was able to examine one of the twins (Weber, 1919), but no evidence of intestinal polyposis was discovered till later. Jeghers, McKusick, and Katz (1949) collected their own and all known cases bearing on the subject in a paper entitled "Generalized Intestinal Polyposis and Melanin Spots of the Oral Mucosa, Lips and Digits: A Syndrome of Diagnostic Significance." An excellent example of this syndrome with gastric as well as jejunal polyposis was shown by N. C. Tanner (1951) at the Royal Society of Medicine (Clinical Section) on December 8, 1950. Similar familial pigment spots of the lips and mouth without known intestinal polyposis have been published, from time to time. The complete syndrome may be regarded as a fifth kind of "phakomatosis" in J. van der Hoeve's use of the term (Weber, 1951)—see below.

Naevus and Naevoid Diseases and the "Phakomatoses" (Naevus Tumour Diseases) of van der Hoeve

J. van der Hoeve (1938) has grouped the four developmental diseases—Recklinghausen's neurofibromatosis, Bournville's disease (tuberous sclerosis, epiloia), the Lindau-Hippel disease, and the Sturge-Kalischer-Weber disease—as what he terms "phakomatoses." The Greek word φακός (lentil,* birth-mark) is medically equivalent to the Latin *naevus*. I think one must agree that van der Hoeve's phakomatoses are of naevoid nature. So what I have termed neurofibromatous naevi would be included under the heading "neurofibromatosis, a developmental naevoid disease." But if what I have termed "xanthomatous naevi" be regarded as minor localized and non-progressive forms of the developmental metabolic disease xanthomatosis, then xanthomatosis must be accepted as also "naevoid" in nature. This consideration would lead to the question: Are all "inborn errors of metabolism" (A. E. Garrod) to be regarded as naevoid in nature? I am not prepared to go so far, but obviously the whole difficulty is partly one of terminology. To assert that all inborn errors of metabolism are of naevoid nature would be like saying that all conditions resulting from gene abnormalities are of naevoid nature.

"Naevus" and "Naevoid"

In the present state of knowledge I think it is permissible to use the words "naevus" and "naevoid" (that is to say, like a naevus) synonymously. Instead of "naevoid," strictly speaking one should of course say "phakoid," using two Greek words instead of a Latin and a Greek word joined together. However, in this paper I have used the word "naevoid" in respect of conditions which are generally regarded as not naevus, but which I suggest are of naevus-like nature. I speak of a neurofibromatous "naevus," though I regard the whole disease, neurofibromatosis, as "naevoid"—that is, as van der Hoeve would say, a "phakomatosis." Similarly, I would speak of a Pringle's naevus; but the whole disease, epiloia, I would call a naevoid disease—that is, a phakomatosis (van der Hoeve). From my point of view, I would speak of diseases like *telangiectasia macularis eruptiva perstans* and *urticaria pigmentosa* and *inborn urticaria facititia* (which are not generally regarded as naevus conditions) as of naevoid nature. The Sturge-Kalischer-Weber disease or syndrome often presents a trigeminal vascular naevus as a striking feature, but many would object to call the whole syn-

drome a naevus condition, though I think it is obviously of naevoid nature, a phakomatosis of van der Hoeve.

[NOTE.—A list was added of most of the external and some of the internal conditions which Dr. Weber would (often doubtfully) classify as naevi or naevoid, but there was not time to read it.]

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AN EXPLANATION OF THE "PRIMARY ATYPICAL PNEUMONIA" SYNDROME

BY

PHILIP W. ROBERTSON, M.D., M.R.C.P.

Squadron Leader, Medical Specialist, R.A.F.; Clinical Assistant, Royal Infirmary, Liverpool

AND

K. D. FORGAN MORLE, M.D., D.M.R.D.

Consultant Radiologist, Liverpool Regional Hospital Board; Research Assistant, Department of Radiology, University of Liverpool

In the course of the past two years we have seen over 500 cases of a condition which we believe to be an aspiration pneumonia, the pulmonary lesions of which are confined to certain local regions of the lung. This, both clinically and radiologically, is similar to descriptions of primary atypical pneumonia and to many of the so-called virus pneumonias. We wish to dispel much of the mysticism associated with this group of conditions and to destroy the concept of atypical pneumonia as at present described.

The features of our own cases are described; the reported features of primary atypical pneumonia are reviewed, and the two are compared. Reasons are given for our attack on the present conception of atypical pneumonia, and the significance of the altered point of view is discussed.

