The Croonian Lectures
ON
RADIO-ACTIVITY AND CARCINOMA;
AN EXPERIMENTAL INQUIRY.

Delivered before the Royal College of Physicians of London in June, 1909.

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[WITH SPECIAL PLATE.]

LECTURE I.
After thanking the College for the honour it had done him in inviting him to deliver the lectures, pointing out that the inquiry was still incomplete and that contributions to the research had been made by numerous workers in the Cancer Research Laboratories of the Middlesex Hospital, the lecturer proceeded as follows:

The leading idea throughout the whole research has been the undisputed fact that workers with x-rays are liable to suffer from carcinomas of the hand. It is unnecessary to labour this point in view of the complete evidence gathering by Mr. C. W. Rowntree in his Hunterian Lecture before the Royal College of Surgeons of England on March 17th, 1909. From a careful examination of the microscopical sections shown by Mr. Rowntree it has been observed that he is right in describing the x-ray condition which may follow on a somewhat severe and prolonged dermatitis occasioned by exposure to x-rays as a squamous cell carcinoma.

Into the question of the relationship of the x-rays to the carcinoma, whether it is specific and direct or non-specific and, so to speak, accidental, I do not propose to enter here. It will be more convenient to deal with the whole subject at the conclusion of the lectures. For the moment it will suffice to allow that exposure to x-rays and carcinoma of the hand are closely related in certain cases.

The next idea of importance in connexion with the research is that for many years certain physical agents have been considered by the profession to be causally related to cancer of special sites. Thus clay pipes have been incriminated as the cause of cancer of the lip, paraffin and tar, of the gall bladder, and of the cancer of the hands and arms of workers with these substances, soot with cancer of the scrotum in chimney sweeps, gall stones with cancer generally and particularly of the gall bladder. In addition, betel-nut chewing has been associated with cancer of the cheek, especially in Ceylon and the East, where the habit is common; use of the kangri has been associated with "kangri cancer" in Kashmir, while bilharziosis in Egypt has been incriminated as the cause of the bladder cancer. Similarly it has been noted that cancer occasionally develops on old scars, on the floor of chronic ulcers, and on the site of lupus.

An approximation of these two ideas suggested the inquiry whether the clay pipes, the paraffin, tar, soot, etc., emit x-rays or give other evidence of radio-active properties. If the answer to this question were in the positive, a single factor would be demonstrated to be present in a group of physical agents differing to the widest degree from one another, and the probability that each particular variety of cancer depended upon the physical agent usually inculpated would be strengthened, while presumption would be raised for the proposition that the common factor in all the physical agents—that is, their radio-activity—is causally related to the common factor in the pathological conditions to which they all are supposed to give rise—that is, the cancer.

It is remarkable that the cancer in all the cases that have been mentioned above, with the sole exception of that affecting the gall bladder, is squamous cell carcinoma. Moreover, the histological diagnosis is almost invariably to be made with great ease, Malpighian cells, prickle cells, and epithelial pearls being conspicuous. For this reason the present research has been confined to the group of carcinomata, meaning thereby squamous cell, columnar cell, and spheroidal cell, carcinomata as determined by microscopical examination.

The research, therefore, resolved itself into a determination whether clay pipes, etc., and carcinomata material gave evidence of radio-activity.

The two chief criteria of radio-activity relied on by the physician are (1) the action of the substance in question upon a charged electroscope and (2) its action upon a photographic plate in the dark. Of these criteria action upon a photographic plate in the dark is well known from the profession in the production of x-rayographs, but it is upon the electrical properties that the physician places more reliance.

Owing to the fact that the x-ray tube only emits gamma rays, while such radio-active substances as uranium, and thorium emit alpha particles, beta rays, and gamma rays, while they also are far more complex than their chemical names would suggest, it became necessary to consider these substances as well as the x-rays. It is clear that a substance may belong to the x-ray group and yet fail to produce gamma radiations. Thus, "chemically pure" uranium oxide emits alpha particles and beta and gamma rays, but the physician can separate a uranium oxide from this, which is indistinguishable in its electrical reactions, but differs electrically in emitting alpha particles alone. Such uranium is without effect upon a photographic plate, though it affects a charged electroscope.

In addition to their power of affecting a photographic plate in the dark, radio-active substances emitting gamma rays with their high velocity and penetrative power, it will suffice to mention that the beta rays with their somewhat lower but still great velocity and penetrating power, have the property of affecting the photographic plate though separated from the film by such substances as aluminium, etc. This property is an important means of differentiating the action of a recognized radio-active substance, such as radium or thorium, from other substances which apparently fail to possess the power of acting through a screen. How far this differentiation between radio-active and non-radio-active substances may be carried by this method will be discussed later.

Electrically, the recognized radio-active substances have the property of accelerating the discharge of an electroscope whatever the sign of the electricity with which its leaves are charged. This property depends upon the fact that the radio-active substance by the alpha particles (helium atoms charged +), beta rays (negative electrons) and gamma rays which it emits, ionizes the air in the electroscope, breaking the molecules up into constituent atoms, each of which is electrically charged + or -. These charged atoms collide with the charged gold leaves, and such as are of opposite sign to the charge on the leaves neutralize a corresponding amount of electricity on the greater the power of the air in a given time the more rapidly the charged leaves fall together, and the greater the radio-activity of the substance under investigation is said to be.

From what has been said it follows that the various substances dealt with in the present investigation call for consideration (1) as regards their action when exposed to a photographic plate in the dark, and (2) as regards their influence the rate of leak of an electroscope (a) charged +, and (b) charged -. In addition, it is necessary to determine the same points in regard to non-radioactive substances, and, further, to determine the influence of radio-activity upon the division of cells by direct experiment.

In the present lecture I propose to show that certain animal tissues and other substances have the power of acting upon a photographic plate in the dark. In the second lecture I shall consider, as far as possible, the properties and nature of the substances in the tissues which possess this power. The third lecture will be devoted to the consideration of the electrical properties of the carcinomatous and non-carcinomatous substances; while the fourth lecture will deal with the influence of radio-activity upon cell division, and will include a short general survey of the bearings of the experiments.

The Skotographic Action of Certain Animal Tissues and Other Substances.

If a sample of human liver be minced, dried in the hot air oven at 100-110° C., reduced to a powder and some of

* I have ventured to use the word "skotograph," to signify the effect that is produced upon a photographic plate by certain substances in contrast to the ordinary use of the term "photograph," and "skitograph." The effects to which attention is about to be directed are certainly not photgraphs in the ordinary sense of the word, neither are they skitographs, while to term them radiographs would be to assume the point at issue.
this powder be placed on a photographic film in the dark and the plate and powder be kept in contact in complete darkness for a certain length of time, it will probably be found, on developing the plate, that the former situation of the powder is indicated by a more or less considerable, punctate, deposition of silver which corresponds to the area of the calculus in contact with the plate (Figs. 1 and 2). Skoto-
graphic action is not manifested by all animal substances, for example, it is rarely produced by spleen or lung dried and powdered as above, while numerous experiments made with uric acid calculi, paraffin wax, and clay pipes have shown that these substances possess no skotographic power. Similarly certain varieties of micro-organisms possess marked skotographic power, while others appear to be totally deficient.

