Clinico-Pathological Conference

DIFFUSE PROGRESSIVE INTERSTITIAL FIBROSIS OF LUNGS IN INFANCY

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MR. LAUSTE: Our guest speaker tonight is Dr. Claireaux who is Morbid Anatomist at the Hospital for Sick Children, Great Ormond Street. He has recently been appointed to that post having been Pathologist at Queen Charlotte's Hospital. He is an expert on neonatal pathology and takes a particular interest in lung disorders. He is very well-known to pathologists and paediatricians and I would like to extend to him a special welcome and thank him for coming to take part in this Conference. I should like to add that we are indebted to the Nestlé Company who are giving support to this Conference and we do thank them for their generosity.

I will ask Dr. Mann to open the Conference and give details about two infants who were siblings believed to be suffering from diffuse progressive interstitial fibrosis of the lungs.

DR. T. P. MANN: Mr. Chairman, it is appropriate that we should be discussing this condition tonight because here we have an excellent example of a clinico-pathological syndrome. Indeed, it is probably more than an aetiological entity. This unique respiratory disorder was first described briefly by Hamman and Rich in 1935 as an acute and fatal affection in adults. Since this original description, nearly thirty years ago, quite a considerable literature has been built up around this disorder. The majority of reported cases have been adults and the number of published examples must now be well over a hundred. The first account of this condition in childhood was given by Bradley from the United States of America in 1956 who reported the clinical and autopsy findings in a nine-year-old girl. Subsequently eighteen childhood examples of this syndrome have been published in the literature. Of these eighteen, five have occurred in infants under one year of age and one of these is actually Christine, the first case we shall be considering in a moment, (Mann, 1959). If, by the end of

this meeting, it is generally agreed that Christine's brother, the second case to be presented, was also similarly affected—I might say here that clinically this case does not conform to the accepted clinical picture of diffuse progressive interstitial fibrosis of the lungs—but if, nevertheless, you think that it fits into the same pattern then this will be the sixth example I know of occurring in the first year of life. It will also be, as far as I am aware, the first instance of sibling cases although this is now quite well recognised in adults of the same parentage.

Case No. 1.

Christine P. was admitted to this hospital December 1953 at the age of seven months. Complaints were food refusal, failure to thrive, paroxysmal cough and vomiting.

History: First child. Birth weight 6 lb. 8 oz. Two months before admission (age five months) coryza lasting two to three weeks. Simultaneously developed dry cough which slowly worsened and sometimes led to vomiting. No whoop. Motions green during first three weeks of illness. Course of sulphatriad three weeks before admission.

On Examination: Wasting, pallor, cyanosis, respiratory distress and repetitive cough (not like pertussis). Afebrile. Slight injection of throat and right tympanic membrane. Occasional added sounds over lungs. Liver normal in size. Admission chest X-ray: increased bronchial markings.

Clinical course: Steady deterioration in spite of consecutive courses of penicillin, chlortetracycline, erythromycin. Continuous oxygen required. Increasing pallor, cyanosis, dyspnoea and persisting dry irritative cough associated with progressive, diffuse, granular infiltration of lungs in serial radiographs. Body temperature normal except for a spike of 100°F. second day in hospital and range 98°-100°F. just before death. Pulse range 100-180/min. respiratory rate varied between 30-80/min. Terminally liver enlarged and neck veins became distended; no added sounds heard over lungs. Died five weeks after admission and three months after onset of symptoms.

Investigations: WR and Mantoux negative. Hb 85-90%. WBC (8th day) 10,300. (polys 47%). (17th day) 14,200. (polys 64%), (29th day) 16,900 (polys. 58%). Plasma Proteins: 6.9 g/100ml albumin 4.5 globulin 2.4. ESR (week before death) normal. ECG (four days before death) normal. No pathogens in

serial nose and throat swabs. Virus studies not done. The clinical picture then was of a progressive suffocative pulmonary disorder with terminal right heart failure. The following diagnoses were considered by the clinicians during the baby's short stay in hospital: Pertussis, atypical virus pneumonia, miliary tuberculosis, sarcoidosis, lipoid pneumonia, haemosiderosis.

