Chart VII. is from a female patient who had been ill for four days before being admitted to my ward. She was treated with camphor administered hypodermically every four hours, with brandy between the doses. Both lungs presented evidence of extensive involvement, but at no time the dullness of consolidation or bronchial breathing. She was given urea quinine when admitted. For days there was little hope that she would live. On the seventh day after admission she had urea quinine again, which had no marked effect on her general condition. On the tenth day the condition continued to be so bad that I decided to give a dose of vaccine; this did no harm, was repeated in two days, and again within a week, as shown on the chart. After three weeks the temperature fell to normal and the lungs cleared up. Although there was much cough she did not expectorate, so the sputum was not fully examined.

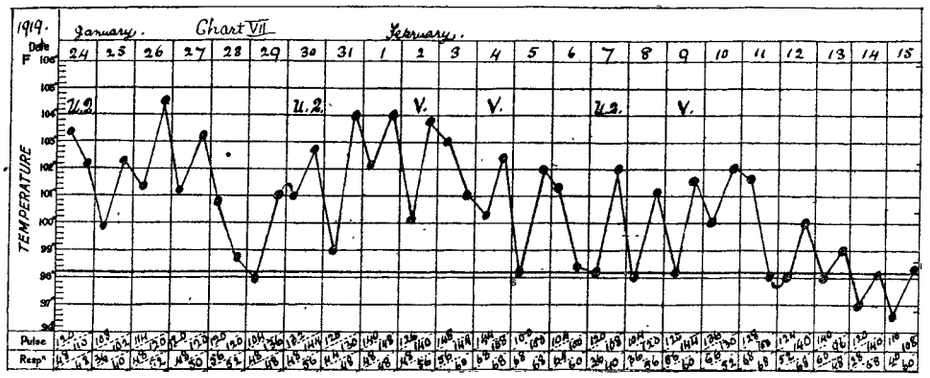
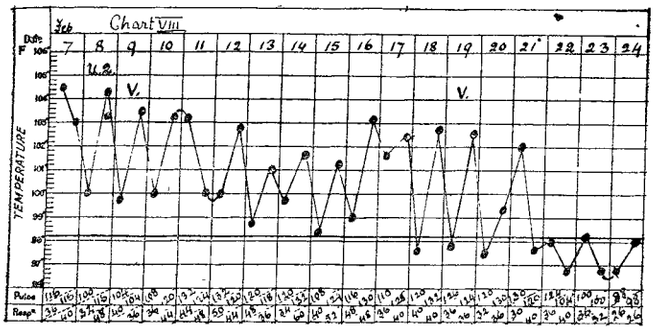


Chart VIII. is from a female patient who had been ill for a week before admission. Both lungs were crepitating all over, anteriorly, laterally, and posteriorly. She was markedly cyanosed, and she was so deaf that she made no response even when I raised my voice in asking her how she was. The pulse was the only reassuring point in this patient. The cyanosis was pronounced and was treated with oxygen inhalation. On the third day after admission she was given 85 millions of the mixed vaccine, but the cyanosis deterred us from repeating this until the 19th. On the 21st there was profuse perspiration, the temperature fell to normal and remained there. On the 23rd she heard my speaking voice for the first time. The lungs slowly cleared up. That this was a case of combined influenza bacilli and pneumococci was shown by culture.



The drugs which I have used have been mentioned, and I must say that I would not like to have had to treat these cases and many others without alcohol and camphor. The improvement under them is often very striking, and has frequently suggested an antitoxin influence. The action of urea quinine is that of quinine and urea; of its therapeutic value there is no doubt, but I have not pushed it beyond what the charts show.

Vaccine Therapy.

The great problem, however, before the profession is the vaccine therapy of the epidemic. From many quarters evidence is forthcoming that preventive inoculation has given satisfactory results. In Edinburgh there is produced at the Royal College of Physicians Laboratory a vaccine which is sent out by Messrs. Duncan, Flockhart and Co.; the first dose (No. 1) contains *B. influenzæ* 30 millions, pneumococcus 100 millions, streptococcus 40 millions; the second dose (No. 2) is double the strength. It is this vaccine I have used. At the same time the profession is warned that inoculation should not be practised "if there is any reason to think that the individual is in the early stages of the disease" (influenza); and "it is not recommended that the vaccine should be used for acute cases," and if it is used only *one-twentieth* of No. 1 should be given. A warning of this kind must act as a strong deterrent, for most of us respect the expressed judgment of authority; and for myself, I have to acknowledge that this warning has biased my judgment and hindered my action. It was only after being in contact with the severe cases that it became impressed upon me that ordinary, or even extraordinary, drug treatment did not supply what was needed. I have used vaccines in certain bacterial infections a good deal and I have not hesitated to use them in increasing doses in very acute cases of colon infection of the urinary tract, and I have only seen good therefrom. Why not, then, in the respiratory involvement of the present epidemic? And yet there was this warning.