It is unnecessary here to enter into the details of the method for obtaining skotographs, or the precautions to be taken in order to eliminate the action of light or of any outside influence of a recognized radio-active nature. These are all given elsewhere. It must be stated, however, that the values assigned to the various plates showing skotographic action were determined by comparing them with the effect produced in a photographic plate by allowing x rays to act upon it through a Benoist's gauge. Since the gauge of aluminium consists of silver plates in thickness from 1 mm. to 12 mm. a graduated deposition of silver takes place on the plate. It was possible to graduate the degrees of silver depositions by this means from 6 to 6; and since the same skilagraph was used throughout, the values given for the various substances and tissues are comparable among themselves.

Tissues from Non-malignant Cases.

In all, tissues from 115 bodies of persons dying from some cause other than malignant disease were examined skotographically. In most instances the examination included samples of liver, kidney, spleen, and lung. The patients were of both sexes and of all ages; they were grouped for purposes of comparison into the following age-periods:

<table>
<thead>
<tr>
<th>Age</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 years</td>
<td>1.7 2.3 0.8 0.9 5.1 1.6 0.9 1.1</td>
<td>2 years</td>
</tr>
<tr>
<td>2 to 20 years</td>
<td>2.1 2.4 0.6 0.4 3.3 2.8 0.4 0.6</td>
<td>20 to 35 years</td>
</tr>
<tr>
<td>21 to 35 years</td>
<td>3.0 2.6 1.1 0.75 3.7 2.3 0.5 0.6</td>
<td>35 to 55 years</td>
</tr>
<tr>
<td>36 to 65 years</td>
<td>2.7 1.6 0.3 0.0 3.4 3.9 0.9 0.5</td>
<td>40 to 65 years</td>
</tr>
<tr>
<td>46 to 55 years</td>
<td>3.3 1.4 0.5 0.0 4.2 2.7 0.8 0.8</td>
<td>55 years</td>
</tr>
<tr>
<td>Over 55 years</td>
<td>3.9 2.0 0.5 0.9 2.6 2.5 1.1 0.25</td>
<td></td>
</tr>
</tbody>
</table>

This grouping of age-periods was made in order to institute a comparison with similar tissues derived from cases of carcinoma. In addition to the above, specimens of brain, heart, breast, liver of sheep and of ox, tissues of mouse, guinea-pig, and rabbit were examined skotographically, but no reference to the results will be made here.

The results of the investigation are summarized in the following table:

Table showing Mean Skotographic Values of Liver, Kidney, Spleen, and Lung in 115 Non-malignant Cases.

<table>
<thead>
<tr>
<th>Age</th>
<th>Liver (10 males, 10 females)</th>
<th>Spleen (9 males, 6 females)</th>
<th>Kidney (10 males, 10 females)</th>
<th>Lung (10 males, 10 females)</th>
<th>Liver (9 males, 8 females)</th>
<th>Spleen (6 males, 4 females)</th>
<th>Kidney (10 males, 10 females)</th>
<th>Lung (10 males, 10 females)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 2 yrs</td>
<td>1.7 2.3 0.8 0.9 5.1 1.6 0.9 1.1</td>
<td>2.1 2.4 0.6 0.4 3.3 2.8 0.4 0.6</td>
<td>3.0 2.6 1.1 0.75 3.7 2.3 0.5 0.6</td>
<td>2.7 1.6 0.3 0.0 3.4 3.9 0.9 0.5</td>
<td>3.3 1.4 0.5 0.0 4.2 2.7 0.8 0.8</td>
<td>3.9 2.0 0.5 0.9 2.6 2.5 1.1 0.25</td>
<td>2.8 2.1 0.6 0.6 3.4 2.8 0.8 0.6</td>
<td></td>
</tr>
</tbody>
</table>

From this table it appears that liver and kidney possess a far higher skotographic power than spleen or lung, and that the female tissue in each case had a greater skotographic power than the corresponding male tissue.

Owing to the large size of the liver and to the fact that it exerts the largest amount of skotographic effect, the figures for it may be examined more closely. It is seen that the skotographic power of the liver in males increases steadily throughout life, with the exception of a fall at the age-period 35 to 45 years. In females this rise in skotographic power of the liver, including the fall at the age-period 35 to 45, is also seen. But whereas the values for the male reach their high point in the age-period "over 55 years," this same age-period in females witnesses a remarkable fall in skotographic power of the liver. Further reference to this point will be made in the last lecture.

The small mean values obtained for the spleen and lung are due to the fact that predominantly these organs exert a definite effect. Two-thirds of the total number of spleens examined skotographically, and two-thirds of the total number of lungs, were absolutely without skotographic power. On the other hand, only one-fifth of the total number of livers examined skotographically were without effect.

Carcinomatous Material.

The skotographic value of the primary mass has been determined in 17 cases of carcinoma; of secondary growths, 29 specimens from 24 cases have been examined; 11 of the cases were male, 30 female. Two primary and four secondary growths were without skotographic effect, or the effect was doubtful. The mean skotographic value of the male primary masses was 2.0, male secondary masses 2.5; that of the female primary masses was 3.6, female secondary masses 3.2. Hence the superiority of the skotographic value of female tissue over that of male tissue obtains also in the case of carcinoma. (Figs. 3 and 4).

Tissues from Cases of Carcinoma.

The skotographic values of the liver, lung, kidney, and spleen have been determined in 72 cases of carcinoma, 41 of which showed important metastases, and 31 insignificant metastases or none at all. The cardinal facts that liver and kidney exert a greater skotographic power than lung and spleen, and that the skotographic power of a female tissue is greater than that of the corresponding male tissue, are shown in this class of case as in that in which there is no malignant disease. But it appears that the carcinomatous condition is not without effect upon the skotographic power of the various tissues. This is best seen by considering the case of the liver. The effect of carcinoma upon the skotographic power of the liver may be considered in two ways:

1. Livers, themselves free from metastasis, may be compared skotographically according as they are derived from cases in which the total mass of carcinomatous material in the body is great or is small.

2. A comparison may be made between the hepatic tissue of non-malignant cases and the hepatic tissue of carcinomatous cases in which the liver is the seat of numerous large metastases.

These two different methods of approaching the question agree in indicating that carcinoma augments the skotographic power of the liver in males and decreases it in females. In the following table are given the figures upon which this statement is founded.

Table to show the Influence of Carcinoma on the Skotographic Power of the Liver.

