AN ATTEMPT TO PROCURE IMMUNITY TO MALIGNANT DISEASE IN MAN.

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IN the previous paper it has been recorded that immunity to transplanted malignant disease can be produced in animals by inoculating them with tumour tissue which has been exposed to a suitable dose of radiation, and that this can be done without risk of a tumour forming at the site of injection. This experimental work has only been done for transplanted malignant growths in animals and we cannot say that the results in spontaneous cancer will be the same; but with these results before us it seemed clearly worth while to test the process in the human body.

Since May 1920, we have been attempting to immunise patients suffering from cancer against their own tumour cells. The number of cases treated (30 in all) is too small, and the time that has elapsed too short, for us to be in a position to form an opinion of much value of the effect on the progress of the disease; the cases will have to be watched for a considerable time. All that we can say at present is that, with efficient technical precautions, the treatment can be carried out without causing tumour formation or serious effects. Some years must elapse before the real value of a new treatment for malignant disease can be determined, and it has therefore seemed to us desirable to describe this method and record the results so far obtained. For this preliminary work, the cases treated were those in which the disease was at such a stage that complete surgical removal was not considered possible, but not so far advanced as to preclude a prospect of life for some months.

The Technique.

At the operation only as much tumour need be removed to provide sufficient material for the subsequent injection. It often happens in breast cases that total removal of the breast is more simple than partial removal. In cases where glands have been involved no attempt has been made to remove all the growth; the tumour, or as much of it as is needed, having been removed, the wound is closed and dressed. Two pockets are then prepared in the abdominal wall, on either side of the mid-line, in the following manner. An incision about an inch long is made down to the deep fascia, and a strong pair of sinus forceps thrust along between the subcutaneous tissues and muscles and then opened out. The pockets thus formed are fan-shaped with the narrow end upwards so that injected material tends to be retained; they are purposely made large in order to increase the area of contact between the patient's tissues and the injected material. If this precaution is not taken it has been found that much of the tissue undergoes autolysis and is afterwards discharged; this may happen even when the injection mass remains sterile. A large-sized drainage-tube is put into each of the openings, reaching nearly to the bottom of the pocket, and stitches are inserted into the skin so that the wounds can be easily closed afterwards.

The whole of the growth removed at the operation is sent to the laboratory in a sterile dish. The specimen is cut up with scissors and the growth separated as far as possible from the normal tissues. It is put into a metal mincing-machine, covered with a sterile towel, minced into the middle of a shallow dish, and spread into a layer of uniform thickness. The rim of the dish having been smeared with sterile vaseline, it is covered with a sheet of mica, put into a slightly larger and deeper dish, and wrapped in a sterile towel to protect the material from possible contamination during the X ray exposure.

After a radiation dose of 2 rads the minced tumour is sucked into an all-glass syringe, fitted with a wide aperture and cannula, which is returned to the ward; the preparation of the material as a rule takes about two hours. In the ward, the dressings are removed from the abdominal wounds, and equal quantities of the irradiated material injected through each drainage-tube; these are then withdrawn, the ligatures tied, and the wounds sealed with gauze and collodion. If the operation has been at all lengthy this can often be done before the patient has completely recovered consciousness, but in any case the proceeding has been found to be almost painless. The quantity of material injected has varied from 4 to 15 c.cms., and in most cases has been more than 8 c.cms. The injection is done as soon as possible after the operation, in order to avoid changes in the material, and no saline is added.

X Ray Technique.

It was necessary to remember that in introducing this material into patients we were inserting tumour cells into the most susceptible of all individuals, and that we were trusting entirely to the radiation to prevent these cells growing. The method of treating the minced growth has followed the lines of the experimental method described in the previous paper, the unit of radiation used being the dose required to kill malignant cells in vitro. As a safeguard, this dose has been doubled. Reference to the work of Wedd, Morson, and Russ[1] shows that an increase in the dose of radiation to this extent only reduces the immunising value of the material by 15 per cent. but that further radiation reduces it more, and eventually destroys it altogether. We feel it is essential in a treatment of this kind that a rigorous X ray technique be adopted. The readings of electrical instruments in the high or low-tension circuits cannot be relied upon to give a correct measure of the dose of radiation. These instruments have their uses, but they do not measure the radiation as it is being delivered, and so do not lead to a correct valuation of the dose.