Well, these then are the details of the first affected child. Nine years later, in February 1962, a second child in this family was found dead in his cot. This was an infant aged four months and here now are the details based on a retrospective history obtained from the parents two years after the event. I should add that the mother and father are intelligent people and reliable witnesses. Thus, when I spoke to them on this occasion I found they were able to recall accurately clinical details concerning Christine's illness, nine years previously.

Case No. 2.

John P. Birth weight 7lbs. Forceps delivery (November 1961). Cord round neck three times. Mother well during this fourth pregnancy. John never robust from birth. Very difficult with the bottle. One feed would run into next. Seemed full after only two ounces. During winter of 1961-62 given two courses of antibiotics for chest infections (appeared to parents to have a common cold on both occasions but general practitioner found signs in chest.) Baby never short of breath. Not "a wheezer". Cough never a feature even with chest infections. For three to four days before death faint cyanotic tinge round eyes and over bridge of nose. Lips never blue as with Christine. Parents were pressing for hospital consultation for day or so before child's death. Father gave last feed before going to bed. This as usual took a long time but not due to dyspnoea. Infant found dead in his cot next morning.

Family History: Following Christine's death two normal children born, now aged eight years and four-and-a-half years. Latter prone to bronchitis; chest X-ray September 1963—normal. Paternal uncle suffers from asthma. No other relatives with chest trouble. No family history of sudden deaths in infancy or childhood.

This, of course, was a Coroner's case and it was fortunate that the post-mortem was conducted by Dr. Elliott because on seeing the surname of this child he realised that there might be a possible link with a previously remarkable case in a family of this name—I refer, of course, to Christine just described.

MR. LAUSTE: Thank you very much. Perhaps now Dr. Elliott would be kind enough to give the pathology on these two cases?

DR. R. I. K. ELLIOTT: In both these children macroscopic abnormalities were confined to the lungs, so for the sake of brevity I will give only the positive findings.

Autopsy on the elder child was performed by Dr. R. W. P. Johnson. There was a small left pleural effusion, but no adhesions on either

FIG. 1.—Lung from case 1 (Brighton) Christine Cut surface of lung under slight magnification showing reduction in number of terminal air spaces and great increase of connective tissue between them. x6.

side. The main bronchi contained a small amount of mucopus. The lungs were voluminous and felt very firm and slightly nodular. The cut surfaces showed many small white flecks, somewhat suggestive of miliary tuberculosis, against an almost solid background. Viewed under a hand lens, the lung tissues appeared almost solid, with a few air spaces scattered here and there (Fig. 1). Although the relative proportions of air spaces and stroma varied somewhat from one area to another, this remarkable change was present in all lobes of both lungs.

The younger child, which I examined myself, had a deformed chest, the antero-posterior diameter being much increased, producing a "pigeon-breast" appearance. There were no pleural effusions or adhesions. The trachea and bronchi contained a little frothy mucus, not purulent. Both lungs were enlarged, and heavier than normal, with the same increase of solid tissue and reduction of air spaces seen in the first child. The changes seemed more severe in the lower lobes than elsewhere, but as before all the lung tissue was involved to some extent. There was a slight increase in pericardial fluid

FIG. 2.—Lung from case 1 (Brighton) Christine P. Sparse air spaces lined by cuboidal epithelium. Marked increase of interstitial tissue. H. and E. x 95.

and the heart was slightly enlarged, mainly due to dilatation of the right ventricle.