<table>
<thead>
<tr>
<th>Age</th>
<th>Non-malignant</th>
<th>Growth Present</th>
<th>Little Growth in Body</th>
<th>Non-malignant</th>
<th>Growth Present</th>
<th>Little Growth in Body</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 35</td>
<td>3.0 2.7 3.5 3.5</td>
<td>3.7 2.0 1.7 4.0</td>
<td>3.4 3.2 3.7 4.2</td>
<td>3.4 3.5 3.7 4.25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>36-45</td>
<td>3.3 3.5 3.5 3.8</td>
<td>4.2 4.2 4.2 4.2</td>
<td>3.4 3.5 3.7 4.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>46-55</td>
<td>3.3 3.5 3.5 3.8</td>
<td>4.2 4.2 4.2 4.2</td>
<td>3.4 3.5 3.7 4.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Over 55</td>
<td>4.0 4.5 4.5 4.5</td>
<td>3.2 2.5 2.5 2.5</td>
<td>3.4 3.5 3.7 4.0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

But consideration of the above table shows that the matter is not so simple. For, although male hepatic substance in the neighbourhood of liver metastases is more skotographic than non-malignant liver while the converse is true in the case of the female, and although male
hepatic substance where there is much growth in the body is more skotographic than when there is little while the converse is true in the case of the female, a small amount of carcinoma in the body appears to diminish the skotographic power of the male liver, while it augments that of the female liver. I do not attempt an explanation of these points; indeed, they need confirmation on a much larger number of cases. The regularity with which female liver has a liver act in opposite directions, in the case of what is apparently a single condition—that is, carcinoma—is, however, such that it suggests the existence of some sort of interaction between carcinoma and the skotographic property of the liver. On the other hand, we may be wrong in considering carcinoma as a condition relative to the two sexes; it has already been shown that male and female carcinomatous materials differ in skotographic power.

The only condition in which a thoroughly satisfactory determination can be made of the influence of carcinomatous growth upon the skotographic power of the tissue in which it lies is that in which one of the organs is the seat of metastasis. This is relatively so uncommon, and when it occurs the chance that the metastasis will be sufficiently large to influence the neighbouring tissue of the organ to any extent is so small that I have only obtained a single example. The case was one of carcinoma of the cervix, and one kidney was the seat of a fairly large number of metastases, while the other was free. The renal substance of the unaffected kidney had a skotographic power of 3, while the renal substance of the affected kidney was absolutely without effect upon the photographic plate. This case, therefore, conforming to the statement already made above, that in the female, carcinoma leads to a diminution of the skotographic power of the tissue in which it lies.

Substances commonly supposed to be causally related to Carcinoma.

Numerous samples of clay pipe, soot, pitch, paraffin wax, metallic arsenic, arsenious oxide, betel nut, choleretic gall stones, pigment gall stones, renal and vesical calculi, have been examined skotographically, the calcui, renal, biliary, and vesical, being the subject of an extended research by Dr. Colwell.2 Skotographic effect was exhibited by one sample of soot out of two examined, by betel nut on all of numerous occasions, by each of twenty-three specimens of choleretic gall stone, more or less "pure," in three out of four samples of pigment gall stones examined, the effect being always very slight as compared with the action of the choleretic calculi, and by thirty out of thirty-eight vesical calculi. Metallic arsenic and arsenious oxide produced effects upon the photographic plate, but in such a manner as the films showed alterations in the development the action cannot be regarded as skotographic. On the other hand, none of nine specimens of clay pipe, of numerous samples of paraffin wax, of four samples of pitch from different localities, of several specimens of coal, yielded the slightest trace of skotographic effect.

In the case of choleretic gall stone the action on the plate extends widely beyond the area of the surface of the calculus in contact with the plate, but in the case of all the other substances the area of silver deposition was coextensive with the area of contact between the substance and film. This is well seen in the skotographs of vesical calculi, in which rings of silver deposition alternate with rings of no deposition in such a way that a picture is formed of the outer surface of the calculus by which the skotograph was produced (Fig. 5). When the nucleus of a calculus, or certain laminae, or the entire calculus consists of "pure uric acid," the corresponding part of the film shows a complete absence of skotographic effect. As a result of this all the indications that herein we have are that choleretic material possesses skotographic power—"pure uric acid," except in the case discussed under the "carbonate." It will be noted that in the case of the soot, coal, and pitch the general effect of these substances is to increase the development of the film. It is probable that choleretic material, when examined after prolonged exposure to air, possesses a skotographic power that is greater than that of the soot, coal, and pitch. The skotographic power of these substances is, in fact, a factor that may be added to the list of characteristic properties of the soot, coal, and pitch.

Attempts at Isolation of the Skotographic Substance.

The skotographic substance, or substances—for there is reason to believe that, in the liver at least, two substances exist which differ from one another in certain reactions—may be in a state of existence in the animal body in a non-soluble form. It is not protein, or fat, or carbohydrate, or coloring matter or mineral salts. Each of these constituents of the tissues has been definitely excluded. It is unnecessary to enter into a detailed account of the method in which this has been done, for it has been recorded elsewhere.4 The following account will suffice.

That it is not protein is indicated by the fact that it is yielded by liver, for example, and not by spleen, while the fact that it is yielded by liver indicates that the cellulyr of the tissue is such. But the non-protein character can be shown by obtaining a completely protein-free extract of the tissue, and proving that this extract still possesses skotographic power. Fig. 7 shows that is the case. It was produced by the following way: Liver of sheep was mixed and allowed to stand under distilled water for eighteen hours. The watery extract was then acidified, boiled, and filtered. To the filtrate three times the volume of basic lead acetate in solution and suspensions was added, and the precipitate was filtered off. Then sulphured water was passed through the filtrate to precipitate the lead, and after the filtrate from this operation had been concentrated to small bulk upon a plan ground with a cast plate and this plate was exposed to the photographic film under skotographic conditions and separated from contact with the film by strands of cotton. It is seen that this watery extract of liver, in which none of the laboratory tests for protein were shown to be present, possesses intense skotographic power. The process for
purification from protein has been checked at every stage, as well as the reagents used, and it is certain: (1) That the skotographic power is not introduced during the process, and (2) that no precipitate formed is a skotographic power, except in so far as they are contaminated with the corresponding filtrate.

That the skotographic substance is not fat as such is shown by the fact that a material which has been rigidly extracted into ether still possesses skotographic power. Thus, all the powdered tissues that were used to arrive at the conclusions given in the first lecture were extracted with pure ether in a Soxhlet apparatus for a minimum of twelve hours being examined, skotographically and method extracts the phosphorized as well as the non-phosphorized fats.

Just as the watery extract of a liver, for example, possesses skotographic powers, so it is possessed by an ether extract. Into the question of the actual constituent of the etheral extract which possesses the power it is impossible for me to enter. The chemical analysis I have not attempted, owing to its difficulty.

That the skotographic substance is not carbohydrate as such is proved by the facts that some of the extracts by which it is manifested contain carbohydrate while others are devoid of it, that it is manifested by etheral extracts, and, as will be shown later, that it survives char-

The fact that the skotographic power is independent of ether-soluble and the ether-soluble pig-

ments of the tissue is shown by the persistence of effect if one of these extracts be decolorized by divided animal charcoal.

