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LOCALIZATION IN THE CEREBRUM AND CEREBELLUM

BERTRAM LOUIS ABRAHAMS LECTURE*

BY

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Bertram Louis Abrahams, in whose memory this lecture was founded, was a medical student in the early 'nineties. He was a Londoner born and bred, had a brilliant career with a University scholarship in physiology and later a registrarship at the Westminster Hospital, and ended as lecturer in physiology and as assistant physician there. He was only 38 when he died, but he had an established reputation as a consultant and a teacher, and he had lived a life full of intense interests and activities—and not only in the field of medicine, for he was an ardent cricketer and Freemason and the organizer of a boys' club. But one of his chief interests was physiology, and so it is fitting that his name should be associated with a lecture on a physiological theme.

One way in which we might call him to mind would be to discuss and so to re-create in ourselves some of the thoughts and ideals which seem to have guided his work. Since he was a teacher of physiology as well as a clinician, he must often have had to face the perennial question of how physiology should be taught as a basis for medical work. If we dealt with this we might think of ourselves as carrying on, as it were, a discussion in which Abrahams must often have taken part 40 years ago. But I am afraid it would be found that there was little new to add to the discussion in spite of all the good advice which has been given from all sides in the past 40 years. The details of the picture have changed, but in its outlines the problem will remain as long as physiology is taught.

Another theme in which Abrahams was keenly interested was that of the general physiological principles which govern the reactions of the cell or the organism to injury. But here the picture has changed too much. Nowadays the physiologist has few principles left; for the emphasis has passed from the general to the particular, from the katabolism of protoplasm to the details of carbohydrate cycles. Moreover, in these uncertain times I think most of us will prefer facts to theories, however narrow the field from which they have come: so I have chosen a very limited branch of physiology, of which the most important thing we can say is that it is going ahead.

The Clinician and Cerebral Localization

The main facts of cerebral localization were established during Abrahams's lifetime and were as much the achievement of clinical medicine as of physiology. Neurology has always encouraged a very close interchange between the clinical and the laboratory worker: in this country, for instance, we have had clinicians like Hughlings Jackson, physiologists like Schäfer and Sherrington, and men who were both, like Ferrier and Horsley. There are obvious reasons why both kinds of investigation are needed for the brain. It is the organ in which there is the greatest difference between man and other mammals, so that the findings from animal experiments do not necessarily apply to man and must be checked and modified by observations on patients; and men can give us far more information than animals in that we can communicate with them and find out what they feel and think. On the other hand, there are many problems involving the motor area in which results can be obtained with far greater certainty from animals than from human disease or accident.

The result of this was that until recently we knew more about the motor area in the monkey and more about the sensory and visual areas in man, though it had taken the head wounds of the last war to provide all the necessary clinical material. Since that war, however, there have been two important developments. One is the outstanding progress of neurosurgery, which has made it a much less formidable business to expose the human brain and has given us maps of the motor cortex in man to set beside those of the chimpanzee. The other development is in the use of electrical methods to investigate the brain in animals, and this has given maps of the receiving areas to compare with the clinical findings in man. I shall describe some of the information obtained by this method, for it is a relatively new physiological technique which is only at the beginning of its usefulness.

A New Physiological Technique

The technique has been made possible by the use of better electrical recording instruments and more suitable anaesthetics. The former depend on valve amplification and need not be considered in detail; the anaesthetics are the barbiturates. These have an action on the brain quite unlike that of ether or chloroform, for they reduce the persistent activity of the cortex (shown by persistent electrical waves) without preventing the arrival of the messages from the sense organs. These messages produce their own electrical accompaniment, which can be recognized without difficulty provided that it occurs against a quiet background. Thus the barbiturates allow us to record what comes into the afferent areas of the brain with a precision quite impossible with other anaesthetics which have a less selective action. In fact, their main disadvantage is that we tend to rely too much on them and to forget what they may be doing to the brain by suppressing all but the simplest activities.

