THE PART PLAYED BY INJURY AND REPAIR IN THE DEVELOPMENT OF CANCER;

WITH REMARKS ON THE GROWTH OF EXPERIMENTAL CANCERS.*

BY

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CAN we demonstrate experimentally the reason for the very localized starting-point of a tumour, although a great number of epithelial cells had been in contact during days and weeks with the cancer-producing agent (tar in the case of the experimental tar cancer)?

Mice were tarred in the usual manner till some of the animals showed early papillomata. Under the microscope these tumours proved to be very localized epithelial hypertrophies. We know that in this stage of the experiment the skin of the mouse tends to form numerous tumours in a very short time when tarring is continued, but that if tarring is stopped at this stage only a very small number of tumours will appear. The tarring was stopped at this stage of the experiment and a few days afterwards incisions were made in the skin, care being taken to make them in places where no papillomata had appeared. These wounds very soon assumed an oval shape and healed in the normal time. There was first a layer of fibrin and dead cells, and under this material we very soon found the first symptoms of healing in the form of new epithelial cells. In the majority of cases we observed in the wounds—healed or partly so—new tumour processes. In some instances there were only two or three tumours in one scar, in others there were many more. I never observed that the whole scar was involved in the tumour process. Sometimes the tumour growths were so numerous that the scar could be localized with the greatest ease. I have said that the tumours appeared in some cases after the scar had healed and the new epithelial cells—that is to say cells never themselves in contact with the tar—produced in these experiments primary growths. We know there is a relation between tar and tumour formation; we now learn from these experiments that the liability to tumour formation can be transferred to daughter and grand-daughter cells without the cells showing any change microscopically, nor in the biological sense. These tumours which we produced just at the place where we expected to see them were very malignant, and sometimes in a very short time the whole scar and the surrounding tissue were replaced by a typical cancer growth. We have thus an opportunity of getting a clearer insight into the local origin of tumours in a skin area where all the cells had been in contact with the cancer-producing material. Every now and then the animals get little wounds. These wounds may be so small that they escape attention. They heal as a rule very quickly, and we may suppose that some of them will produce a tumour in the same way as was shown in our experiments. In a very short time these tumours may be larger than the little (often almost invisible) scars from which they started. These experiments may have a general significance for the local beginning of a tumour.

Some other experiments throw a light on the old question of the manner of extension of a tumour. When we study the first beginning of a tumour we find a local hypertrophic growth. Somewhat later the surrounding cells hypertrophy also, and so on, until there exists on the skin a hypertrophic proliferation generally in the form of a papilloma. The way in which such a papilloma grows seems to indicate an influence of the central parts of the papilloma on the surrounding cells of the living organism, with the result that the latter also hypertrophy. At a later stage the central parts of the papilloma are changed into cancer cells, and we noticed that the cancer cells influenced the surrounding hypertrophic cells exactly in the same way as the hypertrophic cells had before influenced the surrounding normal cells.

These observations on the growth of young tumours, as was demonstrated in 1924 at the cancer congress in Strasbourg, bear out the old view of Virchow. It must be of

great value to show in another way the influence of tumour cells upon the surrounding living cells of the organism.

In the first part of this paper I demonstrated that young (regenerating) epithelial cells, in certain circumstances, are very susceptible to tumour formation. On the strength of that observation I made the following experiment: Mice were tarred on the epilated skin until there appeared a few little papillomata, then we stopped applying the tar. A few days afterwards we made two little scarifications, one which was in contact with the tumour, the other at some distance for the purpose of control. We marked the position of these wounds by rubbing in Chinese ink, and after two or three days they were healed. Only a small black line under the new epithelium showed the place where the fine small scalpel had cut through the upper part of the skin. The little healing wound, which either touched the tumour or very nearly did so, showed some interesting changes. The whole mass of new epithelial cells in this wound changed into hypertrophic growth. We never saw in scars that were not in contact with a tumour changes of the same extent. There must be an influence of the tumour cells on the cells of the scar. We know that these cells were very liable to become neoplastic, and therefore it was possible to show this influence clearly. Just as we have seen in a papilloma, the surrounding cells were predisposed to hypertrophic, and afterwards real, tumour growth.

Summary.