The illustrative cases given above show that inoculation at the beginning of an attack and during the course of an acute attack of great virulence is *not* dangerous. The dose used was seldom less than half No. 1 and sometimes it was the whole. If we can establish that the treatment is not dangerous the air is cleared, and for routine practice a smaller dose might be used to begin with, repeated every few days and increased in size. I have not been able to detect any evil effect, although I have watched the cases with an anxious and critical mind. I can even go further and say that it seemed to me that the patient's general condition improved, that the intoxication seemed to be lessened or restrained. And those who have closely watched the bad cases know how hopeless one feels in face of the deepening toxæmia when all ordinary measures have been used. No patient has died to whom the vaccine has been given.

Doubtless in this case, as in every kind of therapy, there can be no rule of thumb procedure; the power to recognise what effect remedies are having on the individual has to be assumed, although the faculty of sound medical judgment is not universal. In capable hands, however, vaccine therapy seems to me to be the most promising line of treatment, if adopted as soon as definite respiratory signs appear, and if pushed with judgment.

I am indebted to the Royal College of Physicians Laboratory for the cultural observations and to Dr. C. Y. Wang for his personal interest.

EXPERIMENTAL STUDIES WITH SMALL DOSES OF X RAYS.*

BY

S. RUSS, D.SC., HELEN CHAMBERS, M.D. LOND., GLADWYS M. SCOTT, AND J. C. MOTTRAM, M.B. LOND.

1. *Introduction.*

THE subject-matter of the present paper consists of experimental facts as to the effects of small doses of X rays upon the blood of rats and upon the susceptibility of these animals to tumour implantation (Jensen's rat sarcoma).

An attempt is made to show the possible bearing of the salient features of these newly acquired facts upon the present-day treatment of malignant disease by means of X rays. It will be generally admitted that in such treatment attention is usually focussed upon giving the malignant cells a lethal dose of radiation. Two suggestions are put forward here in this connexion. When a therapeutic dose is given to the cells of a tumour the rest of the body receives a fractional dose of the rays. It is submitted that the action of these rays, especially upon the lymphocytes in the

* This research was undertaken at the request of the Medical Research Committee. The expenses were borne by the Cancer Investigation Fund of the Middlesex Hospital, and the research carried out in the Cancer Research Laboratories of that institution.

circulation, may be deterrent to the combative forces which the patient can normally bring to bear against the tumour growth. In the second place the possibility of increasing the resisting powers of the system by means of small doses of X rays is shown to have an experimental basis.

2. *The Effect of Small Doses of X Rays upon the Blood.*

Exposure of a rat to a large dose † of X rays causes profound changes in its blood; the cells most affected thereby are the lymphocytes, other blood cells are acted upon by these rays