Turning to the histological findings, there was little of interest to report in organs other than the lungs, but one or two points need to be mentioned. Neither child showed evidence of passive venous congestion in spleen or liver. Increased cellular infiltration in the portal tracts of the liver has been reported in some cases of Hamman-Rich syndrome, (Scadding, 1960; Davies and Potts, 1964), but there was no sign of it in either of these. Knowing the family history I was particularly careful to examine the pancreas in the younger child; there was no suggestion of fibrocystic change. Finally, comparison of the heart muscle in the left and right ventricles showed, in the elder child, slight hypertrophy on the right side; in the younger child no appreciable change from normal; but there was, as I have said, some dilatation of the right ventricle macroscopically. It is surprising, perhaps, that there should be so little change in the heart in the presence of such gross damage in the pulmonary interstitial tissue.

The histology of the lungs was not entirely the same in both children; so I will describe the picture in the elder child in detail and then indicate how the younger differed, the dif-

FIG. 3.—Lung from case 1 (Brighton) Christine P. Hyaline membrane in air spaces. Mallory trichrome. x 95.

ferences being, I should add, of degree and not of kind; there can be no question that the same basic abnormalities were present in both.

The hand-lens view of the elder child's lung showed solid tissue with a few air spaces irregularly scattered through it. Microscopically this solid tissue is highly vascular connective tissue, full of ramifying capillaries and heavily infiltrated with inflammatory cells, mainly plasma cells and lymphocytes, with neutrophil leucocytes in lesser numbers, and few eosinophils. Much of the collagen in the tissue is in the form of delicate fibrils enclosing spaces which presumably contain a great deal of tissue fluid, so that the texture appears loose (Fig. 2), but heavier fibrosis is often found lying concentrically round the surviving air spaces. These air spaces are larger than ordinary alveoli, are usually lined by cuboidal epithelium, and contain a good deal of cellular debris; quite frequently hyaline material is seen lying against the epithelium, resembling the hyaline membrane of the newborn lung (Fig. 3). The free cells in the lumen are predominantly large macrophages, which are sometimes aggregated together to form giant cells. Larger air channels, the bronchioles and bronchi, contain little

exudate and are not constricted or obstructed in any way.

In the younger child, air spaces are more numerous, but are often flooded with an exudate of eosinophilic debris mixed with erythrocytes and neutrophil leucocytes; macrophages are fewer, but conspicuous when they occur because their cytoplasm is loaded with eosinophilic material. Bronchioles and bronchi are often filled with this exudate and the picture could be interpreted as pneumonic were it not for the fact that, even in these areas, the normal alveolar network has already been completely replaced by the coarse trabeculae and irregular spaces that seem to constitute the basic deformity. The picture suggests an earlier stage of the disease, in which death has been brought about by superadded infection.

MR. LAUSTE: I will now call upon Dr. Claireaux to discuss this condition.

DR. A. E. CLAIREAUX: I am very grateful for the opportunity to be here and for your kind hospitality before the meeting. This is a subject which interests me a great deal and curiously enough, my arrival at Great Ormond Street coincided with the first case they had recognised there. As you have heard Hamman and Rich described an acute pulmonary disease in 1935 in which a diffuse fibrosis of the lungs was found at necropsy. They had met three examples between 1931 and 1933 in the medical wards of Johns Hopkin's Hospital and two years later came across a fourth case. A further more detailed report was published by these two authors in 1944 and this is the account generally quoted. All the original authors' patients were adults. Since 1944 the condition has been reported by many investigators and it became obvious that it was not confined to adults. It occasionally presented in young children but was rather rare in infancy. The first childhood case, a five-year-old, to be seen at the Hospital for Sick Children, Great Ormond Street, occurred in June, 1964 and a second example came to light a few weeks later. At necropsy the lung in this condition has a fleshy appearance and feels unduly firm. On slicing there is little evidence of an aerated structure. Histological examination reveals a marked transudation of eosinophilic material into the air-spaces in the acute stage and hyaline membrane formation may be a prominent feature even in the older child or adult. This hyaline material is gradually organised and young collagen appears. At the same time there is a very extensive cellular infiltration of the interstitial tissue of the lung. The cells are

FIG. 4.—First Great Ormond Street case. H. and E. x 92. Lung showing numerous histiocytes and some leucocytes in the alveolar lumen, thickening and infiltration of alveolar septa and fibrinous membrane lining alveolar walls.

mainly monocytes but neutrophil and eosinophil leucocytes are also found. The latter appear somewhat late in the disease process. Should the patient survive sufficiently long, and many die within four weeks of the onset of the disease, the fibrosis becomes more evident and eventually a diffuse interstitial fibrosis of the lung develops. The alveolar walls gradually undergo transformation and become lined by cuboidal epithelium giving the lung a glandular appearance on histological examination. The surrounding lung shows pronounced atelectasis.