The method we have adopted is to run the Coolidge tube as far as possible under the same conditions of spark-gap and heating filament current. Directly the exposure of the minced tumour has begun, measurements of the X rays issuing from the bulb are taken by means of a gold-leaf electroscope which has previously been calibrated by means of a known quantity of radium. The rate of fall of the leaf is proportional to the yield of X rays from the bulb, and as readings of the electroscope are made at least every minute during the exposure, which generally takes about an hour, it will be seen that a valuable check is made upon the dose of radiation. The readings are totalled as the measurements are made; any fluctuations in the output are thus detected, and the time of exposure correspondingly prolonged or shortened.

The tumour is removed and irradiated outside the body instead of being exposed to radiation whilst still in the patient; because if tumour tissue is exposed to less than the lethal dose of radiation no immunity is obtained, as was shown in the preceding paper. In the report[2] issued from these laboratories, and now in course of publication, on the use of a large quantity of radium—viz., the gamma radiation from about 5 gms. of radium bromide, it is shown that with one application it is difficult to apply a lethal dose to tumour cells in the body even with this penetrating type of radiation. The reason for this is that the requisite dose is larger than that which causes vesication of the skin, and although temporary benefit has repeatedly followed the application of less than the lethal dose to breast carcinomata, recurrence has been observed, even in those cases in which the skin has been severely damaged.

It is entirely owing to this difficulty of giving tumour cells in the body an adequate dose of radiation that the method described has been used; it has the great

advantage that outside the body the growth cells can be given an almost uniform dose which can be as large as is necessary.

Evidence of Immunity.

The final result which it is hoped to obtain by this method is that the patient will be able to destroy all tumour cells left in the body after a limited operation. We must, however, be prepared to find that the immunity will vary in intensity, particularly as the nature of the body causing the immunity is unknown and we are not in a position to standardise the agent. The experimental evidence of immunity most easily obtained is the failure of a tumour graft which would grow readily in normal animals. This test gives little information about the degree of immunity, for a graft may fail to grow in an animal which has been treated with an emulsion of normal tissues; the protection in this case is only of a temporary character and is not able to affect the growth of an established tumour; but, on the other hand, a graft will not grow in an animal which has previously absorbed a tumour; and this protection is lasting and strong enough to have destroyed the original growth. The failure of a graft to grow would perhaps be comparable with the failure of a metastatic nodule to become established, so that in human cases, we might expect that the prevention of metastases would be the first evidence of the patient acquiring some degree of immunity. This must, however, be accepted with reserve, for there is at present no definite evidence to show that a metastatic deposit is more easily destroyed than cells around a primary growth.

It has been shown by Mottram and Russ[3] that it is possible to recognise in animals the existence of a state of immunity by taking measurements of the size of the tumours at regular intervals, for, provided other conditions are constant, the rate at which a tumour grows depends upon this immunity. The production of immunity is indicated by a reduced rate of growth, and later by its cessation, and only when the protection is well established does the growth begin to disappear. If similar effects can be obtained in man, successful treatment will be shown by a delay in the progress of the disease, and we can hardly expect to influence large established growths in a short time. Variations in the rate of growth in human cancer are so common under ordinary conditions that great care must be taken before such changes can be attributed to treatment.

As far as we know at present the addition of antiseptics to the irradiated material weakens its immunising properties; there is also some indication that the tumour tissue is of no value if infected with septic organisms sufficient to cause an abscess to form at the site of injection. The dose of radiation given to the material has practically no bactericidal action. For this reason many cases otherwise suitable for the treatment, such as growths in the tongue and rectum, have had to be refused, and cases have been chosen in which the growth could be obtained from a situation where there was neither ulceration of the skin nor exposure to a septic mucous surface. In two cases abscesses have formed although the ulcerated part was excluded from the injection mass; this also happened in two other cases and in all four the disease continued to progress. The local condition rapidly recovered when the contents of the abscesses were evacuated.

