trauma more or less resembling traumata in other regions, and, once occasioned, persists throughout life. At the same time, as it is more than usually protected from outside influences, it is one of the commonest, if not actually the commonest seat of carcinoma. Of these three conditions, the two that are peculiar to the cervix are those which attract most attention when considered in relation to the age for the maximum liability to carcinoma of the cervix, partly because traumata occur in other regions, partly because a period of many years usually elapses between the last parturition and the age of maximum liability; and, considering menstrual blood and seminal fluid as possibly containing the essential cause of carcinoma of the cervix, menstrual blood must be put on one side, if only for the reason that if it were the cause one would expect that vagina and vulva and body of the uterus would not show so marked an inferiority in liability to carcinoma as they undoubtedly do. This leaves the seminal fluid; and it is a remarkable fact in this connexion that the spermatozoon is the most potent instigator of cell division known when it acts upon a specific cell, the ovum, and that an extract of the testis of the herring (which consists almost entirely of spermatozoa) favours the division of the cells of the ova of *Ascaris megalocephala* to an extraordinary extent, and at the same time possesses marked skotographic powers (Fig. 17).*

In the case of the breast it appears to me that the observation of MacCormac that various bacteria possess skotographic powers is of great importance in conjunction with the fact that a greater or less degree of chronic mastitis is so commonly met with in mammary carcinoma. From this point of view, mammary carcinoma may be brought into line with carcinomata arising on old cicatrices and long-standing ulcers, whether these be simple or lupoid. It is, indeed, remarkable that the only varieties of bacteria which have been found to possess marked skotographic powers are those which pre-eminently affect man, the pyogenic staphylococci, *B. tuberculosis*, *B. diphtheriae*, while man amongst the animal kingdom is so much more commonly affected by carcinoma that it may be termed a pre-eminently human disease. When it is remembered that bacteria—especially pyogenic and tuberculous bacteria—may remain latent for years, when it is remembered that the skotographic action, if not of bacteria, at least of other animal substances, may persist for a period, certainly of months and probably of years, the question arises whether we shall not find the essential cause of carcinoma affecting mamma, cicatrices, old ulcers, directly connected with the bacteria underlying the primary chronic inflammatory condition. If this be so, if the bacteria introduced into the breast, possibly during some lactation period, carry with them by virtue of their skotographic power the cause of a carcinoma which develops years later, we should expect the feebly skotographic bacteria to induce carcinoma later in the individual's life than the far more powerful spermatozoa; we should expect the period of maximal liability to a carcinoma of bacterial origin to be spread over a larger range of

years than one of spermatozoal origin, we should expect a later onset of diminution in liability with a carcinoma of bacterial origin than with one of spermatozoal origin, but in both cases we should expect the liability to cancer to diminish in later life. In a word we should expect to find carcinoma of the breast and carcinoma of the cervix showing just those differences of incidence which they actually manifest.

But if, in the case of the uterus, it is difficult to associate the occurrence of carcinoma with peculiarities on the part of the tissue itself, this is even more difficult in the case of carcinoma affecting that part of the alimentary tract lying between stomach and rectum. A glance at the curves of liability to cancer in these regions drawn up for males and for females shows that in males the liability is not only greater but also that it reaches a maximum some ten years earlier than in females, and persists at that maximum for five years longer. We cannot consider that there is so striking a difference between male and female alimentary tissues as this would indicate in the absence of definite evidence on the point. It is easier to imagine that some factor leading to increased division of epithelial cells is more potent in males than in females during the age-period 50 to 69. It would serve no good purpose to discuss here what that factor may be, but it may be pointed out (a) that Sir J. J. Thomson has shown that certain foodstuffs—notably wheaten flour—may be radio-active; (b) I have shown above that many animal substances have properties which may be radio-active, that both definitely recognized radio-active substances, and extracts of animal tissues are able to accelerate cell division in the ova of *Ascaris*; and (c) that, partly as a result of the greater degree to which they are occupied in arduous labour, men consume more food than women.

