Clinicopathological Conference

A Case of Abnormal Thirst

DEMONSTRATED AT THE ROYAL POSTGRADUATE MEDICAL SCHOOL ARRANGED BY PROFESSOR RUSSELL FRASER AND DR. PAUL D. LEWIS

Clinical History

PROFESSOR RUSSELL FRASER (1): We are going to consider a 12-year-old boy (fig. 1a) who came to this hospital in February 1971 because of abnormal behaviour, poor growth, and refusal of both food and liquids.

When he was 10 years and 4 months old he had a period of polyuria and polydipsia with about 10 pints (5·7 l.) intake per day, for which he was admitted to another hospital, where diabetes insipidus was diagnosed. He had haemo-concentrated serum (Na 147 mN). After 8 hours' water deprivation he lost 4 lb (1·8 kg) while when he was given pitressin tannate he produced concentrated urine and lost his thirst. During the subsequent year he grew only ½ in (1·25 cm) and he began to develop behaviour problems: he could not concentrate on his lessons, and was generally very distractable. His school progress was poor and there were several problems involving stealing and other behaviour disorders.

Then a curious change in his attitude towards water occurred: he lost his severe thirst, developed an aversion to fluids, and had to be encouraged to drink. He was admitted to the Radcliffe Infirmary in Oxford, where he was found to be dehydrated, drowsy, and stuporous, but showed no localizing neurological signs. Full examination was done there, including an air encephalogram, and perhaps Dr. Doyle will show us the Oxford x-ray films.

DR. F. H. DOYLE (2): The plain radiographs of the skull and pituitary fossa taken at the beginning of May 1970 showed no abnormality. An air encephalogram, performed under general anaesthesia, provided a good demonstration of the basal cisterns and of the anterior end of the third ventricle. This examination showed no evidence of a mass in the region of the hypothalamus.

PROFESSOR RUSSELL FRASER: Thank you. He then (May 1970) had an exploratory but negative craniotomy. He was transferred to the Royal Berkshire Hospital, where he was found to have a highish blood urea and also a high serum sodium level, which proved correctable if he was persuaded heavily and drank adequate liquid. But if not persuaded, he relapsed. After his operation he was given as maintenance therapy thyroxine, 0·1 mg/day, and prednisone, 2·5 mg/day, just in case he might have a hypopituitary state. At this stage he was seen by us.

He was now quite a small 12-year-old boy, below the 3rd percentile for heights, but he had been growing perfectly well until the age of...

FIG. 1a—The patient aged 12 years. Patient's growth in height (redrawn from Tanner and Whitehouse Chart.)
10 (fig. 1b). His build was normal. His pupils were usually widely dilated, and spontaneously varied in size. His behaviour also fluctuated strikingly. In the ward he was a hyperkinetic wanderer and quite a problem to supervise. He would disappear down the stairs and around to other parts of the hospital before the nurses noticed what was happening. He was generally euphoric—constantly producing what he thought were jokes or flippant phrases—and really quite a co-operative cheerful little fellow, subject to this restlessness. He could not concentrate on anything, and unless he was strongly pressed he did not bother to drink or even to eat. His I.Q. on formal testing was 79; various mental functions were more or less evenly impaired—in other words, there were no hints of cerebral deterioration.

His pulse rate was usually at least 100 per minute, and his blood pressure tended to be a little low. His temperature was usually raised, but on forcing fluids, it would fall to normal (fig. 2). We felt that he was constantly underhydrated, despite our persuasion. Occasionally he would vomit. All his tendon jerks seemed to be increased, including the jaw as well as in arms and legs. Though the plantar reflexes were flexor, on one side he had a persistent ankle clonus. These quadriplegic neurological features became a little more obvious during his last few months of life. The E.S.R. ranged between 42 and 65 mm in one hour. His blood urea and serum sodium and bicarbonate levels were also constantly raised. In May 1971 as well as a high serum sodium he had also a high cholesterol.

This psychic disturbance might be called hypomania plus distractability of a greater degree than would be expected in hypomania, but oddly associated with somnolence. While anybody was there to His flexor, on constantly underhydrated, few months of life. The E.S.R. also happened. He would vomit. All his tendon jerks seemed to be increased, including the jaw as well as in arms and legs. Though the plantar reflexes were flexor, on one side he had a persistent ankle clonus. These quadriplegic neurological features became a little more obvious during his last few months of life. The E.S.R. ranged between 42 and 65 mm in one hour. His blood urea and serum sodium and bicarbonate levels were also constantly raised. In May 1971 as well as a high serum sodium he had also a high cholesterol.

