ADENO-PAPILLOMA OF THE RECTUM.

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THE patient in the following case, a woman aged 53, had haemorrhage from the rectum four years, and received palliative treatment of some kind, off and on, during that period. On December 12th, 1900, she had profuse haemorrhage with a protrusion, and called in Dr. Swanson of Liverpool, who found a condition suggestive of piles, but on reducing the protrusion found it to be something unusual. He called me in next day, and I found what appeared also to me to be haemorrhoids, though somewhat warty. But as an operation was arranged for the following day, I did not disturb the parts in which bleeding had only recently ceased.

Operation.—On dilating the anus a large polypus of a warty nature became manifest on the anterior rectal wall, having a long narrow neck. This was held in Doyen's broad-ligament clamp, cut off, and the stump sewn with sulpho-chromic catgut, passed through and through with a needle at each end, tied and knotted after each passage. The points of suture were numerous, deep, and close together. In this way, on releasing

Photo of specimen lying in a basin in spirit, May, 1911, by Fred. Halliday, museum attendant, University of Liverpool.

the clamp no bleeding occurred, and the operation was finished. It was clear that, although the pedicle was narrow when held in the clamp and when the polypus hung down, the wound would have gaped widely and bled freely if it had not been very thoroughly sutured, and would have been difficult to seize again had haemorrhage not been completely controlled, owing to the great elasticity of the bowel walls. Complete success resulted.

Remarks.—The papillary growth has an adenoid structure with columnar epithelium. The specimen has been in the museum ever since, spread out unaltered, as shown in the photo. It measures $3\frac{1}{4}$ in. by 3 in.

Attention may be drawn to the ingenious practice our museum attendant adopts of photographing some specimens under water or other colourless clear liquid, whereby inconvenient contrasts of light and shade are avoided. As previous examples, see BRITISH MEDICAL JOURNAL, June 6th, 1908, p. 1351; April 17th, 1909, p. 947. In contrast, see May 16th, 1908, p. 1173, where the specimen, from a galactocoele, had to be photographed in air. The most important part—a coil of milky paste—came out perfectly, but the cyst wall and separate contents were necessarily blurred by exaggerated lights and shades.

A DETACHMENT of the Salvation Army which has been at work in the Dutch East Indies for some ten or fifteen years is to have placed in its charge a colony for lepers, about to be established on an island not far from the capital of Sumatra. Its labours in this connexion will not be altogether a new departure, as for the past three years it has been in charge of a leper hospital at Pelantoengan, which is maintained by the Dutch Government, and accommodates 160 patients. The number of lepers in Java alone is estimated to be as many as 12,000.

SURGICAL INTERFERENCE IN CANCER.

(AN EXPERIMENTAL STUDY.)

BY

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It has long been the experience of surgeons that there are certain cases of malignant disease, mostly of a chronic and slowly growing form, which, after operation, flare up, recur rapidly, spread quickly, and soon end the patient's life. The explanation usually offered is that the operation has been incomplete; some of the cells of the cancer have been set free at the operation and have grown and disseminated rapidly. Their local growth has been aided by the removal of the pressure which the tumour has exerted on the surrounding parts. The rapid dissemination and formation of metastases is explained by the opening up of lymph spaces at the operation and the extensive formation of young capillaries which occurs during the healing of the wound.

The chief phenomenon in these cases is the rapidity of the recurrence and its increased malignancy—that is, increased rate of growth. Why should such fragments as have escaped the surgeon grow more rapidly than did the original tumour? It is highly improbable that in every case the operation has been undertaken at the very moment when the neoplasm was going to acquire greater virulence, and the disease was going to flare up of its own accord. The cancer cells are looked upon too much in the light of independent units which have broken away from the control of the organism as a whole. The reaction of the surrounding tissues and of the body in general is taken too little into consideration.

