The arteries of the ear in such a cat contract on stimulation of the nerves or on injecting adrenin, but not the dilated veins and capillaries.

Shock.

The work of Dale and his co-workers indicates that shock produced by histamine has its origin in primary failure of the peripheral circulation. All the capillaries open and venules dilate at once, and there is increased passage of fluid from the blood into the tissues, and so the circulation fails while the heart is beating efficiently. While Dale injected histamine, I watched the venules dilate in the mesentery and the flow slow down and almost become arrested in these and in the capillaries, but have not so far been able to see the opening up of closed capillaries, probably because the capillaries are already dilated by exposure. Histamine is formed by decarboxylation of the amino-acid histidine, which is derived from proteins, and it is conceivable that such substances are produced in trauma. Herein we have an explanation of shock differing from that of acid causation put forward by Almroth Wright.

Be it noted, histamine acts in the cat anaesthetized by ether, but not in the normal cat or one anaesthetized by nitrous oxide and oxygen. The last is by far the best anaesthetic for preventing shock, and as P. Bert proved forty years ago, and Dale and I have confirmed recently, may be given with ease and safety and efficiency of depth in a pressure chamber at + 7 lb. pressure. An operating chamber can easily be constructed so that the patient, surgeon, and anaesthetist are all within the chamber at slightly increased atmospheric pressure. The effect of inhaling gas and oxygen, given in the usual way from a bag in such a chamber, is an increase of partial pressure, or concentration, of both in the blood, and deep anaesthesia with no want of oxygen.

Effects of Oxygen Inhalation.

The beneficial action of oxygen inhalation in relieving oedema and chronic ulcers has recently been made evident to me by the use of an oxygen tent bed, constructed for me by Messrs. Siebe, Gorman, Ltd. This tent bed allows 30 to 40 per cent. oxygen to be breathed in comfort for days, with intermissions for meals. The oedema disappears, the part becomes warm and of good colour, the granulations healthy, the edges of the ulcer flatten, and the skin hastens to spread over the ulcer.

The question arises as to how the capillaries contract and dilate. It is generally assumed, but unproven, that it is due to changes in the swelling of the endothelial cells of the capillary wall. I suggest that it is due to the tissue cells outside the capillaries; these, by swelling or shrinking, control their own blood supply. By increase of waste products with higher osmotic pressure they take up fluid from the blood in the capillaries and swell, and so contract the capillaries. By chemical-physical changes resulting from the taking up of fluid from the blood the osmotic pressure falls, and the fluid passes back into the blood or lymphatic channels.

I have pointed out what happens in the salivary gland on excitation of the chorda tympani, and how the membranae propriae and other membranes confine tissue expansion so that the capillaries and veins may be narrowed but not occluded. I do not believe fluid is transuded out by the force of the heart producing a filtering pressure, but that the heart just succeeds in maintaining a flow in the capillaries with no excess of pressure for other purposes, and the tissues by inhibition swell or shrink, taking or giving up fluid.

Charles Bolton, narrowing the inferior vena cava to one-third by a rubber ring, has shown that oedema results in dogs, not when the temporary small rise of venous pressure occurs at first, but later, when the venous pressure has returned to normal. Oedema is due to ill nutrition of the tissues, not to increased vascular pressure and filtration, whether it arise from poor flow and want of oxygen in heart disease or from a chemical poison in kidney disease, or from a bacterial toxin.

The swelling of the tissues in oedema, by pressing upon the venules, raises the capillary pressure.

I have measured the pressure in a case of hydrocephalus with the infant lying horizontal. It was nearly 15 mm. Hg. On raising the head from the pillow the pressure

rose owing to my hands squeezing the head which was a bag of fluid. The capillary venous pressure in the pial vessels must have risen *pari passu*, there is no mechanism for shielding them from the pressure of the fluid. I moreover found, on drawing off the fluid, that the pressure sank to 0—that is, to atmospheric pressure—and the soft wall of the skull by its weight sagged in. So it remained for hours, until the fluid was re-secreted.

