Normal Physiology of the Respiratory Mechanism.

Normal automatic or unconscious breathing is effected through a so-called "respiratory centre," which is in reality made up of a number of anatomically separate areas situated in the pons and medulla. This centre is stimulated partly by afferent proprioceptive impulses from the alveoli of the lungs and the thoracic musculature, but mainly by the concentration of carbonic acid in the blood stream. The efferent impulses are conveyed along the lower neurones to the chest muscles and diaphragm.

Though the respiratory centre normally acts independently as a reflex phenomenon, it can be influenced by cortico-bulbar activity. Thus voluntary impulses, conveyed along the pyramidal tract, are capable of inhibiting or accelerating the respiratory centre so that an individual is able, temporarily at least, to hasten or retard his respiration rate, to take shallow or deep respirations, to assume an irregular rhythm, or to inhibit all respiration. Moreover, the respiratory centre is under the influence of other cortico-spinal impulses, which are correlated with the various respiratory irregularities occurring under emotional stress. Thus fright is associated with a temporary inhibition of respiration; pleasurable excitement with an acceleration. The gasping respirations which accompany crying and sobbing also illustrate the influence of the emotions upon the activities of the respiratory centre. There is a good deal of evidence—both experimental and anatomical—to suggest that these phenomena are conveyed along very definite psychomotor pathways. Spencer has demonstrated that these tracts originate in the prefrontal cortex and pass in close proximity to the optic thalamus to end in the lower pons. It is along these routes that the characteristic facial movements and respiratory changes are affected with emotional stimuli. It appears also that the pyramidal tract exercises partial inhibition over these psychomotor (or facio-respiratory) pathways; hence marked emotional instability and even spasmodic laughter and weeping after bilateral ablation of the pyramidal tracts are observed, as in pseudo-bulbar palsy. This normal inhibitory effect of the pyramids, though taking place partly in consciousness, is mainly a subconscious influence, and probably depends anatomically upon the presence of transcortical projection fibres between the precentral and prefrontal cortices.

The Disorders of Respiration.

The pyramidal tract cannot be implicated in the clinical manifestations of disordered respiration because of the absence of the characteristic changes in reflexes and the conservation of voluntary control. The respiratory centre itself does not appear to be the site of disease; there is little or no similarity in the diverse respiratory disorders to the dyspnoea of bulbar disease. It is improbable, too, that a medullary lesion would affect the centres subserving respiration and spare the other important nuclei closely aggregated in this region. Moreover, pathological evidence has failed to support this theory. Changes in the proprioceptive impulses or alterations in the chemistry of the circulating blood have never been demonstrated; the afferent stream of impulses to the medulla therefore seems to be intact. The efferent neuro-muscular mechanisms have been held responsible by some; it is improbable, however, that any such changes are present in all the types of disorder, although doubtless they are a factor in some. Thus rigidity, myoclonus, or tremor of the diaphragm can be demonstrated in patients showing a cogwheel type of respiration. It is obvious, however, that the pathogenesis of respiratory disorders as a whole is to be sought outside the efferent pathways.

Psychical and Sleep Disorders.

Stress has been laid upon the frequent occurrence of psychical and sleep disorders in association with respiratory upset; the association with the emotional instability of the patient lends weight to the view that the psychomotor pathways, with their transcortical projections, are the probable site of origin. An interruption in these latter fibres would abolish the unconscious control normally exercised by the pyramids over the emotional factors of respira-

tion; we would expect, then, to encounter an unstable type of respiration, influenced by every variety of emotional play. The conscious and voluntary control, which we believe to be the function of the long cortico-bulbar fibres of the pyramids, persists; consequently the patient is able, by exerting a determined effort of will, to check or even arrest the abnormality of breathing. Many of these respiratory upsets are of a striking and alarming nature even to the onlookers. It is not surprising that the patient himself is profoundly impressed by the phenomena, and the emotion of fear thus engendered tends to maintain the abnormal respiration. The disease tends, therefore, to perpetuate itself, owing to the complete emotional instability and the lack of equanimity and self-confidence.

Reference has been made to the occurrence of respiratory disorder during sleep; many authors have pointed out that towards nightfall the patients become restless and excited, and frequently noisy and unruly—in striking contrast to their diurnal somnolence and placidity. Simultaneously there is an aggravation in the respiratory disorders. These facts can be reconciled with a tiring-out of the processes of inhibition which have been active throughout the daytime, so permitting conduct and respiratory anomalies to manifest themselves unchecked.