Is the removal of the pressure of the neoplasm and the consequent diminution of the tissue tension a sufficient explanation of the increased malignancy of the recurrence? When this pressure is removed the cancer cells that remain can grow rapidly, at any rate till they have filled up all the available space, and by the increase in their bulk have brought the tension back to what it was originally. But a carcinoma, especially if chronic and of slow growth, is never under very great tension, since if it were necrosis *en masse* and sloughing would be frequent. The edges of every carcinoma are composed of healthy cells, which send out irregular processes, often extending a great distance, into all the available spaces of the surrounding tissues. If the pressure were great we should expect the edge of the neoplasm to consist of a mass of tightly packed flattened cells in all stages of degeneration. Its outline as a whole would be roughly spherical, and the surrounding tissues would show signs of compression. Again, after the operation the wound is usually carefully closed; in many cases even the skin has to be extensively "undercut" to enable its edges to be brought into apposition. Large spaces are therefore rarely left, and such spaces as do remain are very soon filled up with exudate and granulation tissue, which brings the tension back very rapidly to its original point, if, indeed, it does not exceed it.

We, therefore, do not think that the increased malignancy of the recurrence occasionally seen in surgical practice can be explained either on the hypothesis of diminished tissue tension or on that of the operation having been undertaken at the moment when the disease would have flared up had it been left untouched. We cannot agree with Bashford's¹ statement as to "the baseless nature of the opinion that surgical interference causes a tumour to become more malignant or necessarily to disseminate," since we have not infrequently observed identical phenomena during the course of our experiments on the transplantation of cancer in mice. We have therefore analysed our material and collected it (in the form of this paper) in the hope that we may be able to throw some light on the subject.

It is necessary here to give a definition of what we mean by the terms "virulence" or "malignancy." When we say that the virulence of a tumour has increased, we mean that its rate of growth in a given time has become more rapid. On comparing the size that a new growth has attained in a given number of weeks with that of its local

*This work was carried out in the Research Laboratories of University College Hospital Medical School.

recurrence in the same number of weeks, and finding the latter to be greater, it does not necessarily follow that its virulence has increased, since it may have grown from a much larger fragment than did the original tumour. On finding, however, that from week to week its bulk has increased more rapidly than did that of the parent neoplasm, it follows that the recurrence has become more virulent.

The rate of growth of any given carcinoma must depend on two main factors—the rate of growth characteristic of its component cells and the susceptibility of the individual affected. It is found in practice that, if a number of mice be inoculated with a given cancer, a certain proportion will develop tumours which on the whole will grow uniformly until they eventually destroy the animal. There are, of course, variations in the rate of growth in individual mice of the same series, but these, as a rule, are not so great that it is not easy to establish a mean, and to be able to state that the tumour is a slowly or a rapidly growing one. Other mice will develop tumours which will grow to a certain size and then decrease, and eventually disappear. Other mice, again, will not develop a tumour at all. In the great majority of all experiments a certain percentage of the mice inoculated are immune to the cancer. The graft which has been introduced is unable to grow owing to some adverse factors in the constitution of the mouse.

The percentage of successes in a given experiment depends, therefore, on the balance of these two factors—the rate of growth of the cells of the carcinoma and the susceptibility of the individual. Every carcinoma has a certain mean potentiality of growth; its cells proliferate at a certain rate (as compared with another carcinoma). Whether it finds a suitable soil will depend on the way the individual reacts, and whether the blood supply is adequate to the demands of its cells.

Among those tumours which succeeded in growing, besides those which after a time are spontaneously absorbed, there are a certain number which show a tendency to diminish in size or even disappear for a time and then to grow again. In many experiments it is found that this "negative phase" in the growth, as shown by the Imperial Cancer Research Fund, coincides in time in the whole series, and that during its incidence the greatest number of spontaneous absorptions and cures occur. Transplantations carried out during this negative phase usually give but a small percentage of successes.

For a graft to be able to grow it is, of course, necessary that its cells should become connected with the blood vessels of its host. This is found to be the case. Once a tumour has reached a fair size one or more large blood vessels are found running to it from the nearest big artery. These vessels increase in number and size with the growth of the tumour, so that the latter is always well supplied with blood. Bowen² has shown that complete occlusion of the blood supply results in necrosis of the tumour and cure; partial occlusion may prove successful in cases in which there is a tendency to spontaneous cure. He also points out that complete obliteration is impossible if there is infiltration of neighbouring structures with cancer cells.