Cases Treated.

Details of 12 patients treated before July, 1921, are appended.

CASE 1.—A. G., female, aged 43, was admitted to hospital in March, 1920, for a large inoperable carcinoma of the left breast of one year's duration. Nine tubes of radium were inserted (436 mg.). In June the growth was movable but slightly ulcerated. It was removed locally; the tissues were minced and exposed to radiation and 10 c.cm. were then inserted into a pocket in the abdominal wall. This was retained for a week but then discharged septic. In this case it was known from the specimen removed that growth cells must have been left behind on the chest wall. For six months there was no recurrence, then nodules of growth began to appear and grew very slowly. Before the operation patient had complained of shortness of breath, this gradually got worse and she died in October, 1921.

CASE 2.—E. R., male, aged 57, was admitted suffering from a large sarcoma of the neck, first noticed in June, 1919. An operation had been done in December for removal of the growth, which recurred in March, 1920. On admission there was a large projecting mass on the left side of the neck extending from the margin of the jaw to the clavicle. The skin was red, but not ulcerated. In June, 1920, part of the growth was removed; it was minced and exposed to radiation and 8 c.cms. were then inserted into a pocket in the abdominal wall. This tissue was completely absorbed. The primary growth continued to progress slowly, the skin ulcerated, and hæmorrhages from the wound began to occur. The patient died in October, 1920; no post-mortem examination was held.

CASE 3.—A. T., male, aged 29, had a sarcoma of the right testis removed in July, 1918, and in September a laparotomy was performed for a swelling in the abdomen. He was found to have a localised mass of growth in the mesentery; this was considered inoperable, and the abdomen was closed. In December, 1920, laparotomy was again performed, and the growth, which was now the size of a cricket-ball, incised. The contents, consisting of hæmorrhagic soft tissue, were scraped out and irradiated, and 10 c.cm. returned into a pocket prepared for it in the abdominal wall; it was completely absorbed. Microscopic examination showed the growth to be a very cellular round-celled sarcoma. In January, 1921, two tubes of radium, 120 mgs., were put into the growth cavity for 14 hours. The patient remained in good health until July, 1921, when he complained of pain in the region of the stomach, and a swelling began to form. In October the abdomen was opened and a mass was found to have reformed of about the same size as before. The centre of the growth was necrotic and bloodless, the periphery being soft and very vascular. The contents were again scraped out and tissue from the vascular part irradiated; and 15 c.cms. reinserted into a pocket in the abdominal wall being well absorbed. The patient did well after operation, improved slightly in general health, and returned to his home.

CASE 4.—E. B., female, aged 56, attended the hospital in June, 1920, with a large inoperable medullary carcinoma of the left breast. In July she was treated by exposure to the gamma rays from 5 g. of radium bromide. As a result the growth was reduced in size and became more movable. In November, 1920, she was admitted, the growth then being fixed to the chest wall and the skin much involved; there were hard fixed glands in the left axilla and supra-clavicular triangles. The growth was excised locally, the tissue minced, irradiated, and 8 c.cms. inserted into a pocket in the abdominal wall. This material became septic and an abscess had to be opened. The growth continued to progress and multiple recurrences were found on the chest wall in December; patient died in July, 1921.

CASE 5.—M. G., female, aged 66, first noticed a lump in the left breast in October, 1920. In November she was admitted to the hospital; the breast was elevated, the nipple much retracted, and a hard mass was to be felt in the upper and outer quadrant. The skin was not ulcerated. The patient was very obese and no enlarged glands could be detected. In November the left breast was removed, the pectoral muscles being left and the axillary glands not touched. The specimen contained a mass of carcinoma measuring about 5 by 4 cms. and was microscopically a spheroidal-celled carcinoma. The growth was minced, and after irradiation 10 c.cms. were returned into an abdominal pocket. The material was retained and absorbed. In January, 1922, this patient was in good health and no recurrence could be detected.