Now, of course, his pituitary was under suspicion; the E.C.G. proved relatively normal, showing no signs of deficiency of adrenal or thyroid function. His hypothalamic function was also suspect. We did an intravenous insulin tolerance test (fig. 3), in which the hypoglycaemia normally induces a hypothalamic response leading to raised plasma cortisol and growth hormone levels. An interesting dissociation has been seen here—he has no response at all in his growth hormone level, while he has a normal ACTH releasing mechanism, as shown by normal cortisol release. Defective growth hormone (H.G.H.) production is also indicated in his hyper-responsiveness to administered human growth hormone in the H.G.H. acute metabolic test (fig. 4).1 Check of his water balance by serum Na showed this level to rise during the test, so the 50% fall in serum urea after the H.G.H. injections was due to better hydration. We also did a test of T.S.H. (thyroid stimulating hormone) secretion by the pituitary using T.R.H. (thyroid releasing hormone) intravenously; the serum T.S.H. level promptly rose in the normal way.

We examined his water control mechanism during a water deprivation test (fig. 5) at the time when he was not interested in drinking water at all. He starts with supranormal plasma osmolality and haemoconcentration. During the ten-hour observation period his urine volume falls, as expected in a normal subject, while his vasoressin level* quite definitely rises. So he can increase his vasoressin output, perhaps a little surprising in view of his previous period of diabetes insipidus, though those are rather low levels for such a high plasma osmolality.

Another striking feature which we cannot explain was his astronomically high angiotensin† levels found at various dates both when he was dehydrated and also after forced rehydration. His aldosterone level was found in the normal range. As you probably know, angiotensin affects thirst and is possibly involved in more than just maintaining the serum sodium concentrations. Perhaps his constant lack of water may have been a factor; nevertheless, restoring his hydration acutely did not restore the angiotensin levels to normal.

Two lumbar punctures were done, and both showed high levels of protein (82 mg/100 ml in March and 58 mg/100 ml in May 1971), while the Lange curve was also a little abnormal too. A barium meal and intravenous pyelogram were done because of his striking abnormalities in water handling, and both were normal. Skull radiology including an air encephalogram was also done again, seeking an abnormality in the region of the hypothalamus. Will Dr. Doyle please show us these?

*Kindly estimated for us by Dr. C. Edwards of St. Bartholomew’s Hospital.
†Kindly estimated for us by Dr. G. Boyd and Dr. M. B. S. Jones of St. Mary’s Hospital.
SKULL RADIOLOGY

DR. DOYLE: The plain x-ray films of the skull in February 1971 again showed no abnormality. The air encephalogram failed to demonstrate a mass in the region of the hypothalamus. The general radiologists were puzzled by an apparent discrepancy in the size of the lateral ventricles and by the thickness of the lower half of the septum pellucidum shown on this anteroposterior tomographic section (fig. 6). Radiologists more experienced in neuroradiology, on assessing the examination as a whole, thought that the appearances were within normal limits. This was the final agreed comment from our department.

PROFESSOR RUSSELL FRASER: Well, we had both a clinical syndrome and a lot of metabolic data pointing to hypothalamic disorder, but it was difficult to define the nature or position of the lesion. As he had a persistently high E.S.R. we were anxious to be sure that he did not have a treatable condition such as systemic lupus or a granuloma. We asked Dr. G. Hughes to measure the DNA binding in serum. This was normal, but, alternatively, might he have a sarcoid lesion there? We therefore discharged him for a period on heavy doses of corticosteroids, but the latter had no effect on his syndrome. So the evidence was all against his having a treatable granuloma.

His subsequent progress was slowly downhill and finally he became more confined to bed, more confused, and more quadriplegic, and eventually went into coma and died at the age of 13 years and 7 months.

Our final diagnosis was that he had a progressive hypothalamic disorder, though we were unsure about its nature; we felt it must be a tumour, though it had proved so difficult to define.

Dr. J. B. Burke, who referred him to us is here today. Is there any further point, Dr. Burke, which you could add to his history?