1. Injury may have a direct influence on tumour genesis in an extensive area of epithelial cells that are susceptible to tumour formation.

2. Former experiments have made it probable that in the earliest stages of tumour formation the peripheral cells may have an influence on their immediate neighbourhood. When we effect contact between the youngest tumour cells and cells which we know are very susceptible to develop a tumour, then we can clearly see the direct influence of the tumour cells on the other cells of the organism.

It will be the purpose of cancer study to obtain a better insight into these intercellular activities.

SEQUELAE OF ENCEPHALITIS LETHARGICA:

NOTES ON 128 CASES.

BY

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DURING the spring and summer of 1924 there were under my care in Belvidere Fever Hospital, Glasgow, 143 patients suffering from encephalitis lethargica. Of 132 patients who were discharged from hospital, 128 were examined twice within a year at roughly six-monthly intervals.

The Degree of Impairment.

During the acute attack the cases were divided on a clinical basis according to the outstanding clinical feature—namely, lethargic, choreiform, myoclonic, psychotic, hyperalgesic, ophthalmoplegic. They were also classified according as the attacks were mild or severe, and these classifications were used to ascertain what correlation, if any, existed between the degree of impairment and the type and severity of the original attack. The results of examination a year after the attack are embodied in the following table.

Group.	Type of Attack.		
	Mild.	Severe.	Total.
I. Cases with no impairment	37	12	49
II. Cases with slight impairment (working or attending school, but with difficulty)	28	13	41
III. Cases with marked impairment (unfit for work or school)	7	21	28
IV. Cases with very marked impairment...	—	10	10

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It will be seen that there was a fair degree of correlation between the original type of attack and the degree of impairment that followed; that the mild cases more often recovered, and that the severe cases more often were impaired. It would also appear that a higher proportion of attacks with a "positive" bias—using Walshe's classification—were followed by impairment, when compared with those of a "negative" character.

The Two Main Types in Cases with Marked Disablement.

Where the sequelae and degree of disablement were marked two classes could be recognized.

A. *The "Restless Naughty Child."*—In this class the most constant features are insomnia, nocturnal restlessness, asthenia, pallor, psychic changes, and tics. During the day the child is restless and fidgety, "constantly on the move," as the parents say. He is very often noisy, irritable, nervous and easily frightened, bad tempered, impudent, and lacking in respect.

One boy had on several occasions threatened to commit suicide; in the street he would address strangers with complete familiarity and frequently behaved in a cruel manner to his younger brothers and sisters. As tested by the Binet-Simon scale there was no impairment of intelligence, in fact, there was a tendency to precocity.

In the mental processes of these patients, however, a characteristic impairment is to be found. They cannot maintain concentration on any one subject for any length of time; it is as if the mind, like the body, partook of the general restlessness. At night they are very troublesome; they roll, turn and toss about in bed, stand up and stamp, spit, sing, whistle, shout, clap their hands, and make peculiar noises—grunting, "cheeping," clucking, and blowing. One boy wanted to sharpen something with a knife all night long. This continued to a late hour until exhaustion brought sleep which lasted until late in the following forenoon. In a boy it was reported that on alternate nights the insomnia was absolute, the entire night being spent in restlessness and excitement; in the intervening night he slept heavily for about twelve hours.

In the worst example of this kind, a boy of 6 years, there was a striking degree of precocity combined with very definite evidences of moral degeneration. At one time he contracted a habit of vomiting, and without effort or apparent feeling of sickness he could bring up mouthfuls of undigested food, which he would, if allowed, consume. He would also attempt to embrace everyone who came near. A year after the original infection he was in another hospital, and deterioration was so marked and he was so difficult to deal with that removal to an asylum was being contemplated.

Nineteen patients, most of whom were between 7 and 14 years of age, fall into this class of the "restless naughty child." The kind of attack which was by far the most productive of these sequelae was the severe choreiform type. Of a total of 35 children dismissed from hospital, 18, or 51 per cent., had developed these changes.