Present Series

Material.—The cases have been drawn from young men who had already been passed by a medical board and who were undergoing the first few weeks of initial

*Phakos (lentil) is of course used also to mean the crystalline lens of the eye. When I first heard of "phakoma" (naevus "tumour") I was puzzled concerning what a tumour of the crystalline lens could be.

basic military training in recruit training camps. Nearly all were radiologically normal on entry, but a small number were picked up by the mass miniature radiography examination. Large numbers of young men are for the first time concentrated in such training camps; each week there are repeated intakes from all parts of the country, and at the same time comparable numbers of trained men are posted to other units. Upper respiratory infections are common in such an environment, and the pulmonary lesions to be described followed such infections. Similar cases are often seen in civilian radiological practice but are not included in this series.

Clinical Features

There was no constant clinical picture, as the illness varied greatly in intensity and duration. Most patients were moderately ill for the first 24 to 48 hours, and, though some were seriously ill, none died. Most were febrile and felt miserable, their discomfort being aggravated by troublesome pain and cough. In some the illness was slight and would not normally entail absence from work.

A few days after the onset of an upper respiratory infection one or more of the cardinal signs of pulmonary disease developed.

Cough was invariable, often of a characteristically harsh and repetitive nature. In a small number of patients stress fractures of the ribs were detected.

Sputum was usually absent or scanty in the early stages but was almost invariably present later in the course of the illness. In many instances this was yellowish green in colour and obviously purulent. *Blood-staining*, though often unnoticed by the patient, was a frequent finding.

Chest pain was often present and in many instances was pleural in type. In others it consisted of an ache or discomfort, or an awareness of "something wrong in the chest." Characteristic pleural pain was most common in association with anterior pulmonary lesions, while those with involvement of the lower lobes experienced either referred pain in the shoulders or abdomen, or complained of backache. The site of the chest pain was frequently of assistance in locating the lesion, though rarely the pain was referred in the first instance to the opposite side.

Dyspnoea was seldom noted and certainly could not be regarded as a characteristic feature. Significant loss of weight did not occur.

Fever was in many cases quite high initially, but in the majority had subsided within a few days. It was common for there to be several days of low-grade pyrexia before the temperature finally settled. Occasionally there was a second rise in temperature.

The frequency of these clinical features was as follows:

Cough	100%
Sputum (initially)	78%
Sputum (subsequently)	practically 100%
Blood-staining of sputum (noted)	18%
Chest pain	58%
Referred pain	9%
Dyspnoea	1%

Signs

There was always an upper respiratory tract infection either at its height or in the decline. This usually consisted of coryza, nasopharyngitis, tonsillitis, or sinusitis and requires no further description.

Physical examination did not usually reveal any generalized chest disease but sometimes signs suggesting a general bronchitis were found. Such generalized signs tended to mask the presence of local abnormality.

Local chest signs consisted of added sounds in the form of crepitations and coarse moist sounds, together with diminished air entry and impaired percussion note over the site of the pulmonary disease. Such signs were often strictly localized to small areas of the chest wall and in general they were difficult to elicit and could not be relied upon. Further, they bore little relation to the extent of the pulmonary disease revealed by radiography.

Course

It was not easy to estimate the duration of the illness on clinical grounds alone. The initial cold or nasopharyngitis ran its customary short course. Recovery from the general illness was usual within a few days though productive cough and chest pain and the radiological changes sometimes persisted for several weeks. The effect of sulphonamides and penicillin on the clinical course was difficult to interpret; even in those cases in which there was some evidence of response little corresponding radiological improvement followed.

Clinical Pathology

Laboratory examinations were restricted to examinations of the sputum and the blood. In most cases the sputum was examined repeatedly by direct means for tubercle bacilli, with negative results. On culture there was usually a heavy growth of those organisms normally found in the upper respiratory tract. Occasionally a predominant organism such as *Streptococcus viridans* was found. Detailed bacteriological study of each case was not undertaken.

The total white-cell count was not as a rule significantly raised, the usual range being from 7,000 to 14,000 per c.mm. Rarely counts of up to 20,000 per c.mm. were found, when the rise was mainly due to a polymorphonuclear leucocytosis.

The erythrocyte sedimentation rate was occasionally estimated and was usually found to be raised, sometimes considerably.