And, finally, that it is independent of the mineral constituents of the tissue is shown by the fact that after a tissue, which possesses a temperature of 300° C. (see below) — is shown by the fact that the ash of a tissue which possesses marked skotographic power is entirely without effect upon a photographic plate in the dark.

Any skotographic power of any tissue is completely removed if it be first extracted with water and subsequently with ether. This appears as true as the accompanying figure (8), in which the upper fourth shows the effect of the original substance, the second fourth shows the effect of a watery extract, the third that of an etheral extract made subsequently to the watery; the bottom fourth, over which there is an absence of skotographic action, was exposed to the solid residue after the watery and etheral extractions. A similar absence of skotography occurs when a tissue characterized by the decomposition of the original skotographic material which are soluble in water and those which are soluble only in strong acetone may be divided. They are apparently the same as those which are contained in the watery and etheral extracts as well.

But though it is clear that the skotographic power is not a property of protein as such, there is no doubt that it is a property of certain organic substances, as distinguished from several that are probably not organic. As will be said later the skotographic power is not destroyed even though the substance manifesting it be heated to a temperature of 300° C. Such a temperature chars the substance, and no doubt breaks up much of the protein, but from it a material, often of polymorphic crystalline character, but highly deliquescent, can be separated which exerts a skotographic effect, as shown by the fact that it chars on further heating. By repeated solutions in water and precipitation with absolute alcohol this crystalline material can be divided into a honey-like non-crystallizable and a colourless crystallizable portion. The skotographic power resides chiefly, if not entirely, in the honeylike, highly deliquescent material. This material is dialyzable with ease, and carries with it the actual skotographic substance. Further than this analysis has not gone.

Conditions Determining the Manifestation of Skotographic Power

It has been shown above that I have not succeeded in isolating the skotographic substance, though it has been stripped of certain materials with which it is usually associated. It has therefore been necessary to investigate the skotographic property upon crude material, and for this purpose the ether-extracted, dried, and powdered original material and watery extracts from it are freed from protein in the way already described, have chiefly been used.

Relation of Substance to the Photograph Film: Contact: Proximity and Sensitiveness.

All the photographic effects to which reference was made in the first lecture were obtained by allowing the powdered tissues to lie in actual contact with the photographic film, but there is no doubt that they can act at a little distance. This becomes clear in considering the watery extracts, for when they were under investigation contact with the film was always excluded. Attempts were made to determine the maximum distance at which recognizable photographic effect is produced by exposing a glass plate bearing the watery extract to the photographic plate at an angle. In this way, and using photographic plates specially sensitized for x rays, it was found that the watery extract used for producing Fig. 7 of this work could effectively be received when it is separated from the film by a distance of 15 mm.

The question of screens between the material and the photographic film is one of fundamental importance in trying to arrive at a conclusion as to the nature of skotographic action, and must, therefore, be dealt with in some detail.

It may be stated at the outset that interposition of a screen of the order of thickness of that used in examining the effects of recognized radioactive materials such as uranium or thorium between the animal substance under investigation and the photographic film completely eliminates skotographic action. This is true whether the screen be metallic (for example, aluminium) or non-metallic (for example, mica), however intense the screen may be in the absence of a screen, or however long (up to six weeks) the exposure may have been, and even though it had been carried out at 55° C.

On the other hand, the matter is not simple, as the following experiments show:

If a flat section of a betel nut or of liver be coated with a thin film of celluloid and the whole be exposed to a photographic plate in the ordinary way, it will be found that the greatest deposition of silver occurs on that part of the plate which was separated from the substance by the celluloid. That this effect is not due to the celluloid itself is shown by the fact that an old film of celluloid is entirely without skotographic effect, and in the betel nut experi-
ment the cellodin had been painted on the nut two years before it was exposed to the photographic plate (Fig. 6).

In the second place, if an albuminate of thorium be made by allowing a solution of the nitrate to fall into egg-white, the resulting precipitate after drying and powdering fails to affect the photographic plate through a film so thin as that produced by brushing a minute quantity of egg-white over tissue paper, though a fair deposition of silver occurs when the albuminate is separated from the photographic film by tissue paper uncoated with egg-white. Such an albuminate of thorium contains about 10 per cent. of the radioactive element by weight. Even in this case it is possible that such direct skotographic effect as was produced was due to uncombined radio-active salt, since the precipitate was not set for four hours before hydrolysis. In other instances, where the precipitate with thorium was washed thoroughly with hot water before drying, it failed to produce an effect upon the photographic plate even though it were actually in contact with it during exposure; nevertheless, such samples of albuminate showed the presence of considerable amounts of thorium on analysis.

Hence under special conditions a vegetable or animal tissue may produce skotographic action through a thin film of cellodin and a recognized radio-active substance may fail to affect a plate through a film of egg-white of probably even a greater tenuity.

Effect of Temperature.
Within the limits of 3° C. and 100° C. it may be said that the skotographic action of the tissues is independent of the temperature provided that the exposure be longer at the lower temperatures. Thus a degree of silver deposition which can be attained by exposing a cholesterein gelatin plate to fifty-eight hours at 22° C. to the photographic plate can only be obtained after an exposure lasting for weeks at the room temperature, and probably for several months in the ice-chamber at 5° C. Exposure of the substance to a plate at a dry heat of 100° C. is an unsatisfactory procedure but if the exposure be shortened to about half an hour, silver deposition is not general, but is confined to the part with which the substance under investigation was in contact. The general temperature at which these papers were taken was 55° C. and the length of exposure was eighteen hours. Except in certain cases, Imperial special rapid plates were used, and development was by 1 in 20 Rodinal.

I have dealt above with the temperatures at which the substance has been exposed to the photographic plate, but the substance itself may be exposed to a much higher temperature without undergoing complete loss of skotographic power. I have not been able to determine with exactness the highest temperature to which a skotographic substance may be raised without undergoing complete loss of its power; but it is certain that a skotographic wet extract painted in a thin layer upon a No. 1 coverslip and exposed to dry air at about 280° C. for five minutes will probably afford evidence of skotographic power, while a similar coverslip exposed to about 300° C. will not. In any case it is certain that the skotographic power is not destroyed by a temperature (about 200° C.) which chars the substance itself and therefore in large measure disintegrates it.

Light and Darkness.

Leaving on one side such points as the fact that the change in the photographic plate is not due to the hygroscopic character of the partially purified skotographic substance, the gradual disappearance of the power on continued exposure to air, is a curious way in which occasionally there occurs a recrudescence of skotographic power in a watery or acetone extract, the fact that the power is independent of the acidity, basicity, or neutrality of a watery extract—points which have been made the subject of many experiments and are of great theoretical interest—I pass to certain experiments instituted in order to compare the skotographic power of animal tissues with that manifested by woods and held by Russell to depend upon the presence of hydrogen peroxide.