It is usual to talk of the cancer or its graft as "establishing" its blood supply. This term is an unfortunate one, as it produces the idea that the cancer cells exert some influence on the host by means of which his blood vessels are, so to speak, compelled to send off branches for their maintenance. What really happens is essentially the same as what occurs when any foreign body lodges in any animal's tissues, and is merely an expression of the reaction of the animal to such a foreign body. If a needle is embedded under the skin, granulation tissue rich in capillaries is formed around it, whose phagocytes attempt to remove the needle. When they fail to do this, the latter becomes encapsuled by fibrous tissue, which is the next best means of removing it as far as possible from the economy of the host. The same process occurs when a graft from a cancer is introduced, the only difference being that its cells are living. Leucocytes appear around the graft and granulation tissue springs up, with the purpose of destroying its cells. These cells, however, being alive, possess the property not only of resisting the defensive mechanism of the host, but of turning his blood supply to their own use, in very much the same way as do

numerous parasitic micro-organisms. Once they come in contact with the capillaries of the granulation tissue, they are able to utilize them, and as they multiply so will the capillaries. The cells of the graft are merely able to utilize the blood vessels of the host, once they have reached them, but not to attract them. Were it possible for the host not to react in any way, the graft would inevitably perish.

If we admit the improbability of the assumption that in every case in which removal of a tumour is followed by a rapid recurrence the operation has been undertaken at the moment when the disease was going to flare up spontaneously—when, in other words, a negative phase was just over—there is only one possible explanation of this phenomenon. This is that the surgeon has so altered the part that such pieces of cancer as have been left behind are now able to grow under more favourable conditions. We hope to be able to show from our experiments that a tumour of a slowly-growing series often recurs rapidly after operation, that such rapid recurrence may even take place during a negative phase, and that the transplantations from the operated tumour (which has recurred rapidly) into healthy mice do not show an increased rate of growth in any way proportionate to that of the recurrence.

The surgeon can, by operating on a tumour, render the conditions of growth of such cells as have remained behind more favourable in several ways. One of these is by diminishing the tissue tension. We have already given our reasons for thinking that this is not an adequate explanation. The others are by removing such barriers of old fibrous tissue as may have been formed around the neoplasm, and by increasing the blood supply to such of its cells as he has been unable to remove.

Every chronic carcinoma is surrounded by a layer of more or less dense fibrous tissue. Even at the spots where the growth is spreading there is usually time for such a barrier to be formed by the surrounding tissues. On removing the tumour as widely as possible, well beyond its visible limits, it is inevitable that this capsule be removed as well, and a raw surface substituted. If the edges of the wound are brought well into apposition, the raw surfaces stick together (by means of the exudate which is poured out). This exudate soon becomes organized; young granulation tissue is substituted for the old fibrous tissue, and any cancer cells that remain are easily able to grow in this. In so far as this removal of the firm fibrous tissue diminishes the resistance to the growth of the cancer we are prepared to allow the influence of tissue tension, but think that we are dealing with an alteration in the nature of the soil rather than with one of the pressure.

We have already said that every tumour is usually well supplied with blood. If the skin of a mouse which has been inoculated with cancer in the groin and has developed a tumour in the subcutaneous tissue of the side be reflected, large blood vessels are seen running to it from the axilla, the inguinal region, or from both sources, depending on the situation and size of the tumour. If two independent tumours have developed, as is not infrequently the case, it is usual for the anterior to be supplied from the axilla, and the posterior from the groin. Both may, however, receive their blood supply from the same source. Vessels are generally seen between the two tumours, so that a free anastomosis takes place. Before entering the growth the vessels, as a rule, break up into one or more main branches. They are large, and may even attain the size of the trunk from which they spring. A large amount of blood is, therefore, continually being brought to the tumour, which, in spite of the fact that there is usually a considerable amount of central necrosis, is adequate for its nutrition and enables its cells to proliferate.

What happens when the surgeon removes the main mass of the tumour but leaves some small fragments behind? The result will be different if such fragments are left in organic connexion—that is, if they remain surrounded by connective tissue and with intact blood supply, or if they consist of cells left loose in the wound. In the former case, although the main vessels going to the tumour have been ligatured, those supplying the fragment will promptly dilate, a collateral circulation will be established, and a much larger amount of blood will be available for its nutrition than before. This

increased blood supply will be permanent, and, as the cells proliferate rapidly in response to it, will become yet greater. The cells will be able to grow readily in the young granulation tissue which has been formed as a result of the operation. This granulation tissue contains a large amount of capillaries, so that the growing cells of the cancer are, for some considerable time at least, under the most favourable conditions as regards their blood supply. In this case we should expect an early and rapid recurrence with an increased rate of growth—that is, malignancy.