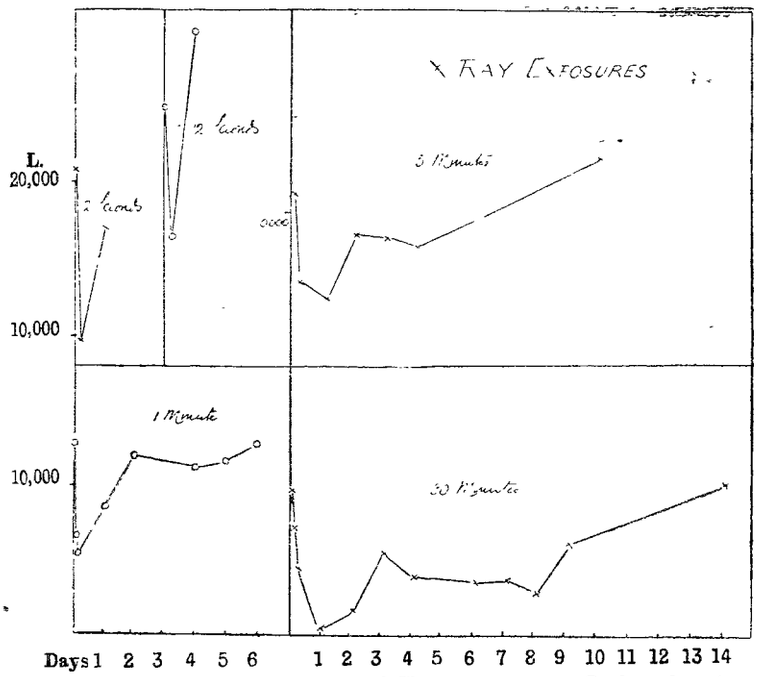


FIG. 1.—Effects of varying periods of X ray exposure. L, lymphocytes; the figures give lymphocytes per c.mm.

but generally to a much less extent. Our attention is here practically restricted to the behaviour of the lymphocytes.

A series in which the time of exposure was varied from 30 minutes to 2 seconds yielded the result that in each case, one hour after the exposure, the number of circulating lymphocytes was reduced to about 50 per cent. of the initial content; this is shown in Fig. 1. It is seen that the time elapsing before the lymphocytes return to the normal number is longer the more prolonged is the X ray exposure.

The character of the recovery curve has, within limits, a much more quantitative connexion with the dose of X rays administered than has the initial disappearance (1 hour after) of the lymphocytes, for, as stated, this is practically the same over a wide range of doses.

A more detailed study of the disappearance and return of the lymphocytes has been made for various doses. As an example, Fig. 2 shows this for an exposure of one minute, total blood counts being made every hour until recovery was well advanced.

We have obtained identical results upon the lymphocytes with unscreened "medium" X rays and with very "hard" X rays screened by 7 mm. of aluminium. It is necessary in comparative work of this kind to adjust the intensity and degree of radiation so that equal amounts of X rays are absorbed by the animals in the two cases. Under these conditions similar effects are observed.

† Reference throughout to the dose of X-rays will be to the length of *time* of exposure. The quantitative side is detailed in Section 6.

From the results of many experiments devised to determine the nature of the action of the X rays on the lymphocytes, it has been concluded that the action is a direct one upon these cells in the circulation. One such experiment was as follows:—

A rat completely screened by lead except for a region over the heart was exposed to a parallel beam of X rays; the exposure was adjusted so that the circulating blood should receive the same amount of X rays as it would by exposing the whole animal for about 1 minute. The fall and recovery curves of the lymphocytes were obtained and charted in the manner indicated—e.g., Fig. 2; the actual recovery curve obtained lay between the 1 minute and 3 minute curves.

The fact that the lymphocytes disappear from the circulation in such large numbers after an exposure lasting

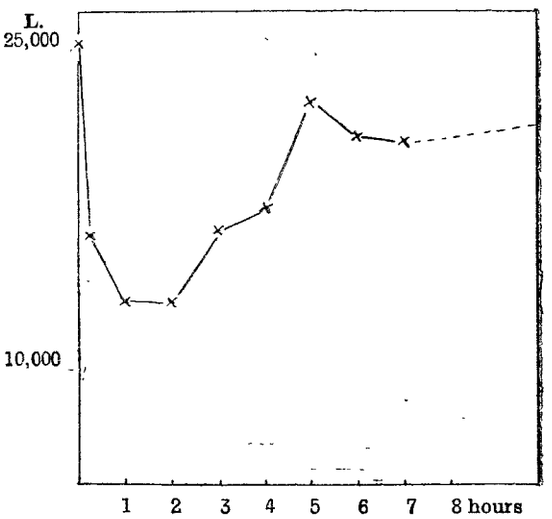


FIG. 2.—Disappearance and return of lymphocytes after exposure of one minute.

but 2 seconds leads us to doubt very strongly that this is due to their destruction, especially as they reappear with great rapidity. It is not a direct local effect of the radiation upon the tissues, for no local accumulation occurs in an irradiated area, nor have we detected any alteration in the general distribution of the lymphocytes, though the lungs, liver, and kidney have been examined from this point of view.