The researches of Pavlov have done much to throw light upon the physiology of the highest cortical processes; they have revealed that many of the seemingly complex activities of the cortex are in reality the resultant of definite conditioned reflexes and their antagonistic inhibitory influences. The study of behaviour in animals after ablation of small areas of cortex demonstrates that there is a temporary upheaval of the normal conditioned reflexes, and that the inhibitory processes are affected to a much greater extent than the excitatory. More extensive damage to the brain produces a permanent weakness of the inhibitory processes. A similar state of affairs appears to exist in many cases of post-encephalitic respiratory disorder, where there is an obvious impairment of inhibition on the part of the patient, although the conditioned reflexes can still be checked temporarily by unexpected extraneous stimuli (external inhibition).

It appears, therefore, more in accord with the modern conceptions of neurology to regard these "psychical" changes following encephalitis (conduct and sleep disorders, respiratory abnormalities) as essentially physical in origin. I submit that the respiratory disorders are essentially organic in their pathogeny, and suggest that they arise from disorder of the psychomotor pathways controlling the respiratory centres, together with a defective inhibition by cortical control.

REFERENCE.

¹ Turner and Critchley: *Brain*, 1925, 28, 72.

EXPERIMENTS ON THE RADIATION OF TUMOURS.

WITH SPECIAL REFERENCE TO THEIR BLOOD SUPPLY.

BY

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THE clinical treatment of tumours by radiation brings out two outstanding facts: first, that there are wide differences in the sensibility of tumours of different kinds; and secondly, that tumours of the same kind in different patients also vary in sensibility, though the variations are less wide than when tumours of different kinds are compared. At present there is no way of estimating these differences before treatment. The first kind of variation has been considered to reside in the tumour cells, but when different kinds of tumour cells are irradiated *in vitro* the lethal dose is found to vary very little. The second kind of variation must reside in the patient, and has been assumed to be due to a resistance towards tumour growth, which varies from patient to patient. Thus, it is evident that we have no certain explanations for the two most important clinical facts, and in order to elucidate them the following experiments have been carried out.

When a tumour is radiated *in vivo*, then removed at once,

and placed in another animal, the factor of resistance will be avoided apart from its operation during the few minutes in which the radiation is being applied. If, on the other hand, the tumour after radiation be left in the animal for varying lengths of time before removal and inoculation into another animal, then the factor of the host will operate more or less according to the length of time that it is permitted to remain in the host after radiation. By comparing these two sets of experiments the influence of the host will be demonstrated.

Experimental Details.

In order to avoid as far as possible normal variations in tumour growth, a tumour (mouse sarcoma No. 180) was chosen which grows in nearly 100 per cent. This was kindly supplied to me by Dr. Woglom from the Cancer Research Institute, Columbia University. Dr. Woglom stated that "in the ten years or so that we have been cultivating it I cannot remember one single regression." During this investigation 84 control inoculations have been made, with 75 takes; there were no regressions. Of the 9 negatives, 5 occurred in a single batch in which a much degenerated

of four to six days. Just as the number of takes is reduced in this manner so also, as would be expected, is there a difference in the time of appearance of the tumours and their liability to regress. Tumours which grow from the inoculation of pieces taken four to six days after radiation take much longer to appear (about twenty-one days) than tumours growing from pieces taken immediately after radiation (about seven days), and whereas cases of regression and disappearance of tumours occurred amongst the former, none were observed in the latter. These findings go to show that the figures given in the table are not the results of chance, but of the arranged experimental differences.

At first sight these results suggest that there is in the mouse an inhibitory factor towards the growth of sarcoma 180, which accounts for the differences obtained, according as to whether the radiated tumour cells are removed at once or after varying lengths of time. On the other hand, the results can equally well be explained by assuming that the radiation produces effects in the tumour which do not manifest themselves for several days. One such effect has been observed. It is well known that radiation has pro-

tumour was used. The experimental procedure was as follows:

Mice were inoculated in the flank with small pieces of tumour, approximately 1 mm. cube. When these had grown to approximately 4 by 4 mm. superficial area they were radiated with a radium application of 20 mg. of radium element, area 15 by 15 mm., screen 0.35 mm. silver. The exposures were for ten, fifteen, and twenty minutes. Either at once, or after varying lengths of time (from three to seven days), the mice were killed, and the tumour exposed by removing the skin. A thin slice, 1 mm. thick, of the tumour was taken from the surface, divided generally into six pieces, and inoculated into mice.