Should all the outlying processes of the cancer have been successfully removed, but one or more fragments have been left loose in the wound, such fragments will be under less favourable conditions than in the case we have discussed above, since they will have been cut off from their blood supply. They will have to become reconnected with the surrounding tissues and to be revascularized in order to be able to gain sufficient nourishment for continual growth. Before this can happen many will perish. The survivors, therefore, require some time before they can grow to a size which can be appreciated as a definite recurrence. This time corresponds to the "latent period" in inoculation experiments. It usually takes about ten days for the grafts to grow to an appreciable size in mice, but may take much longer. In one of our cases, that of a very slowly growing papillary mammary tumour of the mouse (which died out in the third generation), one of the grafts of the second generation did not appear for thirteen weeks. As three weeks in the life of a mouse correspond to a year in a man's life, it will be seen that we are dealing with a period of time of considerable length. When the recurrence has definitely appeared, its behaviour will be mainly influenced by its blood supply. Should its vascular connexions have been made early, while the surrounding tissues were still undergoing the process of repair, and there was, in consequence, a large amount of granulation tissue present, we would expect its rate of growth to be rapid. Should, however, its supply have been inadequate until after the granulation tissue had been converted into relatively avascular connective tissue, its rate of growth will be slower.

Cells left loose in the wound are under another disadvantage compared to those that have remained in organic connexion. The latter, being processes of the cancer more or less remote from its main body, will be actively growing young cells, since a cancer grows from its periphery. The former will consist, in part at least, of cells from the centre of the growth. Especially is this so in advanced tumours in which the tissues readily break down during the operation.* As all cells have an age limit, at the end of which they die and towards the close of which they become old and their activities diminish, it follows that the isolated nodules, which consist mainly of young cells, will be able to overcome any reaction from the surrounding tissues better, and to grow more rapidly than pieces of cancer composed of cells of all ages.

We will now consider what happens in our experiments on mice when there are two tumours close together on the same side of the body and one of them has been removed, the other being left with its blood vessels as little disturbed as possible. We have operated on 6 cases of this description. In one of these the tumour which was left untouched disappeared completely in fourteen days. It was small and the tumour that was removed was large and firmly adherent to the skin. Also at the time we did not pay any attention to preserving the blood vessels. It is, therefore, not unlikely that we so interfered with the blood supply as to kill the remaining nodule. In the other 5 cases the nodule increased distinctly more rapidly in size than had the original growth and than did the other tumours of the same series. This is a very important point, as, having removed the tumour, it is, of course, impossible to say what it would have done if it had not been touched. It might just have been entering on an active phase. As such an active phase is usually synchronous in all the tumours of a series, we have proof, as far as it can be adduced, that this was not so. It also goes to show that the size that the second tumour eventually attained did

not depend solely on the larger size of the nodule left behind at the operation as compared to that of the original graft from which the first tumour developed. If that were so, although the second tumour might exceed the first considerably in size in a corresponding number of weeks, yet the rate of increase from week to week should be proportionate.

This accelerated rate of growth in these cases is not as great as it is in a recurrence resulting from a piece of the excised tumour being left behind with its blood supply intact. This is owing to the fact that the blood supply in the case of two tumours is more or less independent. Again, the tumour which is left consists of cells of all ages, and not merely of actively growing young peripheral cells. These latter cannot reap the full benefit of the increase in the blood supply, and the growth will be less active than in a fragment consisting practically only of young cells.

A glance at Chart 1 will illustrate this point. What can be more striking than the greater size of the recurrence in

mouse No. 11 over that of the second tumour? This second tumour had grown in three weeks from a nodule which, at the time of the operation, measured 7×8 mm. to a size of 19×17 mm. The recurrence, which must have sprung from a very small piece which can certainly not have measured more than 1 mm. in its largest diameter, reached, in the same period, the size of 24×23 mm.

We think, therefore, that the behaviour, after operation, of two tumours in contiguity lends support to the view that the increased virulence of the recurrence is mainly due to increased blood supply. It is occasionally stated that this increase is due to the heightened general metabolism of the body called forth by the neoplasm, which, on removal of its main mass, is made use of by such portions as have remained undisturbed. That this is not so is demonstrated by the behaviour of two tumours on opposite sides of the body, whose blood supply is quite independent. In such a case, of which we had six, removal of one tumour, even if large, produces no difference in the rate of growth of the other, though this be small.

This is in accord with Bowen's experiments (loc. cit.), who found that ligation of the vessels supplying a tumour on one side of the body produced no effect on the rate of growth of a tumour on the opposite side.

It now remains for us to prove the statements we made above—that a tumour of a slowly growing series often recurs rapidly after operation; that such rapid recurrence may even take place during a negative phase; and that the transplantations from an operated tumour (which has recurred rapidly) into healthy mice do not show an increased rate of growth in any way proportionate to that of the recurrence.

A detailed table of our cases will be found on page 157. Here we intend merely to give a general analysis

* These are the cases in which the tumour is, as a rule, most firmly adherent to the surrounding structures, and in which the surgeon consequently finds the greatest difficulty in removing it completely, so as not to leave some of its processes behind in connexion with their blood supply.

of our experiments. These group themselves into five sets:

1. In which the recurrence is early (within fourteen days, the usual latent period of transplanted tumours) and virulent—that is, its rate of growth is more rapid than that of the primary tumour—11 cases.

2. In which it is early but not virulent—5 cases.

3. In which it is delayed and virulent—6 cases.

4. In which it is delayed and non-virulent—7 cases.

5. In which there has been no recurrence—19 cases.

Here we succeeded in removing the tumour completely.

The above figures show that in 11 out of 48 operations—that is, in 23 per cent.—the recurrence has been both early and virulent, its rate of growth being in some instances two or three times as rapid as that of the primary tumour or as of the tumours of the remaining mice of the series. Tables 1 and 2 contain three such cases between them.

This large percentage in mice, as compared to the relatively small number in man, depends on the relatively enormous size the tumours are allowed to attain in the former animals and on the consequent increase in the difficulty in removing them completely.

Chart 2 illustrates well the fact that such a rapid recurrence may even take place during a negative phase.

CHART 2.

Here all the tumours, except No. 12 (the one operated on) and No. 16, had diminished in size at the time of the operation. No. 16 the week after showed a diminution in size and then grew again at very much the same rate as before. The relatively enormous growth of the recurrence of No. 12 presents a striking contrast to it.

Again, compare Charts 2 and 3. Chart 3 represents the result of the transplantations made from No. 12, Chart 2, at the time of the operation. The grafts grew exceedingly badly. If we leave out of consideration the mice that died during the first few weeks, one tumour only developed permanently, and even this disappeared on the fourth charting and then reappeared. This proves as clearly as is possible that Tumour 12, when operated upon, was in the negative phase. The inoculations made from it grew even less well than did the tumours of the parent series. It also proves that transplantations from the operated tumour into healthy mice do not show an increased rate of growth proportionate to that of the recurrence.

Now compare Charts 3 and 4. Chart 4 represents the growths derived from No. 12 (Chart 2), when the mouse was killed. This chart shows a rate of growth which, for the carcinoma under consideration, is a very rapid one.

Survivors: 15, 13, 10, 6, 5, 4, 3, 1, 1, 1, 1.

CHART 3.

It might be argued that, as transplanted tumours are merely grafts, the negative phase was over. That this is not so is shown by the behaviour of the tumours on Charts 2 and 3, the rate of growth of none of which has

Survivors: 24, 16, 9, 8, 8, 8, 7, 6, 6, 6, 6.

CHART 4.

improved. We may add that the new growth we are dealing with is characterized by the fact that its descendants frequently disappear for a time to reappear (cf. Chart 3, No. 1), so that, should the negative phase have been over, we would have expected one or more of the