Russell found that the skotographic power of a wood is profoundly influenced according as it has been exposed to light, and especially direct sunlight, or has been kept in darkness before exposing it to the photographic plate. If exposed to light, the skotographic power is always intensified; if kept in darkness, it is always dimmed. In the case of animal tissues and of calculli of different kinds this point has been carefully investigated by myself and by Colwell respectively. We agree in finding that our substances do not show the slightest difference in skotographic power, even though they may be exposed to direct sunlight or be preserved in total darkness for a period of six months before them in contact with the photographic film.

Volatility.

Inasmuch as the skotographic power of an animal substance disappears after about a fortnight if it be exposed freely to air, it was thought that the effect might be due to some volatile product. Apart from the fact that it is difficult to imagine a volatile substance which can be produced in that short space of time, it is possible that the skotographic power is not destroyed, the question has been approached directly. By causing a current of air which had passed over cedar-wood oil, or clove oil, or of caj peanuts, to impinge upon a photographic film, it was found that volatility, as such, is not the effective cause of a skotographic effect since a skotographic effect was produced in the case of air charged with the volatile products of cedarwood oil alone. Further, it has never been found possible to carry over the skotographic power of any of the substances used in the present research although they frequently give off volatile products with powerful odours that can be detected in the stream of air impinging upon the photographic film by the sense of smell. Fig. 9 shows the skotographic effect of a current of air charged with the volatile products of cedar-wood oil.

Is Skotographic Action essentially due to Hydrogen Peroxide?

The experiments made bearing on this question were of two kinds. In one set Colwell took a cholesterein gall stone, which yielded a profound skotographic effect, and prepared from it a sample of purified cholesterein. Examined skotographically, this purified cholesterein was absolutely without effect. He now exposed a thin film (made by dissolving cholesterein in chloroform, pouring it as a glass plate, as allowing the chloroform to evaporate) to an atmosphere fully charged with hydrogen peroxide vapour for twenty-four hours at a temperature of 55° C. Similarly he exposed to hydrogen peroxide vapour a vesical calculus normally possessing no skotographic power. He found that now both cholesterein and vesical calculus affected the plate profoundly, but that within twenty-three hours of their removal from the atmosphere of hydrogen peroxide they had completely regained their original freedom from skotographic power. Probably the least traces of hydrogen peroxide have disappeared long before twenty-three hours, but of this there is no proof. This experiment bears upon the length of time during which skotographic power is held by a substance—a subject with which I will claim our attention shortly.

The second set of experiments concerns the so-called peroxydase effect shown by certain tissues. In its best-known form the peroxydase reaction is represented by the gallsacmum test for blood. It depends upon an oxidation of the traces of guaiaconic acid present in the freshly-prepared tinture of guaiacum by oxygen that has been set free from hydrogen peroxide by a substance (peroxydase) present in the substance undergoing the test.

In examining a large number of dried and powdered tissues from this point of view, as well as from that of their skotographic power, I found, speaking generally, that the degree of peroxydase reaction manifested by them and measured against a standard graduated series of blue solutions, varies inversely with the skotographic power.

Table showing Results in Two Series of Ten Consecutive Specimens.

<table>
<thead>
<tr>
<th>No. Tissue</th>
<th>Photographic Value</th>
<th>Peroxidase Value</th>
<th>No. Tissue</th>
<th>Photographic Value</th>
<th>Peroxidase Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>230 Kidney</td>
<td>6</td>
<td>320 Liver</td>
<td>6</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>231 Lung</td>
<td>4</td>
<td>6</td>
<td>311 Kidney</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>232 Liver</td>
<td>3</td>
<td>5</td>
<td>323 Kidney</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>233 Kidney</td>
<td>2</td>
<td>4</td>
<td>324 Liver</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>234 Lung</td>
<td>3</td>
<td>6</td>
<td>325 Kidney</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>235 Liver</td>
<td>4</td>
<td>0</td>
<td>336 Liver</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>236 Kidney</td>
<td>2</td>
<td>0</td>
<td>377 Kidney</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>237 Lung</td>
<td>2</td>
<td>4</td>
<td>358 Liver</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>238 Liver</td>
<td>0</td>
<td>2</td>
<td>399 Kidney</td>
<td>2</td>
<td>6</td>
</tr>
</tbody>
</table>
This fact would seem to indicate that a tissue possessing a large volume of substance splits up hydrogen peroxide has but little skotographic power, and conversely that a substance exerting a great skotographic power contains but little of the hydrogen peroxide splitting property. From this it is but a step to the conclusion (with Russell) that the skotographic property is not by any means a manifestation of the action of hydrogen peroxide upon a photographic plate.

But that this conclusion is not justified is shown by two sets of observations.

First, I have found that skotographic effect may be shown by watery extracts which from beginning to end of their exposure to the photographic plate contain peroxide and are therefore in a condition to split up any hydrogen peroxide that may be formed immediately on its production. The investigation of peroxide and skotographic power do not obtain for dried and powdered carcinomatous material, for such material, whether it produce a great skotographic effect, or a slight one or no effect at all, is devoid of peroxide. Amongst seventeen samples of dried and powdered carcinomatous material examined for the purpose only four contradictions were found. One of these is explicable by the fact that the growth was a pulmonary metastasis, and probably contains enzymatic tissue which has, normally, no peroxide, and the remaining three, all of which were hepatic metastases, gave the least recognizable amount of peroxide.

**Duration of Skotographic Power.**

Strictly speaking, the length of time during which a substance retains skotographic power can only be determined in the case of such materials as have actually been prepared. Thus the question of the production of Fig. 7 was prepared on March 24th, 1908, and inasmuch as a skotograph taken with the same substance a year later (Fig. 10) also shows effect, it is clear that the substance in question retained the power for that length of time. Numerous skotographs taken at intermediate times showed that the power was present throughout.

From the time of its preparation the substance was kept in a clear stoppered bottle in the laboratory without any special precautions. This exposure renders it probable that a substance which at any time shows skotographic power also possessed it at the time of its original formation, and this assumption becomes of importance in connexion with the skotographic power of calcui. Colwell has shown that calcui will often contain intense skotographic action directly after their removal from the body, but he has also shown that intense skotographic power may be shown by a cholesterin gallstone that had been preserved in the museum of the hospital for over twenty years. In the case of vesical calculi he goes much further; for a calculus removed by Percival Pott, who died in 1788, shows well-marked skotographic power (Fig. 11), and faint but definite skotographic power is shown by a calculus removed from the body of a pre-dynastic Egyptian mummy, and therefore at least 7,000 years old. The use of skotographic plates specially sensitized for x-ray work.