What can be done with this kind of technique may be illustrated by the mapping of the visual area of the monkey's brain by Talbot and Marshall (1941). A thin pencil of light is directed to a particular spot on the retina while the striate area of the cortex is explored with electrodes leading to an amplifier and oscillograph. It is found that turning the light on and off produces electrical activity in a very small part of the striate area and that any change in the position of the illuminated spot on the retina is reflected in a corresponding change in the region of electrical activity in the brain. There is, in fact, a precise correspondence between retinal and cortical points which allows us to make a definite map of the retina as it is projected

* Delivered to the Royal College of Physicians on June 8, 1944.

on to the surface of the brain (Fig. 1). Points near the centre of the fovea are connected with the antero-lateral margin of the striate area, and points nearer the periphery with the posterior, mesial part. Thus, allowing for the fact that in the human brain the whole striate area has been pushed back to the mesial aspect of the hemisphere, the connexions between the retina and striate area in the monkey agree with the connexions established for man by Holmes and Lister from the gunshot wounds of the last war.

It is satisfactory to have the human findings confirmed by such a different sort of evidence, and, although the result was not at all unexpected, the important point is that the mapping can be done with a very high degree of precision, so that conclusions can be drawn as to the mechanism of visual discrimination and the like. In the anaesthetized brain, therefore, we can say that a pattern of light and shade thrown on the retina will produce a corresponding pattern of activity in the afferent fibres which enter the striate area. What would happen in the area if there were no anaesthetic is another matter. Even in the simplified conditions given by deep anaesthesia, where all but the most direct pathways are out of action, there is a good deal of editing of the messages on the way up to the brain, and if there were no anaesthetic the pattern arriving there might be much less recognizable because of interactions between neurones at the various synaptic levels on the visual pathway. And the fact that the pattern in the striate area may be recognizable to the physiologist with his electrical equipment is of little help in explaining how it is recognized by the brain in which it appears.

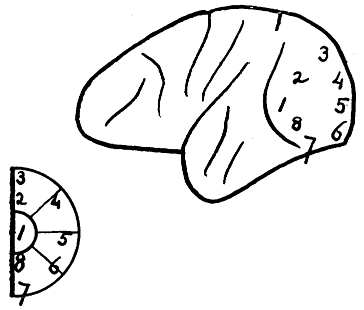

FIG. 1.—Representation of the retina in the visual area of the monkey's brain.

Nervous Mechanism of the Cochlea

It would have been surprising if a spatial correspondence between retina and striate area had not been found—but until recently there was less reason to expect such a thing in the auditory area, and here the electrical method has been particularly illuminating. Within the past two years the nervous mechanism of the receptor organ, the cochlea, has become far clearer, so that we have a much better notion of the sort of messages which it transmits to the brain. They have been studied by Galambos and Davis (1943) from records made from single fibres of the auditory nerve. It was found that each nerve fibre comes from receptors tuned to a particular pitch but capable of reacting to louder notes if their pitch is not far different. This agrees with the familiar Helmholtz conception, but Galambos and Davis have added the interesting point that the message which the auditory nerve fibre transmits to the brain is not itself marked by any particular frequency. It is simply a train of impulses whose frequency varies with the intensity of the stimulus; in fact, it is like all the other sensory messages which reach the brain, and could not be distinguished from them if we did not know that it came from the cochlea and so must signal sound rather than sight or touch.

Now if the pitch of the note can only be inferred from the fact that it has excited the receptors in a certain part of the basilar membrane, it follows that there must be some kind of spatial representation of the cochlea in the brain just as there is of the retina. And it has been found, first in the cat and now in the monkey, that such a representation does exist. When the cochlea is stimulated by sound, electrical activity appears in the appropriate region—the upper surface of the superior temporal gyrus—and with notes of low pitch the maximum activity (in the monkey) is in the antero-lateral, with high notes in the postero-median, part of the receiving area (Licklider and Kryter, 1942). Thus the apex of the cochlea supplies the antero-lateral, and the basal turn the postero-median part (Fig. 2). Just as the movement of a light to and fro across the visual field will produce a peak of activity moving to and fro across the striate area, so the up-and-down note of