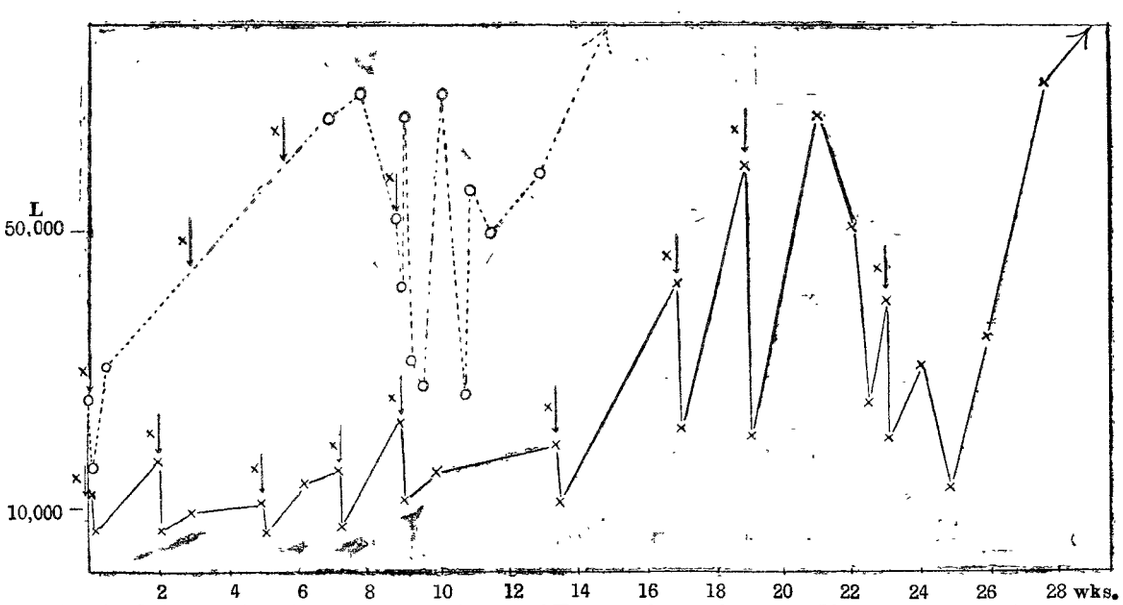


FIG. 3.—Effects on lymphocytosis of small doses of X rays. Arrows indicate a 12 sec. exposure to X rays.

If lymphocytes "in vitro" be given a dose one thousand times as large as that required for these effects "in vivo," no degenerative changes are detectable microscopically and no diminution in their numbers is observed.

3. *The Production of Lymphocytosis by Means of Small Doses of X Rays.*

A rat when given a small dose of X rays (12 seconds) shows a 50 per cent. reduction of its circulating lympho-

cytes 1 hour later; then it begins to recover, and in 24 or 48 hours is normal again.

If the same dose be administered a fortnight later, a similar drop occurs, the recovery is slightly delayed, but the number of lymphocytes finally reached is generally greater than at the beginning. Repeated application of such a small dose may result in a high degree of lymphocytosis, as is seen from the charts in Fig. 3. The circulating lymphocytes in the two cases depicted have increased from 11,000 and 25,000 to 112,000 and 117,000 per c.mm. respectively; corresponding counts for the polymorphonuclear leucocytes were initially 5000 and 5000 terminating in 10,000 and 14,000 per c.mm. respectively.

There is clear evidence of instability in the blood content of these irradiated animals, but the number of lymphocytes rarely drops so low as the normal level, even several months after the exposures have ceased.

Exactly what are the best radiation conditions for the production of this lymphocytosis it is not yet possible to say. Large doses may eventually produce the condition, but are to be avoided owing to their injurious nature. It is uncertain at present whether a small dose repeated at very short intervals produces this result. One batch of 11 animals was given small daily doses (12 seconds) over a period of two months. The average of the lymphocyte counts before irradiation was 19,000, three days after the last dose of X rays it was 27,000, and no marked rise was detected later, although counts were made upon some of the animals for another two months.

In the accompanying table are given a few examples of a marked increase in lymphocytic content and the radiation conditions under which they were obtained.

Table showing Lymphocytes per c.mm. after Radiation.