TABLE OF EXPERIMENTS.
1. *Recurrence Early and Virulent.*

1. Index No. of Mouse.	2. Age of Tumour (in Weeks) at Time of Operation.	3. Size of Tumour at Time of Operation.	4. Latent Period (in Days) of Recurrence.	5. Size of Recurrence after Latent Period.	6. Size of Recurrence at End of Experiment.	7. Average Size of Remaining Tumours of Same Series at Time of 6.	8. Average Size of Transplantations at Time of 6.
		mm.		mm.	mm. Weeks.	mm.	mm.
No. 7	18	22 × 19	14	10 × 2	30 × 16 ... 6	Absorbed	24 × 12
No. 12	4	15 × 13	14	26 × 11	36 × 16 ... 3	13 × 8	6 × 4
No. 9	10	24 × 18	14	26 × 8	33 × 15 ... 3	Absorbed	15 × 9
No. 1	4	25 × 17	7	19 × 8	31 × 16 ... 3	19 × 14	9 × 3
No. 21	9	25 × 16	13	16 × 7	27 × 15 ... 3	15 × 11	3 × 2
No. 6	22	23 × 17	14	25 × 8	32 × 26 ... 5	None	21 × 13
No. 3, 2nd op.	8 (from 1st op.)	32 × 22	14	18 × 9	30 × 22 ... 6	29 × 18	14 × 7
No. 7	13	30 × 18	13	{ 32 × 8 7 × 8 }	{ 35 × 20 7 × 6 } ... 3	Absorbed	None
No. 28	5	20 × 12	12	16 × 8	32 × 20 ... 5	22 × 15	14 × 7
No. 6	6	21 × 12	14	14 × 12	25 × 31 ... 4	11 × 9	13 × 8
No. 11	3	10 × 7	14	25 × 15	25 × 26 ... 3	13 × 7	11 × 5
2. <i>Recurrence Early but Not Virulent.</i>							
No. 16	32	21 × 31	7	8 × 6	14 × 7 ... 4	3 × 2	None.
No. 13	26	40 × 30	14	19 × 7	Absorbed 13	None	Not transplanted.
No. 3	11	22 × 20	14	5 × 3	25 × 20 ... 18	None	17 × 13
No. 6	4	22 × 12	5	2 × 2	16 × 11 ... 3	17 × 10	4 × 3
No. 1	7	48 × 29	14	{ 8 × 5 15 × 8 }	{ 8 × 8 17 × 9 } ... 4	5 × 4	8 × 3
3. <i>Recurrence Delayed but Virulent.</i>							
No. 2	9	26 × 18	21	12 × 8	34 × 20 ... 5	None	25 × 16
—	?	23 × 16	35	4 × 4	36 × 22 ... 10	—	11 × 5
No. 2	18	26 × 12	27	15 × 9	31 × 23 ... 8	None	7 × 4
No. 21	18	30 × 26	20	5 × 3	37 × 20 ... 7	None	15 × 10
No. 7	15	18 × 13	22	10 × 5	22 × 15 ... 7	None	16 × 10
No. 1	10	25 × 12	21	10 × 11	33 × 19 ... 5	26 × 15	Not transplanted.
4. <i>Recurrence Delayed and Not Virulent.</i>							
No. 1	14	33 × 33	37	4 × 2	4 × 3 ... 7	None	7 × 4
No. 9	35	26 × 14	21	5 × 6	6 × 7 ... 5	None	8 × 6
No. 3	6	25 × 18	35	6 × 4	18 × 13 ... 8	None	6 × 3
No. 12	28	24 × 26	17	3 × 4	12 × 12 ... 6	None	10 × 8
No. 36	10	32 × 27	49	22 × 9	27 × 18 ... 11	None	17 × 8
No. 13	16	18 × 20	18	9 × 4	17 × 22 ... 10	8 × 4	None
No. 3	10	18 × 12	35	16 × 6	20 × 9 ... 8	None	10 × 5

tumours in Tables 2 or 3 to have reappeared. Chart 4 demonstrates that, although the tumour as a whole was still in the negative phase, its cells, which had been stimulated to a rapid growth by the operation, went on growing rapidly, even after transplantation.

Stress has been laid above on the rate of growth when the virulence of a tumour has been considered in such mice in whom the graft has "taken," and not on the percentage of "takes" in the whole number inoculated, since this percentage depends in a very great measure on the susceptibility of the individual mice.