B. *The Parkinsonian.*—A feature of the Parkinsonian syndrome is that the same sluggishness which qualifies the thinking and movements of these patients affects also their conative faculties. They have little or no initiative. In the advanced stages they will sit for hours motionless. In less advanced cases it is frequently reported that they will "stay indoors and show no desire to go out." A year after the attack nine patients showed features of the Parkinsonian syndrome to a marked degree, and seven were then in other institutions; in all the condition developed in less than six months after the original attack; in one it appeared immediately after, and in most within one to three months.

In these patients the most common features of the syndrome were muscular rigidity, bradyphrenia, bradykinesia, etc., and salivation. Tremors were uncommon, only one example being noted—a slow rotatory movement of the head. The muscular rigidity was generalized except in one instance—a boy of 11 years, in whom rigidity with a slight degree of paresis was confined to the right side of the face, the right arm, and right leg. In a woman aged 53 the rigidity was so great that the mouth could not be opened nor the tongue protruded, and considerable effort was required to raise the eyelids. In one young woman with advanced Parkinsonism a disturbance of the respiratory mechanism developed; it was due probably to spasticity of the laryngeal muscles, which has been rarely, if at all,

described. Respiration was accomplished by short inspiratory gasps, which were followed by noisy forcible expirations—almost as if she were attempting to blow out a light. The ages of the subjects in this group ranged from 11 to 53 years. Two boys, aged 11, had muscular rigidity, bradyphrenia, bradykinesia, etc., all to a marked extent. The initial attack in all these cases was severe. In eight patients Parkinsonism had developed only to a slight extent. The most common elements in this group were the typical facies and some degree of bradyphrenia, bradykinesia, insomnia, and asthenia. Muscular rigidity was, in these patients, confined to the face. The original type of infection, with one exception, was severe.

The Signs and Symptoms.

The following is a list of the signs and symptoms observed a year after the attack in all patients manifesting sequelae. The total number of cases examined was 128.

Sign or Symptom.	No. of Cases.	Sign or Symptom.	No. of Cases.
Insomnia	55	Tics	13
Asthenia	46	Pallor	13
Day drowsiness	31	Restlessness	11
Psychic changes	24	Headache	11
Nocturnal restlessness	21	Pareses	7
Parkinsonism	17	Neurasthenia	6
Pain	17	Constipation	5
Hyperreflexia	16	Adiposity	5
Hyperkinesia	14	Speech changes (excluding bradyphasia)	6
Eye symptoms:		Abnormal gait (excluding bradybasia)	5
Paresis of accommodation	14	Nocturnal enuresis	3
Anisocoria	10	Absent-mindedness	3
Ptosis	5	Bulimia	2
Blurred vision	4	Furunculosis	2
Diplopia	3		
Squint	2		
Myosis	2		

This table affords some conception of the varying range of signs and symptoms that may be presented a year after the attack. The two symptoms which head the list, insomnia and asthenia, were the prominent features in those patients who were slightly impaired, but still able to follow their occupation, although with more or less difficulty. None of the patients required to be certified mentally deficient.

These notes give some impression of the degree and form of disablement in 128 cases caused within a year by an attack of encephalitis. All degrees of disablement, and many different and complex types, were observed. Disablement—including the slighter forms—existed in 62 per cent., while incapacity to resume work or school was found in 30 per cent.

These figures agree closely with the results of a similar inquiry made in Glasgow. A series of 334 patients who contracted encephalitis lethargica in 1924 was investigated fifteen to eighteen months after the attack, with special reference to the capacity for work. It was reported that 36 per cent. were unfit for work. Some of these patients had been treated in hospital and some at home.

It has been recognized for some time that the existence of disablement due to encephalitis lethargica constitutes a problem which public health authorities have to face. The problem has been tackled in Scotland, as in other countries, by the establishment of a hospital unit where cases are admitted for special investigation and research.

REFERENCE.

¹ Walshe, F. R. M.: *Med. Science*, 1920, iii, 51.

HEALED FRACTURES OF TRANSVERSE PROCESSES.

BY

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IN 1910, and again in 1913, I published a few cases in the *BRITISH MEDICAL JOURNAL* of what I termed pseudo-fractures of the lumbar transverse processes. In nearly all there was no history of injury, and I suggested that they were attempts at rib formation by the costal element in connexion with the transverse processes. Dr. Reginald Morton also emphasized the importance of these conditions from the medico-legal standpoint.