Time of radiation.	Numbers of exposures.	Duration of treatment.	Initial count.	Highest count obtained.	No. of days between first and last count.
30 min. ...	2	24 days.	21,000	45,000	159
5 ,, ...	1	5 mins.	14,000	41,000	224
5 ,, ...	3	94 days.	17,000	35,000	108
5 ,, ...	3	105 ,,	15,000	38,000	222
5 ,, ...	3	103 ,,	22,000	33,000	225
5 ,, ...	8	143 ,,	11,000	72,000	264
1 ,, ...	7	124 ,,	13,000	31,000	144
1 ,, ...	3	79 ,,	15,000	45,000	169
12 sec. ...	9	160 ,,	11,000	112,000	224
12 ,, ...	4	62 ,,	25,000	117,000	125
12 ,, ...	4	88 ,,	34,000	66,000	170

Blood counts of 81 normal rats showed lymphocyte counts ranging from 6000 to 46,000 per c.mm., with an average of 17,000, only four values being above 30,000.

4. *The Part Played by the Lymphocytes in Resisting the Growth of Rat Sarcoma.*

It has been shown in a previous publication by two of us [1] that when sarcoma cells (Jensen's rat sarcoma) are inoculated into rats which have previously been immunised, the failure of the sarcoma to grow is associated with some special activity on the part of the lymphocytes.

The further experimental fact acquired was that if immune rats were given a dose of X rays sufficiently large to cause and maintain a marked lymphopenia, then such immune animals became once more susceptible to the growth of the sarcoma.

These two experimental findings show that the lymphocytes play an important part in determining whether the sarcoma cells grow into a tumour or not. There were several indications, however, that the number of lymphocytes in the circulation was not the only factor to be taken into consideration, and there is now clear evidence for this view. It appears that some mechanism is present in the immune animal which brings the lymphocyte to the sarcoma cells, and this is absent in the normal animal.

There is evidence (vide below) that (1) rats having extraordinarily high lymphocyte counts will bear growing tumours when inoculated, and on the other hand that (2) rats having little more than a normal lymphocyte content can exhibit all the evidence of immunity. The details of the experiments are as follows.

Three rats with lymphocyte counts of 66,000, 112,000, and 117,000 were inoculated with small pieces of the rat sarcoma. The graph Fig. 4A shows that quite as large tumours resulted as in the controls Fig. 4B.

Again, five rats which had been exposed for two months to small daily doses of X rays were found at the end of this time to have the following lymphocyte counts: 22,000, 17,000, 33,000, 28,000, and 19,000. They were then inoculated. Fig. 5 shows (under column A the last five rats) that four of them were immune, and the remaining one bore a small oscillating tumour. The growth of the tumour in normal rats is seen in the same chart (Fig. 5B, the last six animals).

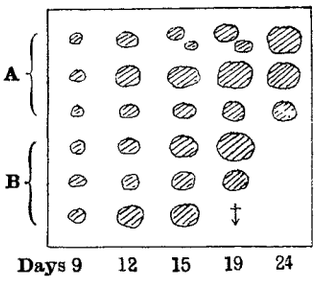


FIG. 4.—Growth of inoculated rat sarcoma in rats with high lymphocyte count (A), with controls (B).

In our opinion these results form a crucial test in deciding that some factor other than mere numbers of lymphocytes in the circulation has to be recognised as playing an essential part in the immune process.