Recently plates have been put upon the market which are specially sensitized for x-ray work. It was thought that a series of comparative tests of the same substances, whose composition and to some extent, indicate whether the skotographic power of the substance under examination was more akin to light or to x-rays. Dried, powdered, and ether-extracted carcinomatous material from a metastasis in the liver and ordinary deal sawdust were examined in this way. It was found that the first appearance of action on the x-ray plate occurred at the end of the sixth and seventh hour of exposure, and on the special instrumentic plate not till the end of the second day. A similar growth being separated from the photographic films by thin layers of ether, and that the ultimate density of silver deposition was greater also on the x-ray plate. When the material was not separated from the photographic film by filter paper, the first appearance of action was observable on both plates at the end of the first hour of exposure; but whereas it was quite marked on the x-ray plate, it was only just distinguishable on the other. In the case of sawdust these differences did not show themselves, the development of silver being far slower on the ordinary plate being very nearly, though not quite, as intense as that on the x-ray plate (Figs. 12 and 13).

**Skotographic Action of Bacteria.**

MacCormac has published the results of an investigation into the question whether skotographic action is exerted by bacteria. He examined in this respect 67 different varieties of micro-organisms, and from the table they may be grouped as below:

**GROUP I. NO SKOTOGRAPHIC ACTION.**

B. Rabinovitch, B. Cohn I, B. Gartner, B. phosphor. albienis, B. intestinalis sporogenes, B. Danguy, B. mycoides, B. coli, V. cholera.

**GROUP II. SKOTOGRAPHIC ACTION FECILE.**

Sarc. flava, B. Flexner, V. Metchnikovi, B. Hoffmann, B. melitenum, B. citreus agilis, B. pyocyaneus, B. phlei II, B. prodigiosus, B. heus.

**GROUP III. SKOTOGRAPHIC ACTION USUAL AND CONSIDERABLE.**

Staph. pyogenes aureus, Staph. pyogenes albus, B. tuberculosis, B. caries, B. bovis, B. diptheriae, "pathogenic throat yeasts."

The importance of these researches will be indicated later.

**SUMMARY.**

If this and the preceding lecture I have shown that certain of the tissues of the human body show skotographic action (liver, kidney), while certain do not (spleen, lung); that a large amount of this property resides in female tissues that possess it than in male of the same kind; that the amount present in the liver increases from infancy to the age of 55 years, but to an unexplained drop in both sexes during the age period 35-45, and that after 55, while it increases still further in the case of males, in females it undergoes a sharp diminution. I have shown that carcinomatous material possesses skotographic power, whether it be primary or secondary, and that female carcinomatous tissue has a higher skotographic value than male; and that the existence of a mass of carcinoma in a tissue modifies its normal skotographic value. I have found that certain substances commonly supposed to be causally related to carcinoma possess the skotographic power to a high degree (cholesterin gall stone), while others are devoid of it (clay pipe, paraffin). I have endeavoured to throw some light upon the nature of the skotographic action manifested by animal tissues and certain other substances, comparing their behaviour with that of woods in which the action has been regarded as dependent upon the formation of hydrogen peroxide, and with that of radioactive substances. On this point MacCormac, working in his laboratory, has shown that bacteria may be divided into groups according to their skotographic power, and that the only group which acts in this way with constancy and to the marked degree, will one, which includes the pyogenic staphylococci and the bacilli of tuberculosis and diphtheria.

The bearing of these observations upon the question of carcinoma may well be considered for consideration in the last lecture.

**REFERENCES.**

Leasner-Barlow, On the Effect Produced by Certain Animal Tissues on a Photographic Plate in the Dark. [J. of the Middlesex Hospital, 1908, vol. xvi, p. 129.]

This is preserved in the Museum of the Royal College of Surgeons, and was kindly lent by Mr. Shattock. Owing to its unique character, the plates have been referred to it by Dr. MacCormac. Hence a flat surface could not be placed in contact with the photographic film. The original skotograph was shown during the lecture, but the markings, though definite, are too faint for reproduction in a plate without retouching, which is, of course, inadmissible.
RADIO-ACTIVITY AND CARCINOMA.

Lectures III.
The Electrical Properties of Recognized Radio-active Substances; of Non-malignant Tissues; of Carcinomatous 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. Electrosopes 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 electrosopes. As a rule two control electrosopes (charged + and - respectively), and eight experimental electrosopes (four charged + and four charged -) were used 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; two 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 gallstone; 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 electrosopes in the dried powdered state to which they had been reduced for scotographic 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 constituents of bone, whether taken from non-malignant or from carcinomatous cases, accelerate electroscope 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 scotographic 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-scotographic.

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 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 the electroscope leak is such that 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 re-examine 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. viii (Fifth Cancer Report), 1906, p. 193. 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 based.

† 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. Medi. Hosp., vol. 25, 3rd Cancer Rep., 1909, p. 160).

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Control Period</th>
<th>Blank Experiment</th>
<th>Actual Experiment</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Electroscopes in which was examined the aluminium disc placed in proximity to uranium nitrate</td>
<td>Mn. -25</td>
<td>Mn. -25</td>
<td>Mn. -27</td>
<td>29 observations for retardation to 10 for acceleration.</td>
</tr>
<tr>
<td>II. Electroscopes in which was examined the aluminium disc placed in proximity to uranium oxide</td>
<td>+66 -66.5</td>
<td>+62</td>
<td></td>
<td>36 observations for retardation to 9 for acceleration.</td>
</tr>
<tr>
<td>III. Electroscopes in which was examined the aluminium disc placed in proximity to pitchblende</td>
<td>-18 -21.5 -26</td>
<td></td>
<td></td>
<td>44 observations for retardation to 2 for acceleration.</td>
</tr>
<tr>
<td>IV. Electroscopes in which was examined the aluminium disc placed in proximity to thorium</td>
<td>-31 -34 -38.5</td>
<td></td>
<td></td>
<td>37 observations for retardation to 9 for acceleration.</td>
</tr>
</tbody>
</table>

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 experiments 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:

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Control Period</th>
<th>Blank Experiment</th>
<th>Actual Experiment</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>V. Electroscop in which was examined the aluminium disc placed in proximity to a cholesterol gall stone</td>
<td>Mn. -3</td>
<td>Mn. -4</td>
<td>Mn. -8</td>
<td>44 observations for retardation to 5 for acceleration.</td>
</tr>
</tbody>
</table>

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 elsewhere:

<table>
<thead>
<tr>
<th>Charge on gold leaves</th>
<th>+</th>
<th>+</th>
<th>+</th>
<th>+</th>
<th>+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carcinoma, dried and powdered</td>
<td>A R R O A O A O</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Above after extraction with ether</td>
<td>A A R A A A A A A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Above after extraction with ethanol</td>
<td>A A A A A A A A</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethereal extract of above</td>
<td>B R B R B R R B</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Water extract of above after extraction with ether</td>
<td>B B R A R B R B</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 liver, 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 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 conclusions being drawn, I pass to the consideration of substances commonly supposed to be causally related to carcinomas.