All these features are shown in the lung of our first patient. The clinical history is that of a girl, aged five years and nine months, when she was admitted to Great Ormond Street, who had been ill since the age of 18 months and had dyspnoea and cyanosis. She had had a recent respiratory infection and was known to be anaemic. The liver and spleen were enlarged. Rhonchi were heard over the base of each lung and radiological examination revealed a combination of pulmonary collapse and consolidation. A biopsy specimen was removed from the right lung at operation and this revealed the changes described above on histological examination.

As we were dealing with the first case of this disorder in our hospital the slides were sent to Dr. Lynne Reid at the Brompton Hospital who agreed with the diagnosis.

The lung was almost entirely consolidated although some peripheral overdistension was noted. Some areas of haemorrhage were present and many of the alveoli were lined by cuboidal epithelium. The interstitial tissue was heavily infiltrated with mononuclear cells and

FIG. 5.—Second Great Ormond Street case. H. and E. x 93. Lung showing bronchiole lined by acidophil membrane. Surrounding lung collapsed and infiltrated with inflammatory cells.

eosinophils were also present in strikingly large numbers. A fairly dense interstitial fibrosis was seen and a number of respiratory bronchioles were lined by young fibrous tissue and others by hyaline membrane (Fig. 4).

The patient is still alive and is being treated with corticosteroids. A more recent biopsy shows a considerable diminution in the cellular infiltrate but the fibrosis, of course, persists.

About one month after the admission of our first case another patient was admitted with a similar history. The second patient was only 18 months old and suffered from pronounced respiratory difficulty. A biopsy specimen of lung was obtained and the appearances are very similar to those shown by Dr. Elliott this evening. Distended respiratory bronchioles are lined by hyaline material and the appearance is very akin to that of the lung of a newborn infant with the respiratory distress syndrome. The cellular infiltration is much less than that seen in our first patient but there is widespread interstitial fibrosis. Many air spaces have bands of collagen in their walls and many are lined by cuboidal epithelium. Some round cell

infiltration of the interstitial tissue is also present but eosinophils which were such a pronounced feature in the lung of the older child, are absent (Fig. 5). This was obviously another example of acute diffuse interstitial fibrosis of the Hamman-Rich type. This underlines one of the difficulties in ascribing the Hamman-Rich syndrome to examples of obscure pulmonary disease in children. There may be a number of conditions, of widely different aetiology, which result in diffuse interstitial pulmonary fibrosis. Hamman and Rich stressed the acute nature of the disease process and the massive cellular exudate composed largely of mononuclear cells. The lining of non-fibrosed air spaces also changes. It becomes epithelialised and comes to resemble foetal lung tissue.

Now that lung biopsy is becoming a more frequent procedure, we are receiving an increasing number of specimens and interstitial fibrosis may not be such a rare diagnosis and not all of these are likely to prove to be examples of the Hamman-Rich syndrome.

MR. LAUSTE: Will Dr. Nash now say something about the differential diagnosis?

DR. F. W. NASH: There is naturally some difficulty in attempting to discuss the differential diagnosis of a syndrome which has both clinical and pathological components in its definition. The latter, which are regarded as distinctive can only be established by histological examination of the lungs. The clinical course of the disease, reflecting a progressive interference with pulmonary function, is by no means distinctive. Characteristically, the child develops a persistent irritant cough with breathlessness which becomes progressively worse until the patient becomes cyanosed, shows symptoms of anoxia, and ultimately dies from respiratory insufficiency, right heart failure (cor pulmonale) or some intercurrent infection. The course may be spread over several months, even as long as a year or two, though a few patients have been known to succumb after a more acute illness lasting only a few weeks.