Hitherto we have said nothing about dissemination, since we have but rarely met with metastases, visible to the naked eye, in mice. If we may judge from our spontaneous tumours, in which we have frequently seen microscopic secondary emboli in the lungs, we would say that such microscopic metastases are probably far from uncommon. To have, however, thoroughly examined under the microscope the lungs and other viscera of every mouse with an inoculated tumour would have entailed an amount of labour which we considered to be unjustifiable. But, even if it is allowed that metastatic emboli are not rare in mice, their frequency is considerably less than that of secondary deposits in man. This appears to be mainly due to the laxity of the subcutaneous tissue of the mouse, into which all our grafts have been transplanted. The tumours are here able to expand in all directions (grafts in mice usually assume a spherical or oval form); cells are therefore not so likely to be separated off. In man, on the

other hand, the subcutaneous tissues are more rigid. The growth, therefore, cannot expand freely in all directions. Offshoots grow out into any available spaces, and these often penetrate lymph or blood capillaries, and are then carried away to distant parts. What applies to the subcutaneous tissue of man applies even with greater force to a neoplasm arising in a solid tissue or viscus. We need but mention the scarcity of secondary deposits in epitheliomata of the skin.

There is not much to be said about the microscopic appearance of the tumours employed, which, with one exception, are all mammary carcinomata. This exception is a squamous-celled carcinoma (32), kindly given to us by Dr. Bashford. Among the others there are two haemorrhagic tumours, one of which has a papillary, the other an alveolar structure; a very cellular alveolar carcinoma with a great tendency to necrosis; and two acinous cubical-celled carcinomata, one of which contains areas of keratinizing squamous epithelium. We have never observed a change in type between the parent tumour and its recurrence. If the recurrence grew more rapidly, it showed a larger amount of proliferation of its cells, which were consequently more closely packed together and more subject to necrosis.

We have now passed in review all our available evidence, and hope that we have been able to show experimentally that incomplete removal of a carcinoma is often followed by a rapid recurrence of greater virulence than that of the original tumour, and that this increase in the virulence is

mainly due to the remaining fragments having a very rich blood supply. It merely remains for us to say a few words on the technique employed at our operations and to give a table of our experiments (see p. 157).

Technique.

Ether has always been used as an anaesthetic. Mice stand it well, and usually run about their cage in a normal manner within an hour of its being stopped. The operations were performed under the strictest aseptic precautions. After sterilizing the skin an incision was made whose length depended on the size of the tumour, well in front of it. On reflecting the skin the tumour, unless it has infiltrated the muscles, adheres to its deep surface. After ligaturing the blood vessels the tumour is removed, together with an elliptical flap of skin to which it adheres. By varying the size of this flap we can remove as widely as is necessary. In such cases in which the operation was purposely made an incomplete one, we cut and shelled the tumour of the skin, and were thus able to leave pieces of it behind in connexion with their blood supply. The wound was closed with silk. No dressings were applied. Primary union resulted in all our cases in which there was no recurrence in the scar itself. Except in one or two of our earliest experiments we have never had any signs of sepsis.

REFERENCES.

¹ Bashford, Third Scientific Report of the Imperial Cancer Research Fund, 1908, p. xv. ² Bowen, loc. cit., pp. 146-158.

ON THE INFLUENCE OF CALCAREOUS DRINKING WATER IN HEALTH AND DISEASE.*

By PERCY G. LEWIS, M.D.,

FOLKESTONE.

In estimating the various influences which combine to make up the elements of any particular climate, it is reasonable to suppose that the drinking water of a locality may be a matter of considerable moment, and the subject of our discussion to-day is "hard water" wherever it may be found. But the water which most particularly concerns us is that which owes its hardness to the presence of chalk in solution.

The question, then, arises, Is any importance to be attached to that fact, and if so, what, and how much?

Now it does not necessarily follow that opinions held by the public, even if they are ever so widely maintained, are correct. Far from it. But we have to recognise the fact that there are many notions held by the public, notions almost amounting to "fixed ideas," which receive a certain amount of medical support. And it is for us to inquire how far these notions are justified, and what foundations in fact they possess.

The majority of persons are profoundly influenced by climatic conditions. The question is, then, Is the drinking of calcareous water one of them?

A large number of different diseases have been attributed to the influence of chalky drinking water, but those more usually alleged are gout, rheumatism, calculus, constipation, biliousness, dyspepsia, eczema, goitre, and arterio-sclerosis. Let us consider and examine the evidence which can be brought forward to establish the reality of these baneful influences.

IN FAVOUR OF BANEFUL INFLUENCES.