Radiology

The one constant feature of all cases was the anatomical localization of the disease to broncho-pulmonary segments or subsegments, so that the appearances depended on the portions of lung involved. In order to define the site and extent of the lesions, and in some instances to see certain retrocardiac and basal lesions at all, it was found essential to have lateral films in every case.

Every degree of abnormality was seen, from dense "ground-glass" opacity to increased density of the bronchovascular markings. Some degree of collapse within the lesion was very frequent, but occasionally this could be detected only by most careful inspection of the films. Some shift in the position of the interlobar fissures and crowding of the broncho-vascular pattern were in most instances the only signs of collapse present. Here, again, the lateral projection was found to be essential because, as one would expect, such local lesions rarely produced gross signs of collapse. Lesions were generally confined to the basal segments of either or both lower lobes, to the lower division of the lingula of the left upper lobe, or to the anteromedial portion of the

right middle lobe. Occasionally lesions in the axillary divisions of the subapical or the pectoral segments of the upper lobe were seen, but these were usually associated with involvement of other sites. Such broncho-pulmonary radiological changes are not of course specific for this condition, because they can be reproduced by any cause of segmental de-aeration.

Enlargement of the hilar glands was rarely noted and in no case appeared to cause bronchial compression. Occasionally glandular enlargement developed subsequent to an infected segmental lesion. *Pleural effusion* was seldom encountered and was always small and quick to resolve. *Abscess formation* within the lesion was encountered twice. On both occasions the cavity was small and was situated in an axillary subsegment of an upper lobe; each rapidly and spontaneously resolved.

The table and diagrams show the distribution and incidence of the lesions in our series of cases.

Distribution and Incidence of Lesions

Isolated lesions:			
Left upper lobe (excluding lingula)	..	..	0.5%
Lingula	..	..	5.4%
Left lower lobe	..	..	29.6%
Right upper lobe	..	..	1.4%
Right middle lobe	..	..	10.1%
Right lower lobe	..	..	23.1%
Combined unilateral lesions:			
Right middle lobe and others	..	..	9.1%
Lingula and others	..	..	5.7%
Combined bilateral lesions:			
Right middle lobe and others	..	..	1.4%
Lingula and others	..	..	2.5%
Right upper lobe and others	..	..	1.1%
Right and left lower lobes	..	..	10.1%
Total:			
Lower lobes	..	..	82.8%
Middle lobe and lingula	..	..	34.2%
Upper lobes (excluding lingula)	..	..	3.0%

Diagrams showing the regions affected. The lesions are principally in dependent broncho-pulmonary segments; a proportion of these lesions is obscured by cardiac and diaphragmatic shadows on the standard postero-anterior projection.

"Primary Atypical Pneumonia"

Definition.—"Primary atypical pneumonia" has been defined by Drew *et al.* (1943) and by Stephens (1948) as a term covering those respiratory illnesses with pulmonary, radiological change for which no causal bacterium, virus, or rickettsia is known. Stuart-Harris (1950) describes the condition as a syndrome of respiratory tract infection characterized by varying symptoms, by radiological changes of particular character, and by lack of response to the sulphonamides or to penicillin.

Occurrence.—The disease has been described from all parts of the world, but principally from military sources. Large series have been reported from the United States Forces (Bowen, 1935; Campbell *et al.*, 1943; Dingle *et al.*, 1944; Owen, 1944), from the British Army (Drew *et al.*, 1943), and from the Royal Air Force (Kennedy, 1943). Other series have been reported from hospital staffs (Reimann and Havens, 1940; Kornblum and Reimann, 1940; Longcope, 1940) and from schools (Gill, 1938; Daniels, 1942). Most authors agree that there is a seasonal incidence, this being maximal in the winter and early spring.

Spread.—No clear evidence of the method of spread has been presented, though it has generally been considered to occur by droplet infection.

Incubation Period.—This has been stated to be between two and three and a half weeks by Kneeland and Smetana (1940), and between 7 and 21 days by Daniels (1942). Several authors describing series from military training centres have noted that most of their cases occurred within two to three weeks of first arrival at the unit (Langmuir, 1944; Dingle *et al.*, 1944).

Clinical Features

Campbell *et al.* (1943) give an excellent clinical description of a series of cases of atypical pneumonia. The onset of the disease is generally similar to that of an upper respiratory infection (Reimann and Havens, 1940).