I have left consideration of the curves obtained for carcinoma of the lip, and of the tongue and other parts of the mouth, to the last because of their great dissimilarity in spite of the similarity of the tissues concerned, and of the identity of most of the conditions to which those tissues are subjected. This dissimilarity of the curves of liability to carcinoma, and particularly the fact that the liability to carcinoma of the lip undergoes no diminution in old age such as is observed in the case of carcinoma in all other sites that we have examined, is strong evidence that some fundamentally different condition obtains in the two situations. The persistency with which the old man clings to his pipe, holding it between his lips, whether actually smoking or not, whether awake or dozing as he sits in the sun or by the fireside, is as characteristic of the ages above 70 as is the toothless condition which commences to set in about 65. On the assumption that the pipe in some way is directly related to carcinoma of the lip, while the teeth are in some way directly related to carcinoma of the tongue and other parts of the mouth, the curves of liability to this disease in the two situations should be exactly as we find them to be.

It may be urged that the observations I have brought forward are nothing more than evidences of that "chronic irritation" which since the time of Virchow has been held to play an important part in the causation of carcinoma. To this my answer must be that the term "chronic irritation" is meaningless, and only indicates that some common factor exists in a variety of conditions that differ otherwise to the greatest extent. Is it not possible that the common factor, which must be capable of stimulating the growth of certain cells while it depresses the growth of others, which must reside in substances of the widest diversity, which must act with varying intensities in different cases though always with comparative slowness, the natural action of which must be progressive so long as it persists, should be radio-activity? The α rays cause carcinoma, they stimulate (like other radio-active substances) the growth of cells, and, again, they retard the growth of cells, carcinomatous material, non-carcinomatous material, extracts of animal tissue, various substances usually regarded as causally related to carcinoma, possess properties resembling those of recognized radio-active substances to a greater or less degree when considered from the physicist's point of view, and there is evidence that they possess powers of stimulating or depressing the division of animal cells. Such similarities are at least suggestive.

* The freedom of lower animals from carcinoma cervicis, I suggest, is explained by their entirely different sexual habits. Its occurrence in an undoubted virgin would be explicable on the lines sketched in the next paragraph.

At the same time as radio-activity—using that term to cover the properties of other than *recognized* radio-active substances for the moment—would serve to explain a large number of the salient features of carcinoma as a disease, it would fall in line with other facts that have been made known more recently, and often affords a common ground for views that appear at first sight to be diametrically opposed.

It would fall in line with the observations of Farmer Walker, and Moore on the frequent occurrence of hetero typical and irregular mitoses in malignant new growths, for all observations go to show that the ova of *Ascaris megalocephala* divide with great irregularity when they are exposed to recognized radio-activity, and the same is true when they are exposed to the influence of any of the watery extracts of animal substances that have been mentioned above. It would fall in line with the observations that there is a deficient secretion of pepsin and trypsin in carcinoma, for Colwell and others have shown that the activity of these enzymes is largely diminished when they are exposed to radio-active influence.⁹ It would fall in line with the observation that the ereptic power of the tissues in carcinoma cases is not diminished more than in other chronic diseases accompanied by wasting (Colwell¹⁰), for exposure to radio-activity does not affect the ereptic power of a tissue extract in the slightest degree. It would fall in line with the fact that certain varieties of carcinoma, notably those which are superficial, are curable by radio-activity; for, as is shown by the cases of diphtheria, typhoid, tetanus, anthrax, rabies, and other microbic diseases, the agent producing the disease is prepotent in elaborating the remedy. It would fall in line with the fact that carcinoma is primarily a disease in which a definite variety of cell—the epithelial—is concerned, for there is evidence that radio-activity has selective powers—for example, in its action upon the specific cells of the testicle and upon the spleen. It would fall into line with the remarkable observations of Ehrlich and Apolant, and of Haaland, that in mice transplantation of one type of tumour may lead, as they believe, to the origination of another type from the tissues of the host, for the cells of a carcinomatous mass are endowed with properties resembling those of recognized radio-active substances in many respects.