Results of Radiation.

When Tumour Removed.	10 min. Radiation.	15 min. Radiation.	20 min. Radiation.
At once	6/6	11/18	4/12
After 3 days	3/6	2/6	5/10
After 4 days	5/6	1/6	0/6
After 5 days	2/4	0/6	0/6
After 6 days	4/6	0/6	0/4
After 7 days	6/6	0/3	2/10

The denominators of the fractions give the number of inoculations, the numerators the number which grew into tumours.

The results show that the chance of the inoculation growing is much greater when the radiated material is removed at once than when removal is delayed for a period

found effects on blood vessels. An early effect is swelling of the endothelial cells, which obstructs the blood flow through the arterioles and capillaries. This obstruction to blood flow is to be seen in the living mouse in the neighbourhood of the radiated tumour. On about the fourth day after the tumour has been radiated the normal pink colour of the skin and underlying tumour disappears, and is replaced by a bloodless yellow colour. I have had occasion recently to radiate chickens. Their skin is very thin and transparent, so that the pink colour of the underlying tissues can be easily seen. Twenty-four hours after a large dose, and two days after a moderate dose of radiation, using square radium applicators, a square white area is seen where the application was made, which is very marked after three to four days, and persists for a few weeks. These observations suggest that the normal blood supply to the radiated tumour may be interfered with at this time. In order to test this the following experiments were made.

Experimental Details.

Tumours were exposed for twenty minutes to the applicator *in vivo*. After varying lengths of time the tumours were removed so as to preserve as far as possible the amount of blood which they contained during life. The animals were etherized. The skin for about 1 cm. around the tumour was burnt through with a cautery, then ligatures were passed under the tumour, and the deep connexions tied off. The whole was then removed and fixed in formol Müller. Sections 5 μ thick were made, stained with aniline fuchsine, decolorized with 0.5 per cent. ammonia solution, and counter-stained with iron haematoxylin. In this way the red corpuscles show up intensely red against a grey background. Control

specimens which had not been radiated were similarly prepared. Using a square graticule in the eyepiece of the microscope, drawings were made, on squared paper, of the red cells seen. In this way a picture of the amount of blood in the capillaries was obtained. No differences between experiment and control were found in the twelve-hour and twenty-four-hour specimens. The results obtained with intervals of two, three, and four days are illustrated in the accompanying figure, which shows the drawings obtained as described. In choosing a piece of tumour to draw, an area of the section was always selected where blood vessels were most numerous and the tumour neither degenerated nor necrotic.

It will be seen that after two days (column 1), and especially after three and four days (columns 2 and 3), the capillaries in the radiated specimens contain very little blood as compared with the control specimens (columns 4 and 5). The areas of fine scattered dots represent haemorrhages, and it is seen that these are more numerous in the experimental animals. The differences which have been observed may therefore be well accounted for by the fact that tumour cells allowed to remain in the body after radiation suffer from an interference with their blood supply, as well as from the direct effects on them of the radiation.

Theoretical Considerations.

Starting from this fact, there arises the question whether the difference in radio-sensibility between normal tissues and tumours is related to effects on blood vessels. It is known that tumours, and especially malignant tumours, have an inefficient vascular supply. Any interference with this will thus operate against them more than against

normal tissues. Further, in many malignant tumours the supply of blood is so poor that necrosis is of common occurrence, apart from radiation. Such tumours are especially sensitive to radiation, after which widespread necrosis may occur. Rapidly growing tumours, which presumably make a large call on the blood supply, and tend to outgrow it, are likewise said to be especially sensitive to radiation. Non-malignant tumours seem to fall into line as their vascular supply is less differentiated than normal tissues, but more than malignant tumours, whilst the sensibility is likewise intermediate. How far this hypothesis will account for the facts of radiation remains to be seen; it is now put forward as a working hypothesis which may prove useful in therapeutics.

Conclusions.