DR. J. B. BURKE (3): When I first saw this boy in 1968 I diagnosed diabetes insipidus and he was treated with injections of pitressin tannate, to which he seemed to respond. Then quite suddenly his mother noticed that he had stopped getting up to pass urine at night and was certainly no longer drinking excessively and she asked me if I thought the injections were really necessary. I said I thought they should be continued. Then one weekend he slept for forty-eight hours and had nothing to eat or drink and was brought to the hospital the following Tuesday, severely dehydrated—yet mentally he was quite bright. I admitted him to hospital and he was re-hydrated by intravenous infusion. I then sent him to Mr. Pennybacker at Oxford, who investigated him. We did not realize that his symptoms were those of severe dehydration related to a very low intake of fluid. He returned to us from Oxford still on vasopressin and we soon realized that apart from bizarre behaviour, the main clinical problem was in inducing him to drink. He would do anything to avoid taking fluid. It would be thrown into a plant, out of the window, or given to another child if he was not being watched and finally for the last two months of his life he was fed by nasogastric tube. He did not seem to realize that he was getting fluid this way, because if offered an ordinary drink it would lead to a most distressing scene, with screaming and fighting to avoid taking it. The amount of food he ate was very small indeed and presumably his good nutrition was maintained because he was not growing and we were managing to give about 800 ml of concentrated high calorie fluid, at first by mouth and later by tube.

PROFESSOR RUSSELL FRASER: Thank you very much. Now can we hear the necropsy findings, please?

Necropsy Findings

DR. P. D. LEWIS (4): A full post mortem examination was carried out by Dr. N. M. Kandawalla at the Royal Berkshire Hospital; no major abnormality of the thoracic and abdominal viscera was found. I am indebted to him for the opportunity to examine the brain.

Externally the undersurface of temporal lobes and cerebellum was discoloured. The mamillary bodies could be identified, and their size was normal, but the floor of the third ventricle bulged and was composed of abnormal granular grey tissue. The cerebrum was sliced in a coronal plane; the poorly preserved tissue was very fragile.

In essence, the slices showed very extensive infiltration by granular grey tissue extending from the septum pellucidum and white matter of the gyri recti backwards to involve the circumference of the third and bodies of the lateral ventricles, as well as the right internal capsule.

In a slice through the posterior border of the optic chiasma and tuber cinereum, granular bluish tissue is seen to expand the tuber and infiltrate the walls of the third ventricle. No normal hypothalamic structures were found under the microscope. The midline structures—fornix and septum pellucidum—are similarly infiltrated. The bodies of the lateral ventricles are dilated, but asymmetrically—the septum being displaced to the right. Their walls contain similar abnormal tissue, which extends through the right lentiform nucleus to the...
internal capsule, which can be defined on the left but not the right. Their walls contain similar abnormal tissue, which extends through the right lentiform nucleus to the internal capsule, which can be defined on the left but not the right.

About 4 mm posteriorly, in a slice through the mammillary bodies, abnormal tissue is seen in the walls of the third ventricle. The lateral hypothalamic area is macroscopically normal. This section, like the previous one, show infiltration and distortion of midline structures and the lateral ventricular walls.

So, macroscopically, there is abnormal tissue in the walls of the third ventricle, replacing at least part of the hypothalamus, and infiltration of the septum pellucidum, fornix, lateral ventricular walls, and the right internal capsule. At this point I should say that the pineal, brainstem, and cerebellum were grossly normal.

Microscopically, the abnormal midline masses are composed of sheets of cells with a high nuclearto/cytoplasmic ratio and prominent vessels. The stroma is free of collagen and reticulin is confined to the region of blood vessels. No glial fibrils are present. Neurones are identifiable—though interspersed with tumour cells—in the lateral hypothalamus and supraoptic nuclei; the medial, anterior, and paraventricular areas were destroyed.

At a higher power (fig. 7a) the abnormal tissue seems in part to be composed of lymphocytes, but these are mixed with large polygonal and spheroidal cells with well-defined boundaries, chromatin-rich nuclei, and mitoses. Beyond the macroscopic edges of the tumour there is extensive microscopic infiltration, especially in the adventitia of blood vessels. A gemistocytic astrocyte reaction and some breakdown of myelin is also present at the tumour margins. A similar pattern of spread is found in the lateral ventricular walls, the tumour cells infiltrating the vessel walls (fig. 7b) and spaying the layers of perivascular reticulin.

This pattern is rather like that found in microgliomatosis (primary brain lymphoma) and the distribution of tumour so far seen is like this neoplasm, but the difference is that in today's case two distinct cell types can always be identified, either in the vessel wall or in the intervening tissue.

Microscopic spread was found elsewhere in the ventricular system; in the wall of the temporal horn, around the aqueduct in the mid-brain, and within the fourth ventricle. It had also occurred in the meninges; the arachnoid of the base of the brain and over the insula contained tumour cells.

This is clearly a malignant neoplasm—infiltrating locally, spreading along the perivascular spaces and in the meninges and C.S.F. pathways. In its dual cytological appearance it is strikingly similar to seminoma of the testis. The primary seminoma-like tumour found in the brain is known variously as pinealoma, atypical teratoma of pineal, and germinoma. It is usually found in relation to the pineal (in young males). Because of the mixture of lymphocytes and epithelial tumour cells, it has been regarded as an unusual (hence atypical) form of teratoma; this view is supported by the occasional presence of areas of tubules, squamous epithelium, cartilage, trophoblast, and other elements. Nevertheless, the presence of the lymphocytes is just as likely—if not more likely—to be evidence of an immune phenomenon, and when this tumour is transplanted into animals the large cells proliferate but the lymphocytes disappear. Whatever its histogenesis, and its relation to the testicular seminoma, it is sometimes found away from the pineal, which may be normal (as here). The floor of the third ventricle/tuber cinereum is a recognized site—hence the term ectopic pinealoma, which is absent when the pineal can be shown to be normal.

The current practice is to call this tumour a germinoma, which does not presuppose its origin and serves to remind us of its link with seminoma.

Discussion

PROFESSOR RUSSELL FRASER: We have a clearly stated pathological diagnosis, but we are not all familiar with that pathology. How often would you expect a tumour like that to be infiltrative rather than localized as a tumour?

DR. LEWIS: They are malignant tumours. On the whole they carry a poor prognosis: they tend to infiltrate and to metastasize, in contrast to the typical pineal teratomas. This particular histological type is always malignant.

DR. KRISTIN HENRY (5): Is this atypical in the sense that usually you have more epithelial cells? There were very numerous round cells in some areas, with very few of the large cells.

DR. LEWIS: Yes, that is true. This is an atypical “atypical teratoma,” which perhaps shows more of the lymphoid element than usual, though this is variable from area to area. In fact some areas showed a preponderance of the large cell over the lymphoid element. Nevertheless, the histology and the site, together with the age and sex of the patient (these tumours almost always occur in young males), leave me in no doubt about the diagnosis.

DR. D. CALNE (6): Were there neoplastic cells in any of the C.S.F. examinations? With a tumour like this, which has infiltrated so much of the C.S.F. pathway, one might expect to find them.

PROFESSOR RUSSELL FRASER: No neoplastic cells were found. The protein level, of course, was quite clearly abnormal, and probably signified the same thing.
DR. LEWIS: The Lange curve result was a red herring, because you can get a first or mid-zone rise in neurosarcoid. I do not know what the change could be due to in this patient.

VOICE FROM AUDIENCE: How do primary lymphomas affect the central nervous system?

DR. LEWIS: They do not spread in quite the same way; they do not seed in the meninges and the C.S.F. pathways. Primary lymphomas of the brain infiltrate into the brain chiefly from the subependymal region, along the vessels but without going through the ependyma and into the C.S.F. or into the meninges.

VOICE FROM AUDIENCE: This lad was getting prednisone most of the time, perhaps unnecessarily, since on his insulin tolerance test there was a normal response of cortisol. It seems difficult to fit in his diabetes insipidus. We know that sometimes as a pituitary tumour increases in size the A.C.T.H. secretion is affected, and then there is relief of the diabetes insipidus itself. Could this have happened here? And further, when the test measuring vasopressin was carried out, how did he have some vasopressin secretion?

DISAPPEARANCE OF DIABETES INSIPIDUS

PROFESSOR RUSSELL FRASER: I do not think that in his case the disappearance of the diabetes insipidus had anything to do with lack of cortisol; it did not return when he was given corticosteroids. But symptoms of diabetes insipidus sometimes go when the patient becomes cortisol-insufficient. There is no evidence, however, that this patient at any stage really was cortisol-insufficient. His normal ability to produce cortisol in the response to hypoglycaemia was demonstrated a year after his development of fluid refusal. We picture that his lesion started in a region of the hypothalamus which impaired the release of vasopressin first of all without completely destroying it, and that later the lesion spread, as you saw, to impair the area involved with thirst appreciation, and that it was the thirst deficiency or hypodipsia which was his major defect in water handling. And that led to a lot of important consequences including his abnormal behaviour and his fever.

DR. LEWIS: I agree. In rats, if you make an isolated lesion in the lateral hypothalamus, you can produce a picture rather like the syndrome of hypodipsia and hypernatrema seen here, and these animals will be averse to water in just the same way as today's patient. It is important to recognize this syndrome because this is common in patients with lesions around the hypothalamus. With Dr. P.T. Lascelles I collected nine of these in an 18-month period. These patients with perhaps a normal total exchangeable sodium, a low blood volume, and a low extracellular fluid volume become stabilized with a low fluid intake, a low urine output, and a very hyperosmolar serum. Clearly they are very much at risk both from dehydration and water overload. So it is important to recognize the significance both of the hypernatrema and of the reduced thirst in these cases.

PROFESSOR RUSSELL FRASER: An analysis of a series of patients who were subsequently diagnosed as hypothalamic disorders (see table) shows that precocious puberty or the opposite, gonad failure, was a common presentation, occurring in 72% of them; next came diabetes insipidus, perhaps often going on, like our patient, to hypodipsia. Other common presenting manifestations you will note are neurological, especially pyramidal or eye signs, or both, as well as other rarer syndromes. In patients with suspected hypothalamic lesions quite often unsuspected visual field defects will emerge, though they did not in our patient. But in several other patients who also presented with diabetes insipidus, and showed no clues on skull x-ray films, the visual fields have given us the clue to a tumour pressing on the outside of the hypothalamic area.

Endocrine:

- Precocious puberty or hypogonadism 72%
- Diabetes insipidus 35%
- Obesity 25%
- Dysthermia 25%
- Nephrosis 18%
- Bulimia 7%
- *Anorexia 7%
- Growth retardation 7%
- Hypodipsia 7%
- Hyponatraemia 7%
- *Stated by our patient: 60 patients with neoplasias (51 neoplastic, seven inflammatory, and two degenerative lesions).

Aversion to fluid

DR. G. F. JOPLIN (7): Dr. Lewis, should we have given the factor of chronic aversion to water more emphasis? This boy was not just indifferent to thirst, but he was positively averse to having any liquid put in front of him, and is this a specific sign of a lesion in the hypothalamus rather than a lesion at the site of the pituitary, which was the alternative location to explain his endocrine syndrome?

DR. LEWIS: Especially in view of the experimental evidence, I think that this is very important and that it is a specific symptom. The nine other patients that I have referred to did not show this—all of them showed a lack of thirst, and some had almost to be force-fed with water, but none showed the same sort of positive aversion to drinking and devisous disposal of unwanted water, analogous to the severe case of anorexia nervosa. I think it is an important and specific symptom.

DR. JOPLIN: Can we be assured that the pituitary in fact was not involved? I know this material was examined elsewhere but have we got assurance on that?

DR. LEWIS: I have not.

VOICE FROM AUDIENCE: You would expect the pituitary to be normal in this situation, probably on the evidence we have. He had no gross disorder of response to hypoglycaemia and he did in fact continue to grow slightly. We did perform a T.R.H. test on this boy and he had a normal T.S.H. response to T.R.H. That implied little, if any, pituitary damage.

PROFESSOR RUSSELL FRASER: The other bit of anatomical evidence we have, I think, about the whereabouts of this hypothalamic lesion was that he was able to release A.C.T.H. during hypoglycaemia, but not growth hormone. The growth-hormone releasing centre, which is believed to be nearer to the ventricular cavity, was evidently destroyed—as was the thirst centre—but not the A.C.T.H. one, which is believed to be further lateral.

DR. CALNE: Would Dr. Lewis comment on what appears to be a conflict between this patient, in whom the hypodipsia was a dominant feature, and the series of 60 cases (see table), in which hypodipsia was not mentioned. Isn't this rather odd?

DR. LEWIS: It is one of those things you have got to look for specifically. It may not be dramatic in a patient who is stabilized at a low water intake and low blood volume.

PROFESSOR RUSSELL FRASER: This was a series of patients culled as long ago as 1954 diagnosed as having hypothalamic disease. It is not a random sample of hypothalamic disease: only the cases they recognized.

Another point—you did, I think, find some of these lesions in the frontal horn of the lateral ventricle?

DR. LEWIS: Yes.

PROFESSOR RUSSELL FRASER: To what extent some of his behaviour pattern was really a frontal manifestation, as against hypothalamic, is difficult to know. At any rate, tracts run between the two. Dr. Calne, would you like to express a view on the basis of his abnormal behaviour?
ABNORMAL BEHAVIOUR

DR. CALNE: With a tumour like this infiltrating so widely through the brain it is impossible to identify which portion was responsible for the behavioural disturbances.

DR. LEWIS: He has lesions of his mammillary bodies and fornix. Did he have a Korsakoff's psychosis?

PROFESSOR RUSSEL FRASER: I think my description of his behaviour was pretty nearly a Korsakoff's psychosis, excepting that Korsakoff's psychosis is not so much a lack of memory but a tendency to confabulate, without correction from the present environment.

DR. LEWIS: Yes, though the confabulation is linked to a failure of recent memory—confabulation fills in the gaps.

PROFESSOR RUSSEL FRASER: That is what we think. Some of these people also get little hallucinations with small animals floating about. But in the lesser degrees of the syndrome such features are not so striking.

DR. JOPLIN: He did indeed have this ability to confabulate. In fact, he often took us in before we realized that this was so. While he was in the ward, he would describe in great detail, and in all sincerity, what he had been doing all the morning, such as going to school. He appeared to believe his own confabulation.

VOICE FROM AUDIENCE: Was this tumour very close to the pineal body? What is the present view of endocrine function of the pineal body?

DR. LEWIS: No. The pineal body sits above the back of the third ventricle, and this tumour was at the front and bottom of the third ventricle; and the pineal was grossly and microscopically normal. The pineal is an endocrine organ, of course, in mammals. It regulates endogenous physiological rhythms, through being indirectly photosensitive. It has an antagonado-trophic action, and produces melatonin with a diurnal rhythmicity opposite to that of A.C.T.H.

PROFESSOR RUSSEL FRASER: Melatonin, which releases the M.S.H.—releasing factor, so we are told, and how much that is involved in the rhythms is hard to say; but these are the functions claimed for it.

VOICE FROM AUDIENCE: Why did you originally think this might be a granuloma? Was it because his E.S.R. was increased? Or was there any other reason? The reason why I ask is because I am familiar with a case practically identical, except for two differences—he did not present with diabetes insipidus (but a high sodium and white cell and coma) and the second difference is that he did not die. And now several years later he still has to be forced fluids and he still has to be on a low sodium—but he is growing. Extensive examinations were undertaken to look for a hypothalamic lesion, and short of craniotomy, nothing could ever be discovered.

PROFESSOR RUSSEL FRASER: There were two reasons we suspected this might be a granuloma; we could not demonstrate an anatomical tumour, and he had a persistently high E.S.R. And, of course, we have seen other cases presenting with diabetes insipidus, going on to get a few pyramidal tract signs, who turned out to have sarcoid, and these are very treatable. We have such a patient who for about ten years has been apparently perfectly well after having been treated by corticosteroids.

DR. LEWIS: Sarcoid in the brain may grow in a tumorous fashion. It need not be just a layer of chronic inflammatory tissue in the meninges, and it may form big lumps within the brain. Neurosarcoid and perhaps an optic glioma or germinoma is perhaps the main differential diagnosis of a hypothalamic tumour in the young patient. Perhaps hypothalamic granulomas should be diagnosed with caution, for I have seen a patient who was diagnosed as Hand-Schüller-Christian disease, and another who was diagnosed as histiocytosis X—both granulomas—which ultimately turned out to be germinomas.

PROFESSOR RUSSEL FRASER: We have covered quite a number of the problems that may be easier to solve in the future with better means of diagnosing the lesions in the hypothalamus.

This Conference was recorded and edited by Dr. G. F. Joplin.

APPOINTMENTS OF SPEAKERS

(1) PROFESSOR RUSSELL FRASER, Professor of Clinical Endocrinology, Royal Postgraduate Medical School.

(2) DR. P. H. DOYLE, Reader and Deputy Director, Department of Diagnostic Radiology, Royal Postgraduate Medical School.

(3) DR. J. B. BURKE, Consultant Paediatrician, Royal Berkshire Hospital.

(4) DR. P. D. LEWIS, Lecturer (Neuropathology) and in Department of Medicine, Royal Postgraduate Medical School.

(5) DR. KRISTIN HENRY, Lecturer, Department of Morbid Anatomy, Royal Postgraduate Medical School.

(6) DR. D. B. CALNE, Lecturer in Neurology, Royal Postgraduate Medical School.

(7) DR. G. F. JOPLIN, Senior Lecturer in Medicine, Royal Postgraduate Medical School.

References