1. First of all there is the undoubted fact that many persons when coming to visit or reside at the towns on the south-east coast do suffer, at any rate at first, from some of the different conditions mentioned, though it remains to be proved that the hard drinking water, rather than other causes, is the reason of this. We shall return to this point later on.

2. Though a number of medical men hold views similar to those of the public, it is difficult to discover how many have spoken with authority on the subject, or how much reason they have given for the faith that is in them, still less have they described the *modus operandi*. From a discussion held by this section in 1907 on the "Influence of Climate in Gout, Rheumatism and Rheumatoid Arthritis," there followed as a main result of the deliberations the opinion that climate had a good deal more to do with the production of these diseases than water. There was a general agreement that warmth, even temperature,

dryness, free ventilation of the district, house construction, the character and habits of the people, were all important matters. Dr. Buckley, who opened the discussion, suspected that the functional disorders of the liver common with people on first coming to the seaside might be the precursor of gout, etc. But these effects are acknowledged to be but temporary. Dr. Buckley, however, said that he was convinced that places where the water was hard and chalky were unfavourable to gout. He apparently based his opinion on the number of patients who go to Buxton for treatment from Folkestone and the neighbouring resorts. There is, however, quite a different explanation than the drinking water of the gout from which these persons suffer.

(a) In the first place, most of these people are not natives of the seaside towns at all, but come to live in them on retirement from more active work. In all probability they acquired their gout long before taking up their residence here, and they, as a rule, probably drink very little, or none, of the local water supply in an un-boiled condition, partaking usually of the aerated or bottled waters at their meals. Moreover, they unfortunately persist in the habits and diets which gave them their gout in the first instance, and which may be expected to bring forth more and more frequent exhibitions of their malady as life advances. Dr. Buckley would find very few, if any, of his patients who were total abstainers, or who imbibed as much as a pint daily of calcareous water.

(b) Sir Hermann Weber, in his *Climatology and Balneology*, says:

It has been suggested that hard drinking water accounts for some of the indigestion and biliousness in visitors to health resorts on the chalk downs of the south coast of England.

He goes on to say that:

There is some evidence that the administration of calcium carbonate (and chalky mineral waters) tends to diminish the amount of uric acid excreted in the urine, and perhaps in some way to lessen its production.

Again he says:

Chalk does not appear in any way to increase the size of urinary concretions. Contrexéville water, which is harder than Bath water, owes most of its repute to its diuretic action.

And:

It is possible the internal employment of calcareous waters might be useful in some cases of chronic and recurrent urticaria, chronic headache, etc.—conditions which are associated with deficient coagulability of the blood.

(c) Nor, if we turn to other authorities, do we find them any more definite. Rumph, for example, states that when much lime is taken with the food some of it remains stored up in the body, and may increase the tendency of calcareous deposits in the cardio-vascular system of old people. Rumph evidently considers this a disadvantage, but on the other hand, if we refer to Sir Clifford Allbutt, we find him of opinion that hard drinking water plays no important part in the causation of arterio-sclerosis. Sir Clifford Allbutt merely regards calcification as a secondary event which does not enter into the process until the lesion is otherwise established. Then, he says, calcification may be some protection to a decaying vessel. In any case, if the degenerative process wants lime, there is plenty to be had both in the body and in the food without calling on the chalk in the water.

(d) The Commission which was appointed by the Home Department in 1851, to investigate the quality of water available for the supply of London, after taking evidence from a large number of medical men and chemists, reported amongst other conclusions as follows:

The only observations from which an interference of the lime in water in deranging the process of digestion and assimilation in susceptible constitutions has been conjecturally inferred, have been made upon water containing much sulphate of lime and magnesia, as the Brighton shallow well water or the hard selenitic water of the new red sandstone, and have no force when applied to the Thames and its kindred waters, as the earths exist in these principally in the form of carbonates.

The objections, then, do not apply to chalky water.

(e) If we turn to books on *materia medica*, we learn that lime salts given in medicinal doses only enter the circulation in very small quantities, and appear in the blood as phosphates. If merely a little enters in this way, how very small a proportion is presumably absorbed from drinking water! Is there any reason for considering it as otherwise than as a negligible quantity? Is there any

* A paper read before a provincial meeting, at Folkestone, of the Section of Balneology and Climatology of the Royal Society of Medicine.