In a case of oedema of the leg, with the patient sitting propped up, the pressure of the fluid equalled about 40 mm. Hg; here again the pressure rose on lifting the leg up, owing to squeezing by the hands, and the capillary venous pressure must have risen *pari passu*, and kept as it is normally, the least bit above the tissue fluid pressure, so as to maintain the venous outflow.

In inflammation the products of tissues damaged by bacterial toxins cause dilatation of arteries and swelling of tissues. The swollen tissues, confined by the membranes, press upon and narrow the veins and capillaries. The blood pressure rises, and we have a more rigid system with fast flow, redness, swelling, and a throbbing pulse in the part. The tissues may swell so that stasis is produced; the surgeon's knife then relieves the swollen, tense condition, and allows lymph with its immunizing powers to escape. Bier's bandages obstructing venous flow may cause increased outflow of lymph, not by transudation under pressure, for capillary pressure is balanced by tissue fluid pressure, but by increased imbibition of tissue cells due to oxygen want. The salt solution treatment of wounds devised by Almroth Wright pulls fluid out in increased amount, and washes the wounds just as the breathing of cool air, with its low water vapour content, by evaporating moisture from the respiratory membrane, draws abundant lymph from the blood and keeps this clean and healthy.

Krogh finds that, after putting in a drop of 20 per cent. urethane on the capillary field and injecting neutral red intravenously, the dye passes through the dilated capillaries and stains the bordering tissue, the stain fading away from the capillary. This he ascribes to increased permeability. It may equally well be due to increased force of inhibition exerted by the damaged tissue cells. The escape of white blood cells during stasis and of red cells on severe injury shows a pathological permeation of the capillary wall; but normally the tissue cell, not the capillary pressure, governs the passage of fluid.

References to literature are fully given by Tigerstedt, *Ergebnisse der Physiol.*, 1920, 18, and Hooker, *Amer. Physiol. Review*, 1921, 1, Part I. See also Krogh, *Journ. Physiol.*, 1920, 53, 26; Leonard Hill, *Proc. Physiol. Soc., Journ. Physiol.*, 1920-21, 54; Leonard Hill and J. McQueen, *Brit. Journ. Exper. Pathol.*, 1921, 2, 1.

DUAL RADIOTHERAPY IN MALIGNANT DISEASE.

BY

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X RAYS and radium are undoubtedly powerful therapeutic agents. But, since the technique required to obtain their complete beneficial results has not as yet been mastered, we are at present unable to make full use of them. Consequently most of our failures must be attributed to the uncertainty of our technique rather than to the agents themselves.

Physicists have given us much help in solving some of the problems connected with x rays and radium. But until they can give us not only an accurate means of measuring dosage to pathological cells lying below the surface of the skin, but also indications of the conditions and dose required to produce a full lethal effect on these cells, our results are bound to be erratic. At present results depend partly on luck—that is to say, on whether the particular dose administered happens to be the most effective one—and partly on the practical experience of the radiologist, which enables him to gauge this with a certain amount of accuracy. It should, indeed, be possible to administer x rays and radium radiations as accurately as drugs. It should equally be possible to have some idea of the prescription required for the case in hand.

There are, perhaps, no therapeutic agents affecting such a variety of diseases, or from which more remarkable

results can be obtained in many cases otherwise hopeless. The work carried out by the x-ray treatment department of the London Hospital in the course of the last ten years bears out this statement. Over 11,000 new cases have been treated, averaging 5,000 attendances a year. This total includes 115 different diseases, ranging from deep-seated and malignant tumours to conditions so superficial as warts and corns. It is clear that control of dosage is essential in the treatment of such widely separated diseases.

Out of the total given above, 1,500 were cases of mammary carcinoma, some requiring prophylactic treatment, others being recurrent or inoperable. Carcinoma of the breast being the largest class of cancer cases, I endeavoured to find out and classify the results of x-ray treatment in the hope of improving our methods. The tracing of hospital patients was impracticable. Statistics are apt to be deceptive. But in the case of patients who were traced, metastases in the thorax accounted for a large percentage of deaths, although the superficial recurrences had been controlled. Was it not possible to control these deep metastases in the same way as the superficial? Clearly, any successful method must fulfil two conditions: (1) It should be possible to administer a dose lethal to pathological cells lying at various depths and in unknown positions; (2) the radiated area should be large. The importance of the second factor is emphasized in a valuable paper on the "The Spread of Breast Cancer," by W. Sampson Handley, in the *Archives of Radiology and Electrotherapy* (October, 1920).

In the hope of fulfilling these two conditions, I devised the dual method of radiotherapy which has been installed in temporary quarters at the London Hospital. Although designed for the treatment of carcinoma of the breast and thoracic tumours, it can be used for many deep-seated conditions, such as abdominal tumours, splenic cases, and it may, I believe, prove of some value in the treatment of pulmonary tuberculosis.

Rationale of Treatment.

The complex question of dosage cannot be discussed here, but I have for some years based my deep therapy on the following principles: (1) Full cell absorption; (2) production of a large number of heterogeneous rays; (3) a filter only thick enough to protect the skin and to cut out rays of little or no therapeutic value. These were suggested by facts supplied by physicists and by gleanings from my personal experience. Although I cannot here go into further details, the results in the more superficial conditions have been up to the present so satisfactory that an elaboration on the same lines, such as with the dual method, seemed justified. Any new scheme for deep therapy should be founded on a logical basis. It must be admitted that our knowledge of the actual influence of x rays on the living cells is meagre; but I think it is sufficient to indicate the lines that should be followed, even though these may have to be altered as our knowledge increases. I do not think the full therapeutic value will be obtained by endeavouring to produce x rays with the penetration of radium at the expense of maximum cell absorption. I suggest that there is some unknown factor in radium radiations which, apart from their high degree of penetration, may account for their therapeutic effect. The reports of the Radium Institute show that the therapeutic results of radium radiations are equal to those of x rays properly administered, their chief value being in cases where the disease is inaccessible to the latter, whilst their disadvantage lies in the limited field of radiation.

Technique.

The shortcomings of our present methods are these:

1. The dose administered to the deep-seated and scattered pathological cells is too small.
2. The area treated is much too limited.

The dual method for deep therapy, of which I have found no mention in the literature, consists of two separate installations, of which one operates a tube in front, the other a tube at the back of the patient, who is in the sitting position, both tubes running simultaneously. After the first full dose has been administered the direction is changed, so that the radiation is now from side to side, the arms being forward and raised. In this way the

deepest parts of the body are subjected to radiations from the four points of the compass, and the resulting cell absorption must be very much greater than with our present methods, although the more superficial, or skin dose, controlling superficial recurrences, remains the same.

By this method, which may be described as a combined cross-fire, the deficiencies of current methods, referred to above, are avoided; that is to say, (1) by working both tubes at the same time from both sides of the body a larger dose is administered to the deeper pathological cells; (2) a very large area is covered.

It is doubtful whether any additional therapeutic effect is to be expected from the coincidence of the rays in the deeper tissues. At any rate, malignant cells in the tissues, lymph channels or blood stream, must certainly come under the influence of the radiations.

The radiation of a large area did not present much difficulty. It merely entailed the manufacture of a protective shield or tube-box with a large opening. I prefer a lead glass shield, but as I was unable to obtain one with an opening large enough for my purpose, I utilized the standard one reversed—that is to say, the smaller opening, blocked by protective material, not only holds the shield in position, but admits the air-blast, directing it to the back of the tube. The larger aperture now faces the patient, giving a very large radiation field, including, at a reasonable distance, practically the whole trunk, axillae and supraclavicular fossae.

I consider it important that the maximum dose the patient can tolerate should be administered at the first and at every subsequent sitting. If this is not done, there is a possibility of the pathological cells being encouraged or stimulated to assume defensive measures against the destructive effect of the radiations. We all know that some kind of acquired immunity, not to be confused with stimulation, may occur. Cases that respond well at first may quite suddenly cease to do so if the treatment is prolonged and the dosage too light.

To put it briefly therefore: "Always hit hard; do not continue treatment once you have achieved your object."

Blood counts are at present carried out in all patients immediately before and after exposure, and at varying intervals subsequently, with a view to ascertaining the maximum dose they can tolerate. But, when once this is established, these frequent blood counts will probably be unnecessary—at any rate in cases of mammary carcinoma. In all cases of cancer the thorax is carefully examined radiologically before treatment, and a plate taken as a record.

We cannot as yet decide definitely how frequent the treatment should be; this must, to a certain extent, depend on the blood changes and other symptoms, the significance of which is still debatable. At first, patients were treated once a week, receiving 20 X skin dose through 3 mm. of aluminium at each of the four areas—the front, back and two sides, giving a total of 80 X at each sitting. Six of these would have completed the first series of 480 X, but it was found that only a few patients could tolerate the full 80 X dose. The occurrence of nausea and vomiting within a few hours of treatment (sometimes lasting as long as three days) demonstrates, I think, the fact that tolerance to x rays has been reached and is limited in different patients. I believe, however, that by working up to the maximum gradually, secondary symptoms may be avoided. These after-effects may not necessarily be the results of x rays; ozone and nitrous fumes may cause the sickness. The whole matter is being investigated.

Treatment is now administered weekly: anteriorly and posteriorly the first week, the second week from both sides, the total dose being 40 X through 3 mm. of aluminium in each week. Although many tolerate it, there are some who cannot stand even this dose.

DOSAGE.

Registration of Dosage.

Accurate measurement of the dose absorbed by the pathological cells composing even a single tumour is practically impossible. At present only a very rough calculation can be made, and even this is dependent on several unknown factors. The difficulty is still greater when we are endeavouring to irradiate a number of cells scattered about in the body at unknown depths and in unknown positions. The best we can do is to measure the maximum

skin dose under certain known conditions and give as large a dose of heterogeneous rays as possible. The calculation of the skin dose used in the treatment of tinea is simple and accurate, but difficulties arise when a filter is inserted. We have the Sabouraud pastille, the Kienböck strip, the Holzknecht strip, and many others by which the dose can be gauged, but most of these are intended for use without a filter. We are waiting for a simple practical unit for filtered rays.

For want of a better I have, for many years, used the Sabouraud pastille on the skin as my unit, Kienböck's strip not being very practical, as an overdose or underdose may easily be given, usually too late to remedy the error. The time factor with a Coolidge tube is fairly accurate, but even here each tube must be tested periodically by some method or other. It is better to take the reading on the skin itself, as the distance of the tube and the thickness of the filter can then be practically disregarded, although this process involves the establishment of a new unit. The main difficulty when using a Sabouraud pastille on the skin is the reading of the slight tint alteration that takes place, but this may be overcome by the use of a tintometer.

I have found from experience that the effect on the skin of an erythema dose through a filter was not the same as without a filter, a fact which, I believe, agrees with the expectations of physicists. Realizing this, would it be possible to fix a unit which would give us the danger dose through a filter? The method I adopted some years ago to gauge roughly the maximum skin dose with a filter, when treating deep-seated tumours, is as follows: A Sabouraud pastille is placed on the skin; when this registers a quarter B tint the skin has received a 10 X dose, irrespective of the distance of the tube or of the thickness of the filter. This was taken as the minimum dose, not as the erythema dose, the maximum which I have applied being a 20 X dose, again measured on the skin through 3 mm. of aluminium. The pastille in this case will read $\frac{1}{2}$ B tint. The $\frac{1}{2}$ B tint and the $\frac{1}{2}$ B dose must not be confused; they are entirely different. Penetration should not be below 9.5 Wehnelt. Caution is required by the operator in using these large doses; they should be worked up to gradually. The margin of error being small, a certain amount of proficiency in the use of the apparatus and in the reading of the pastille changes is essential.

I have given this 20 X dose through 3 mm. of aluminium as often as twice a week in desperate cases with no resulting skin changes beyond deep pigmentation. Such possibilities as late reactions must be risked when the patient's life is at stake.

Possible Dangers.

1. *Blood*.—Massive doses are said to lead to definite blood changes, the details of which cannot be gone into here. With the dual radiotherapy, not only is the total dose large owing to the extensive area of the body subjected to radiations, but the heart, when thoracic conditions are being treated, is being radiated from all sides. I believe, however, that any blood changes that occur are caused by the direct action of the rays on the blood-making tissues, such as the spleen and bone marrow, rather than on the blood corpuscles. So far no blood changes have been found.

2. *Intestines*.—Various organs are said to be influenced by radiations, amongst them the intestines. As the dual method has not yet been applied to abdominal cases this point cannot be settled. A careful watch should be kept on all patients under treatment for indications of possible damage to organs in the field of radiation. Any undesirable effect should be rectified by modification of dosage and frequency of treatment.

Results.

The first patient was treated by the dual method only on February 24th, 1921, and some time must therefore elapse before any reliable data can be expected where an effort is being made to prevent metastases, but in those cases in which the primary lesion has been treated, such as an intrathoracic growth they appear to respond very much more rapidly than with the localized method used previously.

It must always be remembered that the time is possibly approaching when the cure may prove worse than the

disease. In our efforts to destroy malignant cells we may destroy far more than we intended.

The *secondary phenomena* so far noted are of some interest. Few can tolerate the full 80 X dose, nausea and vomiting, lasting from several hours to three days, appearing shortly after treatment. If, however, the dose is halved—two opposite areas only being treated instead of four—the patients may experience a feeling of well-being, which one patient aptly compared to the effect of a glass of champagne. In one case, that of a large intrathoracic growth (the patient was a doctor), the secondary symptoms—nausea and vomiting—were very marked after even the first 40 X dose, yet others experienced no ill effects whatever, even after the full 80 X dose. These secondary phenomena are somewhat puzzling and are being investigated, as other causes besides the direct action of x rays may be responsible.

I have given but a rough description of the method, hoping that others may work on the same lines, and that at some future time interesting comparisons and conclusions may be made.

Radiologists appear to have divided themselves into two schools—those who endeavour to attain *maximum cell absorption* and those who pin their faith on *excessive penetration* at the expense of absorption. The dual method follows the cell absorption line of technique.

FURTHER REPORT ON THE TREATMENT OF SLEEPING SICKNESS.

BY

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In a previous report published in the *BRITISH MEDICAL JOURNAL* of May 22nd, 1920, p. 702, by one of us (C. H. M.), attention was drawn to the treatment of sleeping sickness by combined intravenous and intrathecal injections of organic arsenical preparations (neo-kharsivan). An epitome of twelve cases thus treated was also given.

Since then the number of cases treated and under observation has increased to over 50, and the conclusions we have drawn are that this treatment shows prospects of a possible cure for, at any rate, early cases of this protean disease.

The following is a summary of the technique of the treatment, given in detail in the report previously alluded to:

An intravenous injection of an organic compound of arsenic is given, and after a period varying from one to four hours a certain quantity of blood—usually 20 c.cm.—is withdrawn. This is kept in a vessel, stood in cold water, until the serum separates completely from the formed elements of the blood. The separated serum is then injected into the cerebro-spinal cavity, an equal amount of cerebro-spinal fluid having been previously drawn off. This completes the treatment, and the patient is free to resume his normal life, subject to his reporting from time to time for re-examinations.

The principle of the treatment was based on the theory that the trypanosomes having once reached the cerebro-spinal canal were, after a certain time, immune to any medication via the blood stream; since we have adopted this routine procedure for sleeping sickness cases we have had striking examples of this fact.

The following are examples:

Case 30.

Karungaho, a man with large typical chains in the neck, admitted to hospital on June 14th, 1920. Gland puncture showed numerous trypanosomes and flariae. On June 15th, 0.6 gram neo-kharsivan was injected intravenously; on the 17th 12 c.cm. of cerebro-spinal fluid were drawn off by lumbar puncture. The cerebro-spinal fluid on examination showed trypanosomes.

Case 33.

Wana, a man with large typical glands, was admitted on June 19th, 1920, gland puncture showed trypanosome infection. Neo-kharsivan 0.6 gram was administered intravenously on June 20th, and on the 23rd when 12 c.cm. of cerebro-spinal fluid were drawn off, prior to intrathecal medication, it was found to contain living trypanosomes.

The next case is, to our mind, more striking, and we think proves conclusively our theory.