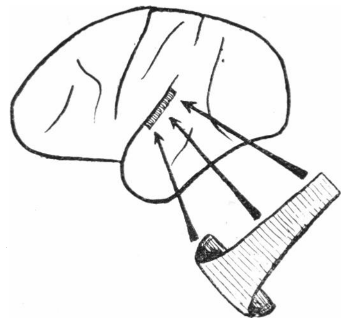

FIG. 2.—Representation of the basilar membrane of the cochlea in the auditory area of the monkey's brain.

the siren will give an activity moving to and fro in the cortex of Heschl's gyrus. To have reached this position is a distinct achievement, and it has cleared the ground for the attack on the main position—the problem of why a nervous signal passing to and fro in the auditory cortex with particular time and intensity relations should start in us the whole train of thoughts and actions appropriate to air raids. But here the attack has scarcely begun, and the position is defended in very great strength.

Relation of Brain to Sense Organs

The signals which reach the brain from the peripheral sense organs arrive in the post-central gyrus (in man and monkey) in the positions we should expect; messages from the hind-limb receptors appearing near the vertex, those from the fore-limb further down laterally, and so on. Again we have a strip of cortex with peaks of activity here and there corresponding to the stimulated sense organs, and we infer what is happening to our bodies from the rise and decline of the messages in different parts of the area. But as the electrical method allows us to deal with animals of all sorts it has brought out some interesting differences in sensory equipment, or rather in the importance to the brain of the sense organs from different parts. For instance, if we compare the receiving areas in the brain of the cat and the pig we find that in the cat there is a large fore-limb area with exact representation of the digits, foot-pad, etc., whereas in the pig the area chiefly represented is the snout, and it is difficult or impossible to detect anything at all from the limbs (Adrian, 1943). The reason is presumably that the cat uses its fore-limbs and claws in skilled movements which

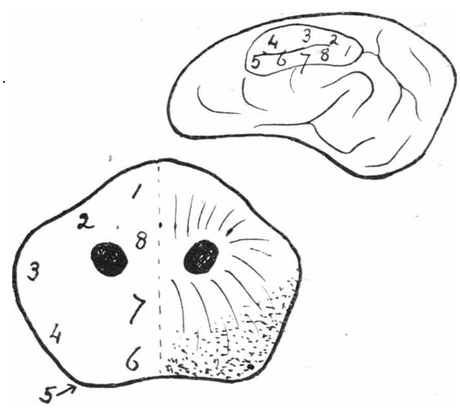

FIG. 3.—Representation of the tactile surface of the snout in the sensory area of the pig's brain.

must be precisely guided by sight and touch, whereas the pig uses its limbs for standing and walking, and for nothing else. All the skilled movements of the pig are made by the snout, and the snout has an elaborate representation in the brain with a precise correlation between points on the snout surface and points in the cortical receiving area (Fig. 3). In fact, judging by the size of the cortical area in relation to the skin surface supplying it, the pig's snout is represented on a scale even more generous than that of the human hand. Thus the snout takes a place as one of the special receptive surfaces like the retina and the basilar membrane.

In other hoofed animals there is the same preponderance of afferent signals from the snout region and neglect of those from the limbs ; but no one can use this method of examining the brain without realizing the importance of the sense organs in this region in every animal but man. It is implied in Sherrington's conception of the leading segments, and is shown not only by the area devoted to it in the brain but by the size of the fifth nerve and the special types of receptor organ supplied by it. The tactile vibrissa of the snout is a good example of an organ which might really be classed as a distance receptor, for one has only to look at the head of a rat to see how the snout, by the aid of its long vibrissae, comes to be literally in touch with objects more than the width of the head away. In man the sensory mechanism of the fifth nerve has lost this function of exploring space, but there are still the large number of sensory fibres to the face and its acute sensitivity to touch to remind us of what is gained and lost by the erect attitude.