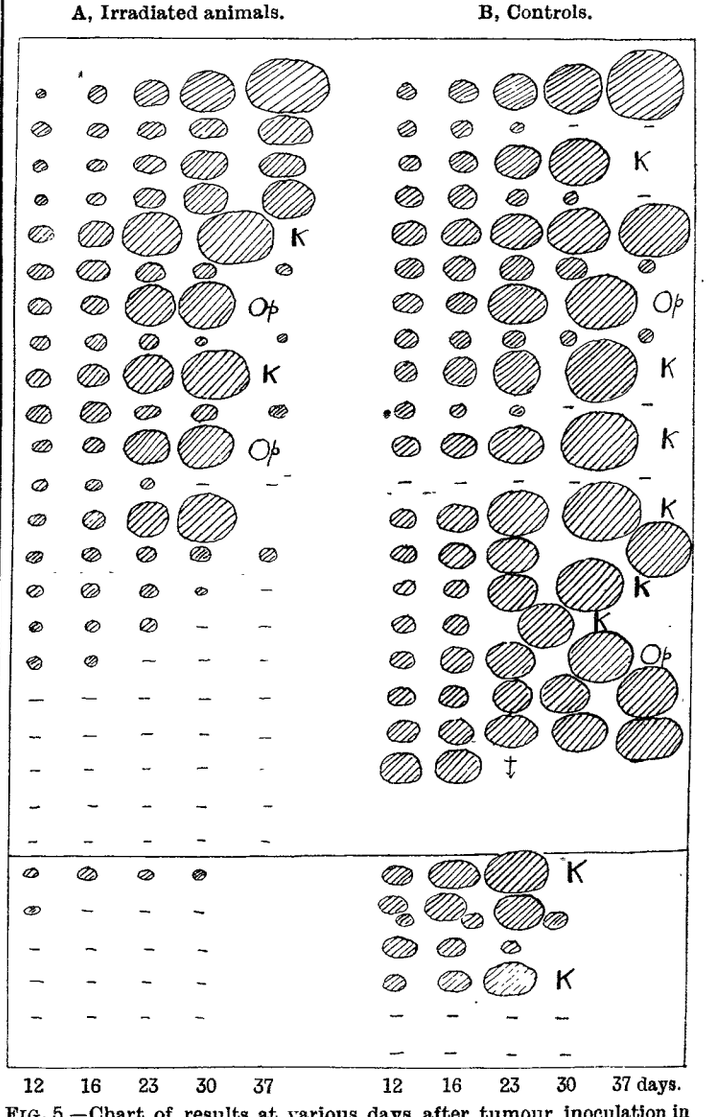


FIG. 5.—Chart of results at various days after tumour inoculation in animals who had received repeated small doses of X rays. K, animal killed; Op, tumour removed by operation.

5. *Production of the Immune Condition by Means of Repeated Small Doses of X Rays.*

The action of small daily doses of X rays upon the lymphocytes was found to cause no such increase in their numbers as resulted from the same dose applied at much longer intervals—e.g., two or three weeks. It was decided to see whether the administration of these small daily doses had any effect upon the animals as regards the subsequent growth of implanted sarcoma cells.

Sixty rats were taken, 30 of which were given small daily doses of X rays (12 seconds) for a period of two months, the remainder being kept as controls. Eleven days after the irradiation had stopped 25 of the animals from each batch were inoculated with small pieces of a growing tumour. Five of the irradiated animals were inoculated 40 days later. Charts of the resulting tumours were kept, the half-scale silhouettes of which are seen in Fig. 5; a much greater degree of immunity towards the tumour grafts is exhibited by the irradiated than by the normal animals.

Such a finding is in striking contrast with the fact that a large dose of X rays (1 hour or more) is capable of converting an immune animal into one in which a graft will grow upon inoculation.

6. *The Quantity of X Rays Signified by the Term "Small Dose."*

The X rays used in the above experiments, except where otherwise stated, were those emitted by a Coolidge tube worked by an induction coil at an alternative spark gap of about 4 in. (4 cm. between spheres, 5 cm. diameter); no screen was used other than a thin sheet of mica covering the aperture of the X ray tube box and a thin perforated sheet of celluloid covering the box in which the animals were placed during the X ray exposure—the distance from the anode to the animal was 30 cm. The composite beam of rays would generally be characterised by the term "medium" or "medium soft."

Details of the current in the primary and in the secondary of the coil, the heating current of the spiral of the tube, give no accurate information of the quantity of radiation emitted by the tube.

It was necessary to have some check upon the constancy of radiation from the Coolidge tube, and any irregularities in the intensity of its rays compensated by a proportionate change in the time of exposure. This check was provided by the use of a small gold-leaf electroscope placed in an adjacent room. An oblique beam of X rays from the Coolidge tube passed through holes in the walls and entered the electroscope, the rate of fall of the gold leaf serving as an indicator of the intensity of the X rays. Such observations were the prelude to all our X ray exposures, and from the general dispositions of apparatus this control could also be put into operation during the exposures if it were thought necessary. The distance of the electroscope from the anode was 6 metres; the air space between the anode and the animals was much less than this (viz., 30 cm.). Owing to the appreciable absorption of X rays by several metres of air the character of the X rays to which the animals were exposed was appreciably different to that of the beam entering the electroscope; so that the latter instrument could not be used as an absolute measure of the dose of X rays given to the animals. The radiation incident upon the animals has been measured photographically and compared with the photographic action of the beta rays from a measured quantity of radium bromide; the photographic imprints from a number of exposures were obtained upon the same photographic plate, which on development allowed of a direct comparison of tints, and could then be interpreted in terms of quantity of radiation.