1. Tumours left for four to five days in the animal after radiation, and then removed and grafted into other animals, succumb more easily than when removed immediately after exposure.
2. This effect is associated with an interference with the blood supply, which occurs four to five days after the exposure.
3. These results suggest the hypothesis that the varying sensibility to radiation of tumours, and the difference in sensibility between normal tissues and tumours, are associated with the variations in blood supply, on which the radiation has a special action apart from its direct action on cells.

ASTHMA WITH MAXILLARY SINUSITIS AND A HEALTHY SUPERNUMERARY PARANASAL SINUS.

BY

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THE patient whose case is recorded below is a medical student, aged 20, whose studies were interfered with by recurrent attacks of asthma. He came to see me on August 7th, 1926, and gave the following history.

He said that he had had bronchitis in October of the previous year, and that after three days in bed asthma developed, the attacks continuing during the succeeding three weeks. He then studied in London for the primary Fellowship examination, and while there was free from attacks, but on returning home, where he remained until the end of January, 1926, he suffered from slight attacks of asthma occasionally, with shortness of breath on exertion. On resuming work at a university in the North of England he had severe attacks for three nights, so he returned home. He had shortness of breath each morning, and asthmatic attacks at intervals of five or six weeks, each attack lasting for a week or two. For three weeks before coming to me he had never once been free from asthma. He had used adrenaline frequently, and had had four injections of peptone during the week in which I saw him.

I found his nose normal, except for a few threads of mucus extending from the septum to the lateral walls; some mucus was present on the floor of the nasal orifice. The tonsils and adenoids had been removed in childhood, but a portion of the left tonsil was still present. The larynx and vocal cords were red, and the trachea, which was easily exposed, was injected. On transillumination both maxillary sinuses were dark. By puncture and washing a mass of mucoid material was expelled from the right sinus; the left sinus showed only a few strings of mucus. Three days later the patient returned, and said that he felt better than for many weeks. Puncture was again performed, and on this occasion a mass of mucoid material was expelled from both sinuses. On the next day puncture of the right sinus revealed the same condition, but the left sinus washing was clear.

On August 14th a Caldwell-Luc operation was performed on both sides, the anaesthetic employed being morphine and scopolamine, with local injections of 1/2 per cent. solution of novocain, and the application of cocaine paste in the nose. On the right side a small normal sinus was exposed, and a counter-opening was made posteriorly below the inferior turbinate; the wound was then sutured. The left sinus was found to be similar to the right, but perforating a thin partition brought to light a sinus lined with polypoid mucous membrane, on the floor of which a strand

of pus was lying. The sinus was scraped with a curette round which was wound gauze soaked in 10 per cent. zinc chloride solution, and the partition, which had completely divided the antero-medial from the posterior lateral sinus, was removed. The sutures on the right side were then taken out and a similar partition was discovered, which, on removal, opened up a sinus presenting the same pathological appearance as the left.

By September 16th the patient had been free from asthma for about a month; on recurrence then, I washed out the sinuses and retained secretion was found. I removed the anterior ends of the inferior turbinates, and enlarged the intranasal opening to enable the patient to use lavage himself. On October 21st the patient, who was regularly washing out the sinuses, reported freedom from the asthma and an increase in weight; he was only troubled now by a slight cough at night, due to the bronchitis which so often follows sinusitis. Two days later he stated that, after washing the sinuses twice a day for a month he had abstained for thirty-six hours from lavage, when a violent attack of asthma supervened, necessitating the use of morphine. This was an indication that the patient was sensitive to his own protein.

The anatomical condition in this patient explains why on two occasions the washings from the left side were negative, and how, although proof puncture had shown the presence of disease on the right side, yet a healthy sinus was found, but, when the partition was removed, a polypoid mucous membrane was exposed to view. I have previously reported the occurrence of similar anatomical anomalies of a less degree in two patients in China. The origin of supernumerary paranasal sinuses is discussed by Schaeffer. It would appear that the medial healthy sinuses originate from the naso-palatine canal, while the diseased sinuses are the true maxillary sinuses. In my case the condition was deceptive as the partition was complete. From the clinical aspect the history of asthma for only ten months pointed to a focus of infection somewhere, yet if transillumination had been omitted from the routine examination the focus would not have been discovered, for the patient had no idea that he had any lesion in his nose; there was no localized oedema or hypertrophy, and no discharge was seen near the middle turbinate. The condition is interesting, as the patient seems to have been sensitized to his own protein, and was always relieved by an adrenaline injection.

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