The presence of *cough* is universally reported, and several authors note that it is sometimes of a peculiar hacking character, which causes distress to the patient and to his neighbours. Harvey (1944) reports 19 instances of rib fracture due to the cough.

Most authors describe the *sputum* as being scanty and mucoid initially but becoming more profuse and purulent. *Blood-staining* is commonly reported, and frank haemoptysis occasionally occurs.

Chest pain is usually situated in the site of the pulmonary lesion (Stephens, 1948) and it is described as often not truly pleural in nature but rather as a dull ache or discomfort. Drew *et al.* (1943) report the occurrence of pain elsewhere probably referred from the chest.

Fever is commonly reported to be quite high at the outset and this may persist for periods of two to seven days; resolution by lysis is the rule. In the more severe cases reported by Kneeland and Smetana (1940) the pyrexia was remittent and lasted for several weeks. Many authors, including Longcope (1940), describe what is termed a "biphasic pyrexia."

Signs

The clinical picture is reported as varying widely between slight illness and severe prostration in the rare serious cases.

Dyspnoea and cyanosis are uncommon, though they are reported in the most severe cases; the pulse rate is not usually much raised.

Physical signs in the chest are often absent or scanty initially, and are often strikingly so in relation to the pulmonary radiological change (Turner, 1945). Allen (1936) and Karpel *et al.* (1945) consider that as the physical signs are so sparse the diagnosis of atypical pneumonia rests on the radiological findings.

Course

Finland and Dingle (1942) state that in mild cases the illness may last for a period of about a week, while the more severe cases may be ill for six to eight weeks. In 851 patients reviewed by Wyman (1948) the average time taken for radiological changes to clear was 15.2 days. The average time spent in hospital in the cases reviewed by Drew *et al.* (1943) was 33 days. Before the advent of "aureomycin" no form of treatment was said to influence the course of the disease; recovery was usual and very few fatal cases have been recorded.

Clinical Pathology

The white-cell count is reported by almost all authors to be within the normal limits or only slightly raised.

Counts of over 15,000 cells are rare (Dingle *et al.*, 1944). The differential count is usually normal.

Culture of the sputum characteristically reveals only the common bacterial flora of the upper respiratory tract.

The cold-agglutination phenomenon has been associated with "primary atypical pneumonia" and it has often been referred to as a diagnostic aid. Scadding (1948), however, points out that the phenomenon appears to be non-specific, while Rich *et al.* (1945) state that it is found in many other conditions not related to atypical pneumonia. Bedson (1950) warns against acceptance of a rising titre of cold agglutinins as conclusive evidence of a specific infection.

Radiology

Most radiological descriptions of this condition are rather vague in detail, though that by Crysler (1946) is an exception. Various authors have described the lesion as consisting of fan-like shadows arising from the hilum and spreading out to the periphery. They are usually well localized though not sharply defined and are stated to be mainly in the "lower or middle zones." "Upper-zone" shadows have been described and so-called migrating lesions involving other pulmonary zones are not infrequent.

Many radiographs (Longcope, 1940; Dingle *et al.*, 1944) showing lesions apparently segmental in type have been reproduced, but cannot be confirmed as such in the absence of lateral projections. However, Drew *et al.* (1943) and Kennedy (1943) point out that the lesions are generally confined to a segment.

The presence of collapse within the lesion has been recognized by several authors (Campbell *et al.*, 1943; Kay, 1945). In the work of others, lack of lateral projections may have handicapped this recognition.

Comparison

It is evident from comparison of the features of "primary atypical pneumonia" with those of our own cases that no significant difference can be found. The illnesses occurred under similar circumstances and followed similar clinical courses. Radiologically the lesions are apparently identical and the results of laboratory investigations are essentially similar.

Aetiology

The view has been widely held that "primary atypical pneumonia" is an infective condition caused by an unknown virus. Detailed studies of the condition were made by Dingle *et al.* (1944), who stated in their conclusion: "It seems most likely that a new agent, probably a virus, is responsible for atypical pneumonia." Bedson (1950) stated that in those cases not caused by a known infective agent there was good evidence that they were of virus aetiology.

This view seems to have arisen largely because no other aetiological factor could be found. The low white count, the lack of response to chemotherapy, and the clinical resemblance to influenza-like illnesses have all contributed to this assumption. Furthermore, most cases were described from apparent epidemic outbreaks. Dingle *et al.* (1944), however, noted in their series that the characteristics of the outbreaks were not similