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RETINAL APLASIA AS A CLINICAL ENTITY

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[WITH SPECIAL PLATE]

Blindness in infants is occasionally seen with apparently normal eyes or eyes in which minimal fundus anomalies are present. Such cases present considerable diagnostic difficulties. Frequently there is uncertainty whether the disks are normal or atrophic, and the term "cortical blindness" is occasionally used, though this is little more than a terminological escape from a real problem. When fundus anomalies are present they are generally ill defined and have an uncharacteristic appearance, such as the occasional diffuse fine pigmentation that goes under the designation of "pepper-and-salt fundus"—a fairly definite recognition that there is some form of retinal atrophy. The after-history of these cases with apparently normal fundi or fundi with minimal anomalies is not well established. The following case reports are presented as indicating that some of these cases, at any rate, are genetic in origin and progressive in character.

Case Reports

1. The M-n Family

Pedigree Chart 1 shows five observed cases of blindness over two generations, with a probable sixth case in an antecedent generation. None of the marriages recorded were consanguineous.

Case 1.—Gerald M., the proband (III, 16 in Chart 1), aged 9 years. Blindness was noted in infancy, and the child was admitted to the Ellen Terry Home at Reigate at the age of 6 as blind and mentally defective. The general appearance of the boy is normal. His head is small, but within normal limits. Apart from mental defect there is no gross abnormality of his central nervous system. At the age of 8 he had a developmental age of about 2½ years. There is no evidence of any environmental factor which might have caused the mental defect. The eyes are outwardly normal. The fundi (Special Plate, Fig. 1) show diffuse and rather gross pepper-and-salt pigmentation, exposure of the choroidal pattern, narrow retinal arteries, and uniformly grey disks, the margins of which are not sharply defined. The pupils react sluggishly to light, but the child does not seem to possess any perception of light. The most incongruous aspect is the disproportion between the relatively slight ophthalmoscopic findings and the gross visual defect.

Case 2.—Ronald M. (III, 13); aged 15 years, eldest brother of the proband. Blindness was noted at 6 weeks, and he was grossly backward from infancy. He was admitted to the Ellen Terry Home, Reigate, at the age of

6 years. Apart from his idiocy he had no other signs of neurological disorder. He was later transferred to Pewsey Hospital, where he died at the age of 15. When examined three months before his death both eyes appeared sunken in. There was severe nystagmus, and apparently no perception of light, as the pupils were inactive. The media were clear. The fundi showed pale atrophic disks with thin vessels, and scattered all over the fundus background were areas of pigmentation and atrophy of the diffuse chorio-retinitis type. Fairly large transverse oval atrophic patches were present towards the central area, placed symmetrically in the two eyes. The retinal appearances were therefore of essentially the same order as those shown by his brother, though at a more advanced stage. Post mortem the brain

CHART 1.—The M-n family. The proband is indicated by an arrow.

showed no gross abnormalities (Dr. L. Crome and Dr. D. Oppenheimer), while the retina showed extensive atrophy involving all the layers.

Case 3.—William M. (II, 5), aged 38, the father of Cases 1 and 2; he is an alert, intelligent man, and has been blind from birth. The eyes are outwardly normal. He has no perception of light and never has had any. Nystagmus of the pendulum type is present. Ophthalmoscopically, the appearances are those seen in his eldest son, though markedly exaggerated. The normal landmarks in the fundi are not readily picked up; the background is not uniform in colour: in the central area it is rather atrophic with a tendency for the underlying sclerotic to show through; elsewhere there is a diffuse whitish sheen broken by much

crude pigment irregularly scattered over the fundi and definitely not of the bone-corporuscle type. The disk itself is ill defined in the surrounding atrophic retina, and the vessels are markedly narrowed. A striking feature is the essential symmetry in appearance of the two fundi.

Case 4.—Mrs. Daisy L. (II, 8), aged 30, an aunt of the affected children. She too is mentally normal, and has been blind from birth. She has no perception of light and never has had any. Nystagmus is present. Her fundi are very similar in detail to those of her eldest nephew.

Case 5.—Mrs. Dorothy M-k (II, 4), aged 40, another aunt of the affected children. Like her brother and sister, she has been totally blind since birth, never having possessed any perception of light. The eyes are outwardly normal apart from nystagmus, and she is mentally normal. Ophthalmoscopically, the appearances are more complicated than in the other members of the family. The right eye shows lenticonus posterior, while the fundus (Special Plate, Fig. 2) shows a uniformly white disk with the vessels barely perceptible. In the background there are many localized atrophic areas with irregular edges, too jagged to fit into the picture of gyrate atrophy. In the left eye the lens is dislocated into the vitreous and the fundus is most unusual. There is little red reflex, most of the retina being detached and dirty grey in appearance, suggestive of much fibrosis. Such red reflex as is present is broken by exceptionally heavy pigmentation. The disk is markedly white and the vessels are exceedingly attenuated. There is no history of trauma.

Excluding the appearance in the left eye in Case 5, as probably complicated by secondary effects of trauma, these five cases show a progressive increase of fundus lesions with age, the mildest being of the proband. It is likely that the trouble originated with I, 1, who died at the age of 53, but had been blind from birth. According to the history given by his son, II, 5, the trouble had been diagnosed as disease of the optic nerve; he is reported to have been mentally normal.

These five cases have in common a history of total blindness going back to infancy, and presumably present at birth. The basic lesion in all five is likely to be retinal in site and progressive in character—a reading supported by the presence of severe nystagmus even in the youngest patient. It is particularly noteworthy that in the youngest patients the ophthalmoscopic appearances are relatively mild and unspecific, as distinct from the heavy involvement seen later in life. The mode of inheritance is clearly dominant.

2. The R-e Family

Pedigree Chart 2 shows four affected children in a sibship of five, the offspring of unaffected and non-consanguineous parents. The four affected children were first seen by one of us (A. S.) in 1949, and presented essentially identical fundus appearances: optic atrophy with some narrowing of the retinal vessels in addition to considerable mottling of the maculae, without any obvious involvement of the rest of the fundus. As there were no neurological associations, and the eldest of the four affected children was 9 years of age and the youngest 1 year old, and as all the children had been affected from early infancy, it was clear that a cerebro-macular affection of either infantile or juvenile type was excluded, while the optic atrophy, as also the age distribution, excluded the possibility of macular dystrophy. No further investigation could be carried out at the time.

This family came recently under the supervision of one of us (C. W.), and thus offered the opportunity of

further examination. The clinical details of these four patients were as follows:

Case 6.—Grace R. (II, 1 in Chart 2), aged 19. Labour was prolonged and difficult; weight at birth was 5½ lb. (2.495 kg.). The child's face was said to have been severely bruised. Blindness was noted in infancy, and appears to have presented considerable diagnostic difficulties. Different observers, judging by the documentary evidence, had regarded the fundus appearances as those of optic atrophy, retinal atrophy, macular degeneration, and malformation of the optic disk. She was slow in attaining the normal milestones of development, and was deemed to be educationally subnormal. Physically she is rather dwarfed. There is no

CHART 2.—The R-e family.

evidence of neurological disorder. In regard to both her physique and her intelligence level she differs from her other four siblings, who are within the normal range. Emotionally she is very immature, and she is in need of special care, being incapable of supporting herself or of managing her affairs without a good deal of help.

When she was re-examined recently the findings in the right eye were those shown in Special Plate, Fig. 3. The disk was atrophic; the retinal vessels were attenuated; there was mottling at the macula, while the periphery showed some sheen with fine pepper-and-salt mottling. The picture was therefore one of retinal atrophy. The lens showed a small posterior cortical opacity. In the left eye the iris was atrophic and the lens totally opaque. There was no perception of light in either eye, and the eyes showed rather marked pendulum nystagmus.

Case 7.—Jennifer R. (II, 3), aged 15. The blindness was noted in infancy. Mentally she is normal. Perception of light was present in the left eye, but only doubtfully present in the right, while both eyes showed pendulum nystagmus. The fundi were essentially similar to those of her elder sister—atrophic disks, marked attenuation of the vessels, and an ill-defined granular appearance over the whole of the fundus. The left macula was ill defined, but the right showed a pigmented scar very much like a coloboma.

Case 8.—Margaret R. (II, 4), aged 12. Here too blindness was noted in infancy, and intelligence is normal. Nystagmus was present, while perception of light was absent. The appearances of the disk and vessels were those seen in her sisters, but the fundus background was distinctly more patterned, as can be seen from Special Plate, Fig. 4. There were areas of depigmentation throughout, with exposure of the choroidal vessels here and there, and possibly hyaline dots towards the centre.

Case 9.—Edward R. (II, 5), aged 11. The history here, and the mental condition, are as in Cases 7 and 8. He has no perception of light. Nystagmus is more marked than in his sisters, while the disk and vessels are very similar. The maculae could not be defined; the fundus background showed in a mild form the same type of depigmentation as seen in his sister Margaret.

In this family the affection was in all probability present since birth, and showed the total blindness seen in the first family. The two youngest members showed a rather more advanced fundus picture than the two

A. SORSBY AND C. E. WILLIAMS: RETINAL APLASIA AS A CLINICAL ENTITY

FIG. 1.—The right fundus in Case 1, a boy aged 9. The disk is grey, the arteries and veins are narrow, and the fundus background shows diffuse mottling of a crude pepper-and-salt type.

FIG. 3.—The right fundus in Case 6, a girl aged 19. There is marked optic atrophy, with fine pepper-and-salt changes throughout the fundus.

FIG. 2.—The right fundus in Case 5, a woman aged 40, an aunt of the boy shown in Fig. 1. In addition to advanced optic atrophy with marked narrowing of the retinal vessels, there is crude pigmentation scattered throughout the fundus with extensive areas of chorio-retinal atrophy.

FIG. 4.—The right fundus in Case 8, a younger sister of the patient shown in Fig. 3. The fundus background shows the same advanced optic atrophy, and a considerably more obvious retinal atrophy is shown by the crude pepper-and-salt patterning. Note the similarity to Fig. 1 depicting a member of a different family.

oldest children, but in all four the pattern was clearly that of an extensive retinal atrophy involving the maculae and disks. Mentally the children were normal, except that the eldest was rather simple. In all probability the mode of inheritance was recessive.

Discussion

1. Retinal Aplasia as a Clinical Entity

The two families recorded here have in common total or subtotal blindness present in infancy, and probably from birth, with a presumably featureless fundus other than an ill-defined macular area and pale disks; nystagmus may possibly be present from the beginning. Cases of this type are not particularly uncommon as isolated occurrences, and the difficulty in diagnosis they present has already been indicated. The present study brings out the fact that not only are some at least of these cases genetic in origin, but that the affection can be either recessive or dominant.

The evidence for a recessive affection is broadly based, for the recent study by Alström and Olson (1957) has clearly defined this entity. Since 1897 elementary education has been compulsory for blind children in Sweden, and there is one central elementary school through which they all have to pass. In an investigation on the material from 1897 to 1948 they paid special attention to the cases recorded as congenital retino-choroiditis without known cause. It became clear that these cases were proband material leading to families, and altogether 105 families were isolated. The material was found to overlap with cases admitted as suffering from "congenital amaurosis" and from congenital optic atrophy of unknown origin. In all, 175 affected and 303 unaffected sibs were traced. Cases examined under the age of 15 years were found to consist of 61% with "retino-choroiditis," 28% with congenital amblyopia, and 10% with optic atrophy. Two cases had cataract on admission to the school. When the collected material was classified into three age-groups—under 15, 15–45 years of age, and over 45—the incidence and extent of retino-choroidal changes were found to increase progressively, while the incidence of congenital amblyopia without fundus lesions declined. The term "retino-choroidal changes" covers a wide range of lesions from minute round pale spots at the periphery, scarcely visible, to heavy irregular pigmentation scattered throughout the fundus. While some optic atrophy and a moderate degree of narrowing of the vessels were common, optic-nerve lesions were not as conspicuous as in cases of retinitis pigmentosa with equally severe impairment of sight. Moreover, in the youngest age-group total or subtotal blindness without any fundus changes was present in some 33% of cases. Associated conditions were cataract and keratoconus—cataract being present in some 10% of the youngest patients and increasingly in the higher age-groups, while keratoconus was present only exceptionally in young patients, but again increased with age. Different members of the same sibship showed the different components to a variable degree. Variations therefore occur not only with age, but as between families and between individuals within the same family. A striking aspect was the gross impairment of vision noted soon after birth or during the first year of life. Nystagmus was a common association, and the electroretinographic response was abolished in almost all cases. Genetic analysis showed the condition to be a monofactorial

recessive affection widely scattered throughout Sweden, with a probable mutation rate of $2.3 \cdot 10^{-5}$. There was no significant excess of mental anomalies in this group. Alström and Olson regard the affection as responsible for about 10% of all cases of blindness in Sweden.

A recent investigation into the causes of blindness in the Netherlands revealed 227 cases of this affection—114 in adults and 113 in children (Schappert-Kimmijser *et al.*, 1959). These observers estimated that 18% of all blind children in Holland suffer from this affection. Of 56 children examined in detail, 14 showed major neurological or psychiatric disturbances, including 5 cases of epilepsy. The affection was recessive and particularly prevalent on the isolated outlying island of Urk, where consanguineous marriages had been common for several centuries.

The findings recorded in the second family in the present study clearly conform to the accounts given by the Swedish and the Dutch observers, down to the detail that in this one family there were variations in the fundus appearances, a mental anomaly, and lens changes.

The occurrence of the same affection as a dominant disturbance is suggested by the report on the first family. The fundus appearances and the clinical course in the two families are so similar that it would be impossible to distinguish—except by the family history—a member of the first family with its dominant inheritance from a member of a family with the recessive type. Alström and Olson have suggested the name of "heredo-retinopathia congenitalis monohybrida recessiva autosomalis." It is obviously not advisable to label the affection as exclusively recessive. Even the designation of "heredo-retinopathia congenitalis" is not very happy, nor is the designation "amaurosis congenita (Leber)" suggested by Schappert-Kimmijser *et al.* The simpler term "retinal maldevelopment" or "retinal aplasia" would serve as well.

2. The Wide Range of Fundus Appearances in Retinal Aplasia

The marked polymorphism of the fundus lesion is clearly seen when comparing the early stages with the end stages. Progressive changes do, of course, occur with all abiotrophies, but generally, as in retinitis pigmentosa, the different stages are clearly recognizable as belonging to the same affection. Retinal aplasia falls within the small group of disorders in which the wide range of appearances during the course of the affection are such that they are not readily recognized as belonging to the same disorder. While this makes diagnosis more complex, it helps in recognizing the significance of unusual fundus appearances. Retinal aplasia is in this respect as protean as choroideremia and generalized fundus dystrophy with their exceptionally wide range of intermediate stages.

3. The Mental Defect

In contrast to the relatively mild mental anomaly in one patient in the second family, the first family showed severe mental deficiency of a non-specific type in the two affected children in the third generation, though the three affected members in the second generation were mentally normal, and the reputedly affected individual in the first generation was presumably also normal. As there was no gross structural defect in the brain of Case 2, as seen post mortem, and the brain is at present being studied in greater detail, it is best to

leave this aspect for future consideration. It is not possible on the available evidence to decide whether a severe mental defect is indeed an inconstant component of the dominant variety of the affection.

4. Differential Diagnosis

Once it is appreciated that retinal aplasia is a congenital anomaly with a progressive course, there is little to take into account in the differential diagnosis of the affection. The following considerations arise.

Congenital Hereditary Optic Atrophy.—It is likely that in some families congenital optic atrophy runs such a severe course that there is blindness from birth. Commonly, however, congenital optic atrophy shows deep atrophic cupping, and there is a relatively mild disturbance of vision with relatively slow progression of the defect. The total or subtotal blindness seen in retinal aplasia is therefore the significant point in the differential diagnosis of the two affections. Thus the progressive course of congenital hereditary optic atrophy is shown by increasing failure of vision, whereas the progressive character of retinal aplasia is revealed not so much by the increase of the blindness—which in most cases is total to begin with—but by the increasing pigmentary and atrophic changes in the retina. The modes of inheritance of the two affections do not help very much, for both apparently have recessive and dominant forms. For the present little is known of the relative frequency of the dominant and recessive types in either of these affections.

Congenital Optic Atrophy of Uncertain Origin.—When an environmental factor cannot be clearly established in a sporadic case of optic atrophy present at birth, the possibility that the infant represents an isolated case of hereditary optic atrophy or of retinal aplasia must be considered. Without the supporting evidence of other cases in the family the diagnosis will remain uncertain until the secondary degenerative changes of the retina in retinal aplasia become manifest later in life.

Aplasia of the Optic Disk.—Here the obvious anomaly of the disk, and possibly also vascular anomalies, are pathognomonic.

Chorio-retinitis of Inflammatory or Infective Origin.—In their early stages the ophthalmoscopic features in the retinitis resulting from maternal rubella during pregnancy, and in the lesions of congenital syphilis, congenital toxoplasmosis, and congenital cytomegalic inclusion disease, are all likely to be considerable, while the visual defect is unlike the total or subtotal blindness seen in retinal aplasia. In the later stages, with possibly increasing visual disability, the history would indicate that the inflammatory disorders began with relatively mild visual disturbances.

Cerebro-macular Degeneration.—The characteristic age of onset and clinical course and the associated neurological disturbances of the different clinical types of cerebro-macular degeneration preclude any difficulties in the differential diagnosis.

Retinitis Pigmentosa and the Macular Dystrophies.—These conditions hardly arise in the differential diagnosis, as the affected children were normal ophthalmoscopically and had normal visual acuity until the onset of the affection at variable periods in life—a sharp contrast to the blindness at birth in retinal aplasia.

5. Possible Pathological Basis

The one histological examination at hand refers to the retina in a boy aged 16, and, as already noted, there was a non-characteristic extensive degeneration of all the layers. Until histological material of a retina at a very much earlier stage becomes available it is impossible to incriminate specifically the neuro-epithelium or any other layer; one can only offer surmises of a general character. The intensity of the lesion at birth presupposes that the retina either had failed to develop into functioning layers or had developed normally only to degenerate before birth. It is tempting to draw a parallel with retinitis pigmentosa. We now know that in retinal dystrophy in the mouse, the Irish setter, and the rat, where the ophthalmoscopic picture and clinical course are reminiscent of human retinitis pigmentosa, the affection is due to failure in the final differentiation in the rod layer, which itself is already laid down and clearly distinguishable (Sorsby *et al.*, 1954; Lucas, 1954; and Lucas *et al.*, 1955). If human retinitis pigmentosa does indeed represent a retina that has developed fully enough to function apparently normally—though presumably not so fully as to give a normal electroretinographic response or normal dark-adaptation—then retinal aplasia might be considered as the counterpart of retinitis pigmentosa in so far as the failure of development has occurred at an earlier stage, so that the retina has never reached functional maturity. On this reading retinal aplasia and retinitis pigmentosa are in fact closely allied affections, aplasia representing an earlier and more severe failure in retinal development. Both affections have a considerable post-natal course. In retinal aplasia this is shown by degenerative changes visible ophthalmoscopically, and presumably histologically; in retinitis pigmentosa the post-natal changes are shown by the development of the typical ophthalmoscopic picture and the steady disintegration of visual functions.

6. The Place of Aplasia Among Congenital Anomalies

Blindness at birth is not a common affection, and when present there are generally obvious physical anomalies in the globe, extending up to anophthalmos. These are the classical congenital defects. Retinal aplasia is of significance in that, like retinitis pigmentosa, it focuses attention on the failure of development affecting not the eye as a whole but a particular tissue. For the present it is enough to raise the possibility that ocular tissues may show developmental arrest at different stages of development (including post-natal development) without necessarily showing the classical features of a congenital defect. In this scheme a congenital defect would represent an anomaly involving the whole organ, aplasia an arrested development of a tissue—an arrest sufficiently severe to prevent normal function—and dystrophy a post-natal degeneration of a tissue that has developed sufficiently to function adequately till degenerative changes set in.

Summary

An account is given of two family groups in which blindness was present early in infancy and in all probability from birth. The eyes are normally formed and the media clear; ophthalmoscopically the initial findings are of either a normal or slightly pale disk, and some mottling of the fundus background. While the blindness is generally total from the beginning, the

ophthalmoscopic features progress throughout life, giving crude pigmentary reactions of the chorio-retinitis type and well-established optic atrophy.

In one family the mode of inheritance was clearly dominant; in the second family it was in all probability recessive. In the first family the two affected children in the third generation showed gross mental defect. In the second family only one of the four affected sibs showed a mental anomaly, and that slight.

The brain and the eyes of the older of the two children in the first family came to necropsy. The brain showed no gross macroscopic anomalies; the retina was disorganized beyond the possibility of recognizing individual layers. The brain is being subjected to a more detailed study.

It is suggested that the blindness recorded here is determined by a failure of the retina to develop into a functioning tissue—aplasia of the retina—and that this undeveloped retina subsequently undergoes secondary degenerative changes. Attention is drawn to a possible parallel with the changes in the more fully developed retina seen in retinal dystrophy—a genetically determined retinal degeneration—in some strains of mice, rats, and the Irish setter.

It is pointed out that the findings in the second family recorded here conform to those described by Alström and Olson in their study on 105 families in Sweden in whom they observed a recessively inherited congenital retinopathy, and to the cases more recently reported from Holland.

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The "Recommendation on the Organization of Occupational Health Services in Places of Employment," discussed at the International Labour Conference in 1959, enumerates the functions of such services, having first stated that their role is essentially preventive. The list of functions includes surveillance within the undertaking of all factors which may affect the health of workers, and advice in this respect to management and to workers or their representatives in the undertaking; pre-employment, periodical, and special medical examinations; training of first-aid personnel and supervision and maintenance of first-aid equipment; education of works personnel in health and hygiene; compilation and periodic review of relevant statistics and research in occupational health. The United Kingdom Government and employers' and workers' delegates all voted in favour of this recommendation. A subject discussed for the first time with a view to the adoption of international regulations at the 1960 conference was protection of workers against ionizing radiation. (*International Labour Conference, 43rd Session, Geneva, 1959*, H.M.S.O., price 35s. 6d.)

CHEMOTHERAPY IN CHRONIC BRONCHITIS

INFLUENCE OF DAILY PENICILLIN AND TETRACYCLINE ON EXACERBATIONS AND THEIR COST

A REPORT TO THE RESEARCH COMMITTEE OF THE BRITISH TUBERCULOSIS ASSOCIATION BY THEIR CHRONIC BRONCHITIS SUBCOMMITTEE*

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Between June, 1955, and June, 1956, bronchitis caused the loss of 22 million working days among men in England and Wales, representing about a quarter of all male sickness incapacity (Ministry of Pensions and National Insurance).

Previous work has suggested that antibiotic treatment is of value in this condition; much of this work has been reviewed by May (1958), who considered the tetracycline group of compounds to be the most satisfactory. These compounds were used in recent investigations by Edwards *et al.* (1957), Elmes *et al.* (1957), Buchanan *et al.* (1958), and Moyes and Kalinowski (1959). Antibiotics may be given continuously throughout the winter on a prophylactic basis, or for short periods at the onset of certain respiratory symptoms, there being no clear evidence that either method is preferable. It has been suggested, however (May, 1958; Moyes and Kalinowski, 1959), that, where the expected number of attacks is small, intermittent treatment is less costly, the converse being true for more severe cases likely to have frequent attacks. The prophylactic value of 1 g. daily of potassium penicillin G and 2 g. daily of tetracycline were compared in a study by Cherniack *et al.* (1959). Penicillin was found ineffective compared with tetracycline in this trial, but 45 out of the 67 patients had demonstrable bronchiectasis, and the duration of treatment varied from 3 to 18 months, the seasonal differences being unstated. The diagnoses of patients lost from study were not stated, and on the whole the findings cannot be taken as applying to patients suffering from bronchitis.

The present trial† was undertaken first because previous trials had been based on small numbers and confirmatory evidence seemed desirable; secondly, the high cost of the tetracycline compounds suggested that the value of

*Members of the Subcommittee are: Dr. P. Baldry, Dr. J. R. Bignall, Dr. R. S. Francis, Dr. S. W. A. Kuper, Dr. G. P. Maher-Loughnan (honorary secretary), Dr. Robert May, Dr. E. N. Moyes, Dr. P. D. Oldham, Dr. Hugh Ramsay (chairman), and Dr. C. C. Spicer.

Dr. R. S. Francis and Dr. C. C. Spicer co-ordinated the work and prepared the report, which should be referred to as "British Tuberculosis Association (1959) . . . etc."

†The investigation was carried out at the following centres: Cambridge chest clinic (Dr. M. J. Greenberg and Dr. R. Bruce). Chertsey chest clinic (Dr. N. V. Birrell). Croydon chest clinic (Dr. R. J. H. Fanthorpe and Dr. J. F. Heffernan). Dudley chest clinic (Dr. M. Sheldon). Dundee chest clinic (Dr. R. N. Johnston). Edmonton chest clinic (Dr. R. S. Francis). Finchley chest clinic (Dr. B. A. Butterworth). Ipswich chest clinic (Dr. P. Embleton and Dr. D. van Zwanenberg). Islington chest clinic (Dr. J. Wallace Craig). Mansfield chest clinic (Dr. D. Davis). Preston chest clinic (Dr. M. R. Geake and Dr. R. S. Nicholson). Reading chest clinic (Dr. A. J. Karlish). St. Albans chest clinic (Dr. T. A. Watkin Edwards). Tunbridge Wells chest clinic (Dr. R. May). Walthamstow chest clinic (Dr. H. Ramsay). Willesden chest clinic (Dr. C. H. C. Toussaint and Dr. J. Mikhail).