In this part of the subject the evidence that I have to offer is of different value in different cases. Examination of chain of evidence, and of cholesterol gall stones 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 pleaded the motto of our college as an excuse: "O θυμος θροσω καθιερωμεν." I have already stated that I find evidence that clay pipes exert an accelerating influence on the electrooscope, whether the gold leaves be charged — or +. In the case of paraffin and cholesterin gall stone the evidence is no less clear, but both substances exert a retardating influence, and the electrostatically charged on the electrification on the charge be — or +. Experiments with different samples of pitch seem to show on the whole that this substance exerts a retardating influence, but there is no reason to suppose that a retardation would be produced by all samples of pitch 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 others produced results. Metallo 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 menzioned above —some of the earliest made in the entire research— I sought to show that the accelerating or retardating power was manifested, even though the substance under investigation was mixed 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 radio-active substances. But owing to the fact that I have found an aluminium disc to become electrically modified by the proximty of a radio-active substance or of a pure cholesterin 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 the radio-active substances induce "antiradio-
active" 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 retardating power by the disc on electroscopic leak. But there is no doubt that a similar surface that has been bombarded by radio-active rays manifests physical change of a gross kind. Thus, the anacthode of an x-ray tube not infrequently becomes perforated in course of time, an aluminium disc with Colwell for four months showed 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 radio-active substances.

This brings us to a consideration of extreme importance. There is no doubt that the main factors in the conclusions of the chemist and physicist cannot be applied to biological problems in the same manner. It is quite necessary to have in mind the effects produced by radio-active rays on the living organism, which are so different from those produced by the inorganic radium compounds. It is supported by the whole of chemical physics and pathology, from so simple an example as the fact that the iron in the living organism is not a mere residue of iron in the stomach. The chemical relations of the iron in the organism are not the same as in the inorganic compounds. The iron is more easily precipitated and becomes more resistant to the action of acid and alkali. The iron in the organism is more easily combined with other substances to form an "organic" compound. It is in the latter form alone that it has been examined by the chemist and physicist.

Even if a series of inorganic compounds of the radia-
active element be examined it will be found that the radio-active as measured by the rate of leak of an electrooscope is not identical for all of them. Thus the evidence of radio-activity and the rate of leak of an electrooscope in which are examined a number of uranates of the alkalis and alkaline earths as well as the nitrate and sulphate of uranium varies inversely as the organic compounds. This is in agreement with the view that the radio-activity of the uranium is linked. From this we argued that radio-activity in combination with the huge protein molecule would show a correspondingly enormous diminution of its influence on the electroscopic leak. Thus 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 sulphate of uranium or ammonium urinate (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.

<table>
<thead>
<tr>
<th>Nature of Leak</th>
<th>Per Hour</th>
<th>in Min.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black uranium oxide</td>
<td>175</td>
<td>177</td>
</tr>
<tr>
<td>Ammonium urate</td>
<td>125</td>
<td>171</td>
</tr>
<tr>
<td>Thallium urate</td>
<td>101</td>
<td>114</td>
</tr>
<tr>
<td>Uanyl sulphate</td>
<td>91</td>
<td>177</td>
</tr>
<tr>
<td>Uanyl nitrate</td>
<td>60</td>
<td>187</td>
</tr>
<tr>
<td>Uranous sulphate</td>
<td>62</td>
<td>159</td>
</tr>
<tr>
<td>Uranium Witte-peptone</td>
<td>121</td>
<td>126</td>
</tr>
<tr>
<td>Uranium serum (pleural fluid)</td>
<td>11.5</td>
<td>85</td>
</tr>
<tr>
<td>Uranium egg-white</td>
<td>13</td>
<td>95</td>
</tr>
<tr>
<td>Uranium spleen-pulp</td>
<td>10.9</td>
<td>55.6</td>
</tr>
</tbody>
</table>

Natural state. Incinerated.

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 the radio-active substances to rest. I mixed a sample of this, a vegetable substance that is not radiating, with protein, a new combination, in combination with protein, and yielded results which have given the animal which the animal system has been found to be with the animal system. The animal system has been found to be with the animal system.
active substances, such as uranium and thorium, indicate that small evidence of radio-activity manifested by an animal tissue does not necessarily mean that such tissue contains only a small amount of a radio-active element. The absence of evidence, or, if it does depend on the relative completeness with which the radio-activity is masked by the albinomous molecules with which the radio-active element is in combination.

By comparing the rates of electroscope 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 impingement 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.

<table>
<thead>
<tr>
<th>Natural State.</th>
<th>Incinerated.</th>
</tr>
</thead>
<tbody>
<tr>
<td>a. Particles.</td>
<td>$\beta + \gamma$ Rays.</td>
</tr>
<tr>
<td>Black uranium oxide</td>
<td>145.8</td>
</tr>
<tr>
<td>Ammonium uranate</td>
<td>102.2</td>
</tr>
<tr>
<td>Thorium uranate</td>
<td>79.4</td>
</tr>
<tr>
<td>Uranium sulphate</td>
<td>57.0</td>
</tr>
<tr>
<td>Uranium nitrate</td>
<td>52.4</td>
</tr>
<tr>
<td>Uranous sulphate</td>
<td>52.8</td>
</tr>
<tr>
<td>Uranium egg-white</td>
<td>4.8*</td>
</tr>
<tr>
<td>Thorium sulphate</td>
<td>24.1</td>
</tr>
<tr>
<td>Thorium nitrate</td>
<td>21.7</td>
</tr>
<tr>
<td>Thorium hydrosulphide</td>
<td>104.0</td>
</tr>
<tr>
<td>Thorium egg-white</td>
<td>3.1*</td>
</tr>
</tbody>
</table>

* In the case of these low values the absorbed aet has been corrected for the number of the electrometer 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 carcinosoma material, with its tendency to accelerate electroscope leak, modifies the electrical conditions of the tissue in which it lies; it is not impossible that the bombardment with alpha particles undergoes 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 SKOTOGRAFIC 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 present able to make, will be into the animal kingdom. Whatever the results we may have obtained, their sole importance as such as biologists, and even more for medical men, lies in any aspersion they may have to the incision of 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 embryonic cells of Ascaris, the ovum. The division of the embryo is a simple one to be followed, and the results are of the simplest, determining the number of cells having undergone cell division, starting from a single ovum. It is a very simple and a sufficiently advanced one to the nervous system. The cell which I have chosen for this part of the research is the embryonic cells of Ascaris, the ovum. The division of the embryo is a simple one to be followed, and the results are of the simplest, determining the number of cells having undergone cell division, starting from a single ovum. It is a very simple and a sufficiently advanced one to the nervous system.
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, 3; and in the twenty-minute specimen there were 21 living and moving worms. Here we have evidence of accelerated development. Evidence of this regards 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.