The Role of the Cerebellum

These are only a few of the points which have been established in regard to the cerebrum, but it is time to pass to a different field. Few neurologists of my generation can have forgotten the satisfaction induced by Gordon Holmes's analysis of the symptoms of cerebellar injury. It was almost the only sign that that mysterious organ the cerebellum had any intelligible function at all. But until quite recently the clinical findings have remained more illuminating than anything from anatomical or experimental sources, and the cerebellum has kept its position as one of the most puzzling parts of the nervous system.

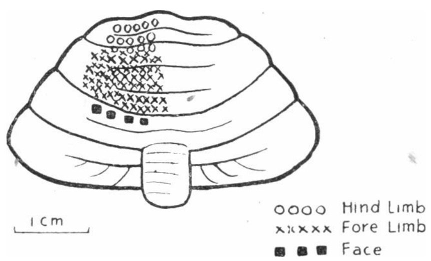

FIG. 4.—Receiving areas for spino-cerebellar impulses in the cerebellum of the monkey.

The newer methods have now brought distinct signs of improvement ; for we have at last begun to get fairly good evidence of localization of function, or at any rate localization of nervous mechanism, in the cerebellar cortex.

A scheme of cerebellar localization was put forward some time ago by Bolk on morphological grounds. It made the anterior lobe responsible for the head, and the ansiform lobes for the arms ; but since then anatomical evidence has shown that the afferent supply from the vestibular nucleus goes mainly to the posterior region and that from the spinal cord to the anterior. This in itself indicates some differentiation of function, and, by stimulating the various tracts electrically, Dow, who is largely responsible for the recent interest in the cerebellum, has verified the general distribution of the different sets of afferent fibres.

But a good deal more can be made out when we explore the cerebellar cortex with a fine needle electrode so as to pick up the impulses as they arrive in the white matter. To obtain a clear picture either the spino-cerebellar or the ponto-cerebellar tracts must be put out of action, since their distribution overlaps to some extent ; but when one or the other is suppressed an arrangement is revealed which is strikingly reminiscent of that in the sensory or motor area of the cerebrum.

The arrangement in the monkey is shown in Fig. 4. The marked regions show where messages arrive in the anterior lobe from the spino-cerebellar tracts when the limbs on the same side of the body are pressed or moved. The map is quite different from that of Bolk ; for messages from the hind-limb go furthest forward, those from the fore-limb go to the culmen. Messages from the face appear in the lobulus simplex, but are not always found, and when they are they come not from neck muscles but from the vibrissae of the face—possibly because the vibrissae have a special function in guiding the head.

The messages to the anterior lobe from the limbs are partly tactile, but most of them come from the deeper endings in muscle and tendon and in the fascia of the hand and foot. The most effective stimulus is always a pressure on the pad

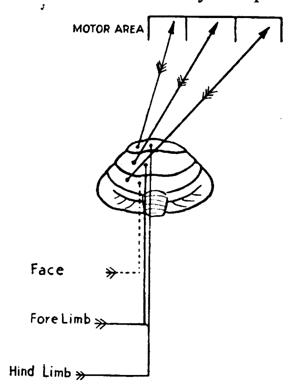

FIG. 5.—Spino-cerebellar and ponto-cerebellar pathways to receiving areas in the anterior lobe and lobulus simplex.

of the foot combined with dorsiflexion of the digits—as though the limb were to take the weight of the body—but all kinds of joint movement and stretching of muscles have been effective. The localization is like that in the cerebrum, with the arrival areas arranged in the order from behind forward for hand, wrist, elbow, shoulder, hip, knee, ankle, and foot.

It is not possible to map out the distribution of the ponto-cerebellar fibres in such fine detail, but by stimulating various points on the motor cortex and picking up the discharges which are relayed to the cerebellum through the pons we can find an arrangement which is substantially the same, the hind-limb area of the motor cortex sending impulses to the most forward part of the cerebellar area, etc.