This type of illness though uncommon in childhood, particularly in infancy, is well recognised, and there are really only two main groups of disorders that are likely to produce it—abnormalities of the heart and progressive respiratory disease.

Let us first consider diseases of the heart. Cardiac embarrassment in a young child soon leads to respiratory symptoms and episodes of pulmonary infection with sometimes wheezy spells which may initially lead to the heart abnormality being overlooked. Acute heart

failure is soon recognised and is not likely to be confused with the progressive disease that we are discussing; but there are forms of cardiac disorder which have a subacute or chronic course closely resembling that of the Hamman-Rich syndrome. In these children the heart is enlarged (though heart size is not always closely correlated with the severity of the symptoms) and the basic disorder is usually either dysfunction of the myocardium, as in fibro-elastosis or the various forms of cardiomyopathy, or a congenital heart lesion with a large left-to-right shunt leading to increased pulmonary blood flow, as with some forms of patent ductus arteriosus and ventricular septal defect. Not rarely increased pulmonary blood flow is complicated by changes in the pulmonary vessels and pulmonary hypertension, adding further to difficulties with respiration. But in all these cases the primary heart abnormality should be established early in the course of the disease. Cardiac enlargement may be detected, perhaps on clinical examination, certainly with the aid of radiological studies; characteristic heart murmurs may be heard in some forms of congenital heart disease, and there are usually abnormalities in the electrocardiogram. In some children there will be signs of right heart failure with engorgement of neck veins, an enlarged liver and, rarely, oedema; though it is as well to realise that in patients with laboured breathing from any cause distended neck veins and a readily palpable liver are difficult to interpret. The important point to make is that though respiratory symptoms may dominate the picture in heart disease, a careful examination will establish the cause early on. In diffuse pulmonary fibrosis right heart strain and then failure usually supervene after several months of illness.

Turning now to respiratory disorders, persistent and progressive respiratory disease may be the result of a large number of pathological processes, and they can be very difficult to distinguish clinically. For convenience it is helpful to consider the following broad groups:—

a) Recurrent inhalation pneumonitis secondary to abnormalities of the upper respiratory tract, larynx and trachea; for example, severe micrognathos (a diagnosis which is immediately obvious), inco-ordination of swallowing, laryngeal obstruction (the various forms of laryngeal stridor), tracheal obstruction due to a congenital web or tracheo-malacia or pressure from outside—not infrequently a vascular ring. Finally, lung pathology may result from a small tracheo-oesophageal fistula, which may

for a long time be misdiagnosed as primary pulmonary disease.

In a few of these conditions the nature of the disorder is immediately obvious. In others the diagnosis will often depend on further investigations including a barium swallow and, if necessary, cine barium studies, direct laryngoscopy or bronchoscopy and perhaps the performance of a tracheogram and bronchogram.

b) Disease primarily affecting the lungs, such as—chronic unresolved pneumonia with, in the later stages, fibrosis and bronchiectasis. This sequence of events is nowadays only rarely met with as a complication of the bacterial pneumonias, but one should of course consider other agents; for example, virus infection, lipid and plasma-cell pneumonia, infection with *pneumocystis carinii* and with fungi. Examination of the sputum, if it can be obtained, or of stomach washings may help in the identification of some of these diseases, but where the diagnosis remains obscure lung biopsy would be justified. Idiopathic pulmonary haemosiderosis—a great rarity—should perhaps be mentioned here. It is thought to be due to abnormal pulmonary capillaries allowing the escape of blood into the lungs, and affected children develop progressive respiratory symptoms with acute exacerbations. These patients are usually anaemic and may develop jaundice in the acute phases, sometimes with enlargement of the liver and spleen. Blood is commonly found in the sputum, vomitus and stools.

c) Generalised diseases with predominant respiratory symptoms. Fibrocystic disease of the pancreas (mucoviscidosis) is not a great rarity in childhood and is one of the first conditions to be considered in the differential diagnosis. Helpful pointers may be obtained in the history—other affected children in the family, meconium ileus in the patient in the neonatal period or coeliac symptoms later on. The most useful diagnostic test however is the finding of abnormally high levels of sodium and chloride in the sweat of these children. Infiltration of the lungs in miliary tuberculosis, leukaemia and the lipidoses can produce severe respiratory symptoms, but the course of all these illnesses in children is usually acute and one soon finds ample evidence of disease outside the respiratory tract. Finally, diseases affecting the small blood vessels and collagen tissues of the body have to be kept in mind; polyarteritis nodosa, disseminated lupus, rheumatoid arthritis and sarcoidosis.

FIG. 6.—Christine P. aged 6 months. Diffuse progressive interstitial fibrosis of lungs.

To conclude one can say that in establishing the diagnosis of the Hamman-Rich syndrome one may have to go through a process of detailed investigation and exclusion; first, of primary heart disease, then of a whole host of respiratory diseases and general disorders with respiratory involvement. The stage will then be reached where the child will be seen to be suffering from severe ventilation difficulties apparently due to primary lung disease of unknown aetiology. The final step would be to examine some lung tissue under the microscope and demonstrate the characteristic histology which has already been described.

MR. LAUSTE: Now we must hear about the radiological aspects from Dr. Rubin.

DR. J. RUBIN: In radiology one is concerned to see how the pathology is shown on the X-ray picture. Christine had a series of three radiographic examinations showing progressive X-ray changes, which I think mirror the pathology that we have heard described. On the first X-ray examination very soon after admission when the suggested diagnosis was broncho-pneumonia, the X-ray picture was that of an ill-defined diffuse generalised increase of the bronchovascular markings and of lung striations bilaterally, and all I could suggest at that time was bronchiolitis. The odd feature was that it was such a uniformly diffuse clouding throughout

FIG. 7.—Letterer-Siwe disease in an 8-month-old infant.

both lung fields. Secondly two weeks later, a further X-ray examination with screening showed a progressively increasing generalised infiltration. There was definite fine mottling diffusely throughout both lung fields with evidence of spasmodic respiratory movements on screening. The possibility of miliary tuberculosis was particularly in my mind because the X-ray picture simulated it, and also haemosiderosis. The Hamman-Rich syndrome was not considered because at that time we had no knowledge whatever of this condition occurring in infancy. Finally the diffuse mottled infiltration became coarse and granular after a further two weeks interval (Fig. 6) and again I considered that the appearances were indistinguishable from miliary tuberculosis. We had to think also of sarcoidosis, an acute collagen disease and other conditions which might give a similar appearance. For example, we have two radiographs here for comparison with the one under discussion which bear some similarity to each other. There is one of reticulosis, or generalised histiocytosis (Letterer-Siwe) which is relatively common in this age group as far as diffuse pulmonary infiltration is concerned (Fig. 7), and another of miliary tuberculosis (Fig. 8). We have a different type of X-ray picture when we come to the kind of case Dr. Claireaux has described in older children which

FIG. 8.—Miliary tuberculosis in a child aged 6 months.

may resemble this film of fibrocystic disease of the pancreas (Fig. 9). Also in the radiological differential diagnosis we must consider malignant infiltration. Thus, our next film shown here (Fig. 10) is one of a malignant invasion from a rhabdosarcoma. Incidentally, it seems to me that the radiological picture in older children and in the adult cases of Hamman-Rich fibrosis described in the literature is not always the same as that found in infants with this type of disorder. Outside infancy we do not see the early clouding of the lung fields progressing from a fine to a coarse diffuse granularity. In older children, unlike infants, we tend to see scattered consolidations and collapse and no uniformity. One cardinal feature to conclude with in the radiological differential diagnosis is that in the Hamman-Rich syndrome of diffuse interstitial fibrosis we do not have emphysema or honeycombing in the lung fields because the alveoli are obliterated.

DR. MANN: It may be of some interest to mention that Hamman and Rich published an account of their first case (a coloured man aged 47 years, admitted to Johns Hopkin's Hospital in 1931) as long ago as 1933 in the form of a Clinico-Pathological Conference. Could I ask Dr. Claireaux to tell us a little more about the clinical aspects of the two Great Ormond Street cases? I am particularly interested in the first child he mentioned who, I believe, he said

FIG. 9.—Fibrocystic disease of the pancreas in a 3½-year-old child.

had survived now for over four years. This seems surprising because diffuse interstitial pulmonary fibrosis is a very lethal condition, especially in children, although admittedly adults have been described who have been kept going for several years with the help of steroids. Incidentally, in the first Great Ormond Street case, I thought the pulmonary changes Dr. Claireaux demonstrated were noticeably patchy, there being a lot of reasonable looking alveoli in the section. I am surprised it is not the diffuse affection one would expect in this disturbance.

DR. CLAIREAUX: I am sorry I said so little about the clinical picture in our cases but I had to watch the clock. The first child I mentioned presented at the age of 18 months with dyspnoea and cyanosis, subsequently finger clubbing appeared. She is now aged six years old. I should have mentioned that the slide I demonstrated (Fig. 4) is the second lung biopsy after steroid therapy and so the process has been modified by treatment. My second slide (Fig. 5) was a primary lung biopsy from our second case and showed the picture which Dr. Elliott has shown us tonight in the Brighton babies.

DR. MANN: Coming back to our cases, the history in Christine was typical of that described in diffuse interstitial pulmonary fibrosis. However, her sibling died a sudden and unexpected cot death and there were quite definitely no preceding symptoms to suggest progressive pulmonary dysfunction although admittedly this infant had not behaved normally from birth. May I ask Dr. Claireaux if he is satisfied our two children had the same basic disorder.

FIG. 10.—Diffuse pulmonary infiltration due to metastases from rhabdomyosarcoma of right forearm. Aged 7 years.

DR. CLAIREAUX: Yes, I think both children had a diffuse interstitial fibrosis of the lungs. Whether this is really the Hamman-Rich syndrome is another question. I believe that certain severe virus infections of the lung may be followed by interstitial fibrosis. Your second case seemed to show a brisk polymorphonuclear leucocytic reaction in the bronchi and it would seem possible that the second child, although suffering from a similar underlying disorder, had a terminal acute infection which proved fatal.

DR. MANN: In view of what you say, are you not surprised our second child had no respiratory symptoms right up until death?

DR. CLAIREAUX: Not entirely. This absence of respiratory symptoms is not all that unusual in cases of sudden death in infancy, e.g., cot deaths. Nevertheless a number of such infants show inflammatory changes in the lungs at necropsy.

DR. MANN: I am thinking in view of the basic pathological changes we saw in this child's lung, are you not surprised by the absence of respiratory symptoms?

DR. CLAIREAUX: Yes. This was a point I found very difficult. The cellular infiltrate in your two cases seemed to be less pronounced than is usual in a typical Hamman-Rich syndrome. The infiltrate in our first case was so pronounced that a diagnosis of histiocytosis was considered.

MR. LAUSTE: Now there is a little time left for anybody else who wishes to contribute to the discussion.

DR. F. MEADE: I think there is probably no

condition which better illustrates the utter dependence of the clinician on the pathologist when it comes to making a diagnosis. However, it is the aetiological factors which I find of the greatest interest in this syndrome. We may be dealing with a viral or chemical cause. We have heard of a possible relationship to rheumatoid arthritis and that there may be a genetic factor operative. I think it is worth mentioning that we now believe there is a genetic factor at work in some cases of bronchitis. There is one other factor that may be relevant to the second Brighton case—I noticed that John was a very difficult feeder. He seemed full after only two ounces. I would like to ask was there anything in the history to suggest regurgitation of feeds? Also, was there any evidence of any oesophageal abnormality at post-mortem?