CASE 6.—S. H., female, aged 53, had the left breast removed for malignant disease in June, 1920. The growth recurred in August in the operation area; patient was admitted in January, 1921, with extensive recurrence on the chest wall, also in the left axilla and supra-clavicular triangle. In January two nodules of recurrence were removed, the growth tissue was minced, and after it had been exposed to radiation, 12 c.cms. were inserted into two abdominal pockets. This was entirely absorbed. Patient complained of slight cough at the time of this operation, but no signs of visceral growth were detected. The cough increased, and in March, 1921, signs of secondary involvement in the lungs were evident. She died in April, 1921, with the multiple visceral metastases. The site of the injected material could hardly be detected at the post-mortem examination.

CASE 7.—E. L., female, aged 63, in November, 1920, a lump was noticed in the right breast; she was admitted to hospital in January, 1921, with a hard mass in the lower and outer quadrant, the skin being adherent and slightly red but not ulcerated; the mass was not adherent to the pectoral fascia. The axillary glands were enlarged. In January, 1921, the breast was removed by a local operation, the pectoral

muscle being left, and the axilla not touched. 10 c.cms. of minced growth, after irradiation, were inserted into two pockets in the abdominal wall. This was completely absorbed. On microscopic examination this growth was a spheroidal-celled carcinoma. In January, 1922, this patient was in good health and no recurrence could be detected.

CASE 8.—L. E., female, aged 58, noticed a lump in her left breast in June, 1920, and was admitted into hospital in January, 1921, with a tumour in the lower and outer quadrant of the breast. It was adherent to the skin but not to the pectoral fascia. There were numerous hard enlarged glands in the left axilla, but none to be detected in the supra-clavicular triangle. In January, 1921, the breast and axillary glands were removed together with part of the pectoral muscle, the glands were found to be extensively involved. The tumour tissue was minced and exposed to radiation, and 8 c.cms. returned into a pocket in the abdominal wall. This was retained for 11 days and remained sterile. On microscopic examination the growth was a spheroidal-celled carcinoma. In January, 1922, this patient was in good health and no recurrence was detectable.

CASE 9.—F. H., female, aged 58, had the right breast removed for carcinoma in July, 1918. The growth recurred in January, 1919; radium tubes were inserted and the growth was excised a week later. In October, 1920, it again recurred in the sub-clavicular glands, and patient was admitted to hospital with a large fixed mass below the right clavicle and much œdema of the arm. In February, 1921, part of this growth was removed, and five tubes of radium (268 mgs.) were inserted for 14 hours. The tumour tissue was exposed to radiation and then returned into a pocket in the abdominal wall. Both wounds became infected with streptococci. The growth has continued to progress slowly. In March more radium tubes were inserted (324 mgs. for 12 hours). Much fibrous tissue contraction has since occurred around the site of the growth, and has blocked the lymphatic supply of the right arm. Patient retains her general health, but suffers great pain from the œdema.

CASE 10.—E. C., female, aged 54, first noticed a lump on the front of her chest on the right side in March, 1919. She was admitted to hospital with a mass measuring 5 cms. by 3 cms. over the right third interchondral space. There was no ulceration, but the growth was slightly attached to the skin and deeper parts. There were small hard glands to be felt in the right axilla and supra-clavicular triangle. On March 11th, 1921, the growth was excised locally, the remainder of the breast and glands being left untouched. The tumour was exposed to radiation and 8 c.cms. inserted into two pockets in the abdominal wall; there was no temperature reaction and the material was retained. In July patient was given a course of X ray treatment to the site of the primary growth. On microscopic examination this was found to be a spheroidal-celled carcinoma. In January, 1922, this patient was in good health and no recurrence could be detected.

CASE 11.—R. C., female, aged 42, she first noticed discharge and bleeding from the right nipple in November, 1919; a lump was found in the breast in September, 1920, and slowly increased in size. She was admitted into hospital in May, 1921, with a hard diffuse mass in the upper and outer quadrant of the right breast, measuring 7 by 4 cms. The nipple was enlarged to twice its normal size; the skin was not ulcerated; enlarged glands could be felt in both axillæ. On May 10th, 1921, the breast and glands in the right axilla were removed, the pectoral muscle being left. The tumour was exposed to radiation and 12 c.cms. inserted into two pockets in the abdominal wall. There was no temperature reaction, and the material was retained for ten days. On microscopic examination this growth was found to be a duct carcinoma; the glands were not infected. In January, 1922, this patient was in good health and no recurrence could be detected.

CASE 12.—E. R., female, aged 39, in March, 1919, a swelling began to form in the right thigh. It was removed in June; in April, 1920, it recurred, and patient was admitted into hospital. In September nine radium tubes (436 mgs.) were inserted into the growth, and in October it was again removed. In June, 1921, patient was readmitted, the mass having grown much larger in the meanwhile. Tissues from the growth were removed, exposed to radiation, and 14 c.cms. re-inserted into two pockets in the abdominal wall. This was completely absorbed. On microscopic examination the growth was a round-celled sarcoma. The patient was then about seven months pregnant; she went to her home in the country nine weeks after operation. Cæsarean section was performed later, and patient was reported to have died in October, 1921.

Remarks.

It will be seen that in some of the cases the disease was very advanced, and that in two. there were probably visceral metastases at the time of treatment. There are five patients with carcinoma of the breast diagnosed by microscopic examination, and treated between November, 1920, and June, 1921. In all these a limited operation was performed, the primary growth only being removed and the axillary glands left, except in Case 11. When last seen (in January, 1922) these patients were all in good health, without evidence of recurrence.

In reviewing these results it must be borne in mind that in almost all the cases the stage of the disease rendered any other form of treatment inadvisable. In view of the results of some of the more recent cases it may be possible to improve upon them by adopting the treatment earlier, when dissemination of the disease has not yet occurred.

References.

1. Wedd, Morson, and Russ: Journal of Pathology and Bacteriology, vol. xviii., 1914.
2. Medical Research Council, First Radium Report (in the Press).
3. Mottram and Russ: Proc. Roy. Soc., B, vol. xc., 1917.

THE X RAY DIAGNOSIS OF GASTRIC ULCER.[1]

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IT may be granted at once that the X ray method of examination is one, and only one, link in the chain of diagnosis, but it is often the all-important link which may be sufficient to give an absolutely positive diagnosis. The Americans always talk of an X ray laboratory, and this is correct, for it is a laboratory method that we use. The results of laboratory work depend on three factors—the personal, the equipment, and the routine method, all of which are essential if the reports from the laboratory are to be reliable.

The Human Factor.—Just as in clinical abdominal work, the larger the experience the fewer mistakes will there be. For the last 16 years we have been groping our way, and gradually the various schools of thought and practice, which have differed very widely, are coming together, and the most effective work I know is obtained by a combination of screen examination to which routine radiography is accessory. In nearly all cases the diagnosis is made from the screen and checked up by plates, but it is the experience of the man who does the screen work that makes the method effective, and particularly his knowledge and skill in palpation of the patient in the upright posture.

Apparatus.—This must be efficient—to attempt abdominal diagnosis with anything less than the best is fatal. The combination of the high-tension transformer and Coolidge tube is the best generating plant there is, but there is one drawback: although necessity makes us use the Coolidge tube we all fear it, for the problems of protection are not yet satisfactorily solved so far as the observer is concerned. The chief difficulty is that visualised palpation is essential for effective work, and, of necessity, the observer is directly in front of the tube, sheltered as far as possible by the diaphragm of the tube box, the patient's body, the lead glass of the fluorescent screen, and protective aprons. I have no use whatever for the perfectly protected screening stand that does not allow of free access to the abdomen, holding that, without palpation, only the obvious cases will be diagnosed.

I cannot refrain from one reference with regard to the X ray laboratory that is outside the scope of my present subject. Screening with palpation is trying both physically and mentally. The conditions under which this work is carried out in this country are often little short of criminal. Already there have been tragic accidents, and many of the workers are in

[1] A contribution to a discussion at the Section of Medicine of the Royal Society of Medicine on Jan. 24th, 1922.