The ponto-cerebellar areas extend further out laterally than the spino-cerebellar, and there is a large region further back which does not seem to correspond to any one part of the cerebral cortex, but has a diffuse connexion with scattered points in it. For the present the relation of this relatively large ponto-cerebellar receiving area to the cerebrum must remain uncertain, and all that can be said is that there are these localized receiving areas in the anterior lobe for the different segments of the body arranged as in the diagram (Fig. 5). Probably there are other arrival and departure areas as well ; indeed, in the rat (Dow and Anderson, 1942) impulses from the limbs arrive in the pyramis further back, and some of the spino-cerebellar fibres end there in the cat and monkey. But although we may be dealing with only one side of the picture it is worth illustrating it in another way—namely, by comparing the size of the culmen (i.e., the part of the anterior lobe concerned with fore-limb messages) in three different animals—man, the pony, and the pig (Fig. 6). The comparison is more than usually speculative because the evidence on which it is based is mainly derived from the cat and monkey, but the three animals are chosen because they do not differ

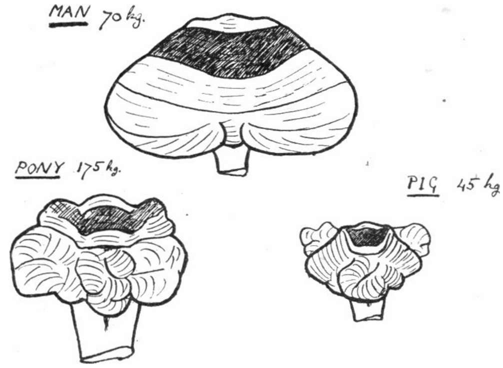

FIG. 6.—Comparison of the culmen (receiving area for the fore-limb) in man, the pig, and the Shetland pony.

very greatly in size and weight but do differ in the use to which the fore-limb is put. There is evidently a great difference in the extent of the cerebellar area to which impulses concerned with the fore-limb are sent; and the comparison is also useful because it draws attention to the large fraction of the cerebellum which does not seem to be employed in any localized representation of the body and limbs. It shows, in fact, that we are still at the beginning of the story.

Conclusion

I have tried to give a sketch of a method of research on the central nervous system in which rapid advance is possible and in which it is difficult to foresee how far it may not go. But, as with all long-range research nowadays, the advance has been held up until the younger generation of physiologists can come back from the more urgent problems which they have to solve. Some day military or naval or air physiology should form the subject of a future Abrahams lecture. Compared with these problems of life and death the academic study of the nervous system seems to-day of very little consequence. All I can hope is that an account of its progress may serve as a reminder of the things which were important to us in better times, and as a reminder of a Fellow of the College of Physicians who lived when those times were taken for granted as the natural consequence of civilization.

Figs. 4 and 5 are reproduced by kind permission of the Editor of *Brain*.

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SOME PROBLEMS IN RIBOFLAVIN AND ALLIED DEFICIENCIES*

BY

HUGH S. STANNUS, M.D., Ph.D., F.R.C.P.

(*Concluded from page 105*)

SIGNS AND SYMPTOMS OF HYPORIBOFLAVINOSIS

The mild constitutional symptoms, including the feeling of being "out of sorts," of loss of "pep," of mental and physical fatigue, might thus be explained, as also perhaps symptoms referred to the heart and gastro-intestinal tract.

All the dermal manifestations support my thesis, I believe. The skin has been regarded as a tissue possessing but a relatively small capillary vascularization, associated with a low metabolism, but this is fallacious. The first statement referred to the number of capillary loops per square millimetre which can be counted by Lombard's method of microscopy and left out of consideration the subpapillary plexus—the plexus which gives to the skin its colour and which itself is made up of giant capillaries. The second statement was based on the tissue-slice respiratory method of estimation, when of course the skin was not exercising any of its normally marked activities. The skin as a whole may be affected, or only those areas whose anatomico-physiological design is specialized in some direction, as I pointed out some years ago.

A mild erythema associated with fine desquamation, referred to by Sydenstricker as pityriasis sicca, may be remarked. It is most easily recognized in the skin of the forehead and face, sometimes on the hands, in the fair-skinned individual. In the pigmented skin of the native the erythema cannot be detected, but the desquamation may be noted.

In other cases the change may be obvious only where the skin is very *thin*, as in the antecubital fossa, or *specialized*, as in the case of the scrotum and in the transitional type of skin about the orifices of the body—the palpebral fissures, the nares, the free margin of the prepuce, the vulva and anus—giving rise to the lesions I have described.

Sydenstricker two or three years after his first communication on ariboflavinosis mentioned pruritus of the scrotum and vulva, but made no reference to any visible lesion. On the other hand, an excellent photograph of the scrotal condition was reproduced by Spies and Cooper (1937), but with the subscription "pellagrous dermatitis of the scrotum and thighs." The lesions of the prepuce, vulva, and anus do not appear to have been recognized by American observers. Possibly they have not distinguished them from the urethritis, vaginitis, and proctitis which occur in pellagra.

The seborrhoeic lesions about the nose and in the nasolabial folds are a good example of the disturbance in an area of skin which normally possesses a rather different anatomico-physiological arrangement from the rest of the skin. Whether these lesions are of the same nature as those described by Smith, Smith, and Callaway (1941) under the designation "dyssebacia" is uncertain, as they held that the condition they described was not cured by any one of the known vitamin B_2 complex factors but did respond to autoclaved yeast or liver extract.

The affection of the vermilion portion of the lip—cheilosis—is another example of the incidence of the lesion being associated with anatomical specialization, for here the capillary loops are notably very much closer together than in other parts of the skin.

The best description of the changes in the skin capillaries is contained among observations made by Márquez Blasco and Peraita (1940) upon patients suffering from nutritional deficiencies during the Spanish Civil War. They found that, using a dermal capillaroscope, pathological changes, least marked in simple cases of pellagra, were progressively more accentuated in proportion to the advent and advance of symptoms indicating involvement of the nervous system, including loss of visual and auditory acuity—symptoms which I shall come to shortly.

Angular Stomatitis

The angular stomatitis calls for some words of comment. The term—not a very happy one—was originally used by myself, and seems unfortunately to have persisted. It is difficult to find a better as, so far as I know, there are no words in any language which distinguish between the opening into, and the cavity of, the mouth. Angular stomatitis at least serves to distinguish the lesions so named from "cheilosis," the lesion of the vermilion of the lip, though some American authors—wrongly, I believe—include both under cheilosis.

If the corners of the mouth be examined carefully, with the mouth open but produced into a pout, it will be observed that the vermilion portion of the lips does not encircle the mouth at the angles, but passes internal to the delicate fraenum which has become visible—that, in fact, the lips are prolonged on to the inner side of the cheek. This accounts for another common feature in this condition—namely, the presence on the inner side of the cheek of a linear lesion comparable to the angular stomatitis on the skin outside.

That the lesions of riboflavin deficiency become worse if nicotinic acid be given has been noted by several observers without any explanation. I suggest it is due to the pharmacological vasodilator action of nicotinic acid on an already damaged capillary endothelium.

These lesions are, I believe, characteristic, and with experience I think it may be possible to distinguish them from others produced, it has been suggested, by dentures, etc., and from the condition sometimes to be seen in those with turned-down corners to the mouth, patches of herpes, impetigo, lichen, etc. The introduction of the expression "pseudo-ariboflavinosis" by Ellenberg and Pollack (1942) is, I think, much to be deplored.

This leads me to mention the word "perlèche," a term adopted from the French which one would like to see banished from our medical literature. As pointed out a few years ago by myself (1941) in dealing with the history of this affection, it has become a habit—a bad habit, copied by one author from another, in ignorance of its original significance—when referring to angular stomatitis, to give as a synonym this foreign word. It was first used by a French doctor named Lemaistre in 1886 as the title of an article—"*De la perlèche: du streptococcus plicatilis.*" He described a condition—which closely resembles angular stomatitis—that he had observed to be common among children in the neighbourhood of Limoges,

* The Lumleian Lectures (abridged) delivered before the Royal College of Physicians of London, April 18 and 20, 1944.