DR. MANN: Clinically there was no evidence of vomiting or regurgitation. There was no history of choking attacks; just this great difficulty of getting feeds into the baby.

DR. ELLIOTT: I would like to say that pathologically there was no evidence of any oesophageal abnormality nor did the appearances in any part of the lung really resemble the sort of lipoid pneumonia you get in children who inhale milk feeds. With milk inhalation the lungs present a fairly typical picture and they are certainly much less cellular looking than the ones we saw here.

MR. LAUSTE: Well, we are now very short of time as our speaker has to return to London. I propose, therefore, asking Dr. Mann to say a few words about the aetiology and treatment of this condition.

DR. MANN: Considering first the treatment of diffuse interstitial pulmonary fibrosis, this is, of course, most unsatisfactory. Our first case, Christine, improved dramatically when first placed in oxygen and this sort of response has been noted by most authors. Physiological studies indicate that amongst other things, we are dealing with a reduced diffusing capacity in this affection and one would therefore expect oxygen to help, at least initially. The only other therapeutic agents of value are the corticosteroid group of drugs. These may lead to symptomatic improvement and occasionally prolong life for several years. I must emphasise that once started the patient's life usually becomes dependent on the drug.

Turning now to pathogenesis, there are one or two points to bear in mind. Firstly, there is the familial occurrence of cases to which Dr. Meade has just referred. This I would have thought had happened too often to be coin-

cidental although as far as I know ours is the first description of the disorder in siblings. The other point Dr. Nash has spoken about, is that this sort of diffuse pulmonary pathology may be found in association with other well defined disorders, such as disseminated lupus erythematosus, rheumatoid arthritis, rheumatic fever and even polyarteritis nodosa. In discussing aetiology we must also bear in mind the very wide age range of cases which stretches from infancy right up to the seventies. Looking through the literature, many causes for diffuse interstitial pulmonary fibrosis have been advanced. Thus, it has been suggested that this affection may result from the inhalation of some toxic chemical substance (this is unlikely in children), that it may be a response to a yet unidentified infection, virus or otherwise, that it may be a localised manifestation of a collagen disease. Lastly, the concept has been put forward that we are dealing here with a hypersensitivity state. In this connection several authors have wondered whether this condition might arise from sulphonamide sensitivity and it is of interest to note that Christine had sulphatriad before she was admitted to hospital and sulphadimidine was given subsequently. I am afraid I was unable to get any precise information about drug administration in the second child.

May I conclude by saying that reading through the literature one gets the impression that we may well be dealing here with the end-result of the activities of a very wide range of aetiological agents but probably the most favoured theory today is this one of a hypersensitivity state, possibly an auto-immune reaction. There are several features in support of this hypothesis. For instance, Dr. Claireaux has told us about the presence of eosinophils in the lung lesions; then there is the raised level of globulins in the blood found in some cases (not in Christine, though) and I suppose it could be said that the familial occurrence of

cases perhaps favours a genetically influenced mode of tissue response. Also supporting this type of mechanism is the favourable response to steroids in some instances and the fact that the serum globulins, when raised, fall with such treatment. Finally, I must mention briefly the experimental work of Read in Australia. (1958). He prepared an "anti-rat-lung serum" in rabbits which when injected into the tracheas of rats produced a range of pulmonary lesions which were interpreted on an allergic basis and which had a counterpart in the spectrum of histological changes seen in diffuse progressive interstitial pulmonary fibrosis.

I wonder if Dr. Claireaux can add anything about aetiology from the pathological side?

DR. CLAIREAUX: I would only like to say that I think there is a possibility that some patients may have a dysgammaglobulinaemia. Also, that fluorescent antibody studies on our material have so far proved negative.

MR. LAUSTE: I am sure you will agree that this has been a most interesting and valuable conference. I would like to thank all those who have taken part, especially Dr. Claireaux.

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