<table>
<thead>
<tr>
<th></th>
<th>Complete Development</th>
<th>Failure of Development</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>193</td>
<td>7</td>
</tr>
<tr>
<td>2 minutes exposure</td>
<td>193</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>169</td>
<td>31</td>
</tr>
<tr>
<td>6</td>
<td>166</td>
<td>34</td>
</tr>
<tr>
<td>9</td>
<td>165</td>
<td>35</td>
</tr>
<tr>
<td>12</td>
<td>174</td>
<td>26</td>
</tr>
<tr>
<td>15</td>
<td>157</td>
<td>43</td>
</tr>
<tr>
<td>20</td>
<td>133</td>
<td>61</td>
</tr>
</tbody>
</table>

Movement and Absence of Movement in Fifty Completely Developed Embryos.

<table>
<thead>
<tr>
<th></th>
<th>Living and Moving</th>
<th>Motionless</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>45</td>
<td>5</td>
</tr>
<tr>
<td>20 minutes exposure</td>
<td>30</td>
<td>20</td>
</tr>
</tbody>
</table>

This antagonistic influence of x rays upon the development of the ova of Ascaris megalocephala has already been described by Perthes, and Bonney and I fully confirm his results, both with regard to the main proposition and with regard to the observation that, though division of the cells may go on for a certain length of time, exposure to x 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, Cattley 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 x 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 x-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-

mality 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 x rays or radium. In particular, there is no significance in 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 Thoria or Uranium Oxide upon Cell Division in the Ova of Ascaris megalocephala.

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

September 30th.—1-cell stage. 2-cell stage.

October 1st.—1-cell stage. 2-cell stage.

October 2nd.—Control. All cells in morula stage. Thoria-exposed. All cells in morula stage, but the morula appears to be composed of fewer cells than in the control.

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

October 8th.—Living Incomplete Embryos. Embryos.

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 communication 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 autoradiographic 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 rapidly than in the control—that is, retards development—while a similar extract of the tiss-
es 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 x rays and radium, may be of the greatest interest 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
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 discussion, 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 time permitting to me I should summarise my results, and, as far as may be, consider establishing 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 conversively 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 collodion 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 power altogether. In the latter respect they are comparable with clay pipes, insomuch 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 the discharge of an electroscope. 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 certain plants and animals may be a phenomenon of considerable importance. Already this line of research is indicating that certain animal extracts having skotographic powers resemble those of radio-active substances in so far as they 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, and I showed in the last lecture that combination of a radical element with a protein molecule modifies the rate with which it induces the discharge of an electroscope, and its photographic powers.

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 this question 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 confine myself to a few salient points, offering you something in the nature of an impressionistic 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 carcinogenic and skotographic conditions may depend upon some common underlying cause—for example, heredity. Thus, our mode for the incidence of prostatic kidney and greyness of hair would probably run parallel courses, but no one would infer that the other be a casual relation to the other. But when one finds that the liability of liver, kidney, lungs, spleen, and bladder to cancer is a parallel 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 carcinomatosus 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 accelerating, while others possess retarding, powers on development a difficulty, for it is clear that for the occurrence of a carcinoma it is 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 carcinoma metastasis is carried by embolism, tissue permeation or other means plays as considerable a part in determining the occurrence or non-occurrence of a metastasis as the transported carcinoma cell. This is shown by the great variations in regard to metastasis met with even in carcinoma of a single site. We cannot believe that a fundamental difference obtains between the cells of one carcinoma of the cervix uteri and those of another, either as regard their "malignancy" or their liability to transport to the lymphatic glands, liver, etc. and yet as a reference to statistics collected at the Middlesex Hospital will show, more than half of the autopsies on cases dying from carcinoma of the cervix reveal an entire absence of metastasis. The only reasonable explanation of this fact is that carcinoma cells are 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 Ascari8 megalopulchra are such that in them may perhaps lie the solution of the question.

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 causes. One of the most noteworthy points in connexion with carcinoma is that a mass will kill, being, carcinoma, which would probably not kill if (cateria 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 interesting points are disclosed. This has been done for 1,221 cases of cancer at the Middlesex Hospital of which details as to age are available. The cases are distributed as follows: Uterus, 2,295 cases; breast, 2,125 cases; alimentary tract from stomach parts and the number of females 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. 15.

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, moreover, 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
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 later almost completely for five or more years, as the uterine, and particularly in the cervical, changes following the menopause are amongst the least marked of climacteric changes, and in any case are minute compared with the modification following 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 subject 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 reached out of reach of an indefinite 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 trauma in other regions, and, once occasioned, persists throughout life. At the same time, the factors more or less provided from other 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 attach more or less directly to menstruation when compared with the age for the maximum liability to carcinoma of the cervix, partly because trauma occurs in other regions, partly because the period of many years usually elapses between the last menstruation 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 this reason. From it the commonest seat of carcinoma is 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 Aescaris magnaevulosa to an extraordinary extent, and at the same time possesses marked skotographic powers (Fig. 27).

The cancer of the breast it appears to me that the observation of Mac Cormack 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 common amongst women. From this point of view, mammary carcinoma may be brought into line with carcinoma 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 progestin staphylococi, B. tuberculosis, B. diptherita, 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 of months and probably of years, the question arises whether we shall not find the essential cause of carcinoma affecting mammas, cicatrices, old ulcers, directly connected with the bacteria underlying the 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 later, we should expect the feeble skoto-

*The freedom of lower animals from carcinoma cervicis, I suggest, as explained by their differently different sexual habits. Its occurrence in confirmed virgin would be explainable on the lines sketched in the next paragraph.

years than one of spermatozoon origin, we should expect a later onset of diminution in liability with a carcinoma of bacterial origin than with one of spermatozoon origin, but in both cases we should expect the liability to cancer to diminish more or less rapidly. In the case of carcinoma and 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 the rectum and recto-sigmoid. 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 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 which may bring about these alterations of both the essential radio-active substances, and extracts of animal tissues are able to accelerate cell division in the ova of Aescaris; and (c) that, as a result of the greater degree of sensitiveness of the animal tissue to abnormal men, 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 another occasion. The peculiarities of the incidence in spite of the similarity of the tissues concerned, and of the identity of most of the conditions to 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 occurs 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 sleeping, as he sits in his sunlit room, 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 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 the subtlest of 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 some radio-active activity? If these 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, as well? After all, the radio-active substances usually regarded as causally related to carcinoma, possess properties resembling those of recognized radio-active substances to a greater or less degree when compared with the essential radio-active properties of these carcinoma. Such similarities are at least suggestive.
MEMORANDA.

[June 26, 1909.]

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 removable 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 I, thirty years reading, 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 65, 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, no irritable sensations. I gave enemata in the ordinary way, and after nearly an hour I only removed some small scybala 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 Biggins 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 great pressure, the skin and muscles of Adam's head were forced out, which enabled me to gain an inch or two at a time. Continuing this manoeuvre, the whole 32 in. of the tube were at last passed inside the sphincter. I felt the pumping tension slightly relaxed, and the bowels were in a state of continued purging for a little while 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.