On the other hand, it would not be opposed to a belief in "cancer houses and localities," for there is no reason why the soils of districts or the materials of which houses are built should not differ in the degree to which they are radio-active, nor why the local radio-activity should not be in certain instances so considerable that cancer arises in successive inhabitants time after time. In a sense the electrical department of every hospital is a "cancer house." It would not be opposed either to an infective or non-infective, a contagious or non-contagious, an animal or vegetable parasitic, a parasitic or non-parasitic, an hereditary or non-hereditary view of cancer, for it would only be concerned with the question whether the inculcated agent is radio-active or not. So far as certain bacteria possessed the properties we are considering, the carcinoma associated with them might be regarded as bacterial and infective, but the bacterial and infective properties would be accidental and non-essential. So far as the agent which leads to hereditary transmission was provided with "radio-active" properties cancer would be hereditary, but the inheritance of cancer would be accidental and non-essential. Similarly it would not be opposed to Cohnheim's theory of embryonic rests, to Virchow's theory of mechanical irritation, to von Hansemann's theory of anaplasia, to Ribbert's theory of tissue tension, to Adam's theory of habit of growth—for it would constitute the underlying force required by each.

There remains the question whether by applying radio-activity we are able to produce carcinoma. To this question I can only reply that numerous experiments have hitherto resulted in failure. I have exposed rats and mice to the action of α rays or to uranium or thorium for months; I have kept a glass tube containing radium in the abdominal cavity of a rabbit for months; I have exposed the ears of rabbits to α rays for prolonged periods and under different circumstances; but, so far, the only cases of carcinoma resulting from exposure to radio-activity are those which have occurred in the human sub-

ject. Yet the experiments I have mentioned have not been without importance, for, as Rowntree¹¹ has shown, the changes in the rat's tail, and even more those in the rabbit's ear, resemble those in human α -ray dermatitis, while there is in certain places a well-marked overgrowth of epithelial cells. In the case of the rabbit's ear, indeed, he finds that the epithelium on the under, or indirectly exposed, surface shows an irregular arrangement of the hypertrophied epithelial cells which appears to be on the border-line between non-malignancy and malignancy. When we can determine that that border-line shall be crossed, one of the greatest steps towards a discovery of the cure for carcinoma will have been made.

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Memoranda :

MEDICAL, SURGICAL, OBSTETRICAL.

TREATMENT OF VOLVULUS.

THE article by Mr. Waterhouse on volvulus, in the *JOURNAL* of May 29th, is most valuable, as pointing out that the site is usually the sigmoid flexure, and so almost always remediable by enemata in the early stage. I believe his advice would have been more useful to the general practitioner, who treats most of these cases, if he had descended to particulars as to how an enema should be given. It may be that the hint I am about to give is found in various textbooks and periodicals, but in thirty years' reading I have never met with it, and only found it out by painful experience. One case, as a sample, will illustrate my meaning. A farmer, aged 63, fell from a load of hay on to the meadow and got concussion of spine followed by partial paralysis of the lower limbs; a catheter had to be passed for two weeks. During the following three years he suffered from constipation, and at the end of this time I was sent for urgently—a distance of eight miles—to see him. I found him with bowel obstruction; the abdomen was tympanitic and as tight as a drum; breathing was shallow, owing to pressure on the diaphragm, but there was no vomiting nor eructations. I gave enemata in the ordinary way, and after nearly an hour I only removed some small scybalae from the lower bowel. It was evident that the obstruction was higher up. I left the patient no better, gave some calomel and opium, and promised to return early in the morning. This I did, taking with me a long tube of soft rubber similar to that used for passing into the stomach. Attaching this to the bone pipe of a Higginson syringe, I gave an enema. The tube when passed through the sphincter is very apt to curl up in the wide or ballooned part of the rectum, and considerable difficulty is often experienced in getting it to enter the upper narrow part, which owing to the curve of the sacrum goes forward at an angle. I pushed the tube as far as it would go, and then, pumping in water under pressure, the bowel dilated in front and I was able to gain an inch or two at a time. Continuing this manœuvre, the whole 32 in. of the tube were at last passed inside the sphincter. I felt the pumping tension relax, heard a gurgling, but continued pumping for a little longer. I now detached the bone pipe from the tube and allowed the water to come away, when the whole gas followed, the abdomen relaxed, and the patient was well.

I have on different occasions had to supplement the tube by a second, and I advise that the tube be 3 ft. or over. I am persuaded this hint of mine may be of service to some sorely perplexed general practitioners.

Castlederg, co. Tyrone.

ROBERT MOWBRAY, M.D.