The unit of reference employed in these experiments is that recently suggested by one of us[6]—viz., the rad—this is the quantity of radiation which, when absorbed by sarcoma cells, causes their eventual destruction on implantation into rats. The photographic impression of the X rays used during an exposure of 12 seconds was found to be equal to that of about 1/200 rad. During the course of this work we have looked upon a 12 seconds exposure as a typical "small dose," and the above comparison of quantities gives a general impression as to the quantity of radiation required for a lethal effect upon malignant cells and the very much smaller quantity of radiation responsible for the effects produced upon the blood which have previously been detailed in this paper.

7. *Discussion of Results.*

A brief survey of some salient experimental findings will preface a consideration of their bearing upon the radiological treatment of malignant disease.

1. The natural immunity which animals usually have towards the inoculation of spontaneous tumours can be broken down by an X ray exposure sufficient to cause the disappearance of the lymphocytes.[2]

2. The acquired immunity which results from the inoculation of blood or other cells into normal animals can similarly be destroyed.[3]

3. The acquired immunity which is found in animals in which tumours have disappeared can likewise be broken down.[1]

4. Tumour cells from a foreign species, which on inoculation will only grow with great rarity, multiply rapidly in an X-rayed animal, until such time as the depleted lymphoid system is well advanced in regeneration.[4]

5. Acquired immunity is destroyed only so long as lymphoid cells are reduced in number.[1]

6. In contrast to these actions, an immune condition can be produced instead of destroyed by suitable doses of X rays, vide Section 5, Fig. 5. Murphy and Morton, experimenting upon mice bearing spontaneous tumours, have obtained a similar effect. After removal of the tumours by operation the animals were given a small dose of X rays; grafts of the tumours were then reinoculated into the animals. In 26 out of 52 mice the grafts did not grow, and there was no recurrence at the site of operation in 41 of the animals. In 29 control animals similarly treated, except that they received no X rays, the grafts grew in 28 of the animals. Local recurrence occurred in 14 cases.[5]

X rays when administered to an animal have therefore two actions, quite apart from their direct effect upon a tumour: (*a*) A large dose of rays by destroying the immune condition will favour the growth of a tumour; (*b*) a small dose by producing the immune condition will help to control and may overcome the growth of a tumour.

The bearing of these facts upon the radiological treatment of malignant disease in man appears to us to be as follows. Whenever a tumour is exposed to X rays the lymphocytes circulating in the blood-vessels of the growth and of the surrounding tissues will be irradiated, or if the site of operation be treated the lymphocytes in the normal vessels and tissues will be similarly exposed. It is clear, therefore, that though the radiologist may be giving the primary growth the dose of radiation required for its disappearance, he may at the same time be indirectly encouraging the development of secondary growths by lowering the natural powers of resistance of the patient, especially if this comparatively large dose is repeated at fortnightly intervals, as in post-operative treatment.

It would appear profitable therefore to take all possible precautions to prevent the destruction of such cells as the lymphocytes, which, there is good reason to believe, play a defensive rôle in many varieties of malignant growth.

Finally, as regards the possibility of using X rays to increase the natural powers of resistance against cancer. It must be clearly understood that up to the present it is only resistance against cancer inoculations that has been increased. Nevertheless, there is a distinct analogy between a graft introduced experimentally and a lodgment of cancer cells occurring at a distance from a primary growth. By the use of small doses of X rays repeated at intervals it may be that the resistance against the development of secondary deposits can be increased in a similar way to that which occurs in the case of an experimental inoculation.

We take this opportunity of acknowledging our indebtedness to the Director of these laboratories for the facilities he has always given us. These and other researches are the outcome of his adherence to a line of investigation in cancer which had its origin in the basic fact that X rays cause carcinoma (vide Croonian lectures on Radio-activity and Carcinoma, Royal College of Physicians, 1909, THE LANCET, June 26th, 1909). We have also pleasure in recording our thanks to the British Thomson Houston Co. and the General Electric Company of Shenectady for their gift of the Coolidge tube used in these investigations.

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3. Murphy and Taylor: Jour. Exp. Med., 1918, p. 1.
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FAMINE RELIEF IN BOMBAY.—The Government has made arrangements with the Bombay Improvement Trust to construct on their behalf temporary dwellings for immigrants into Bombay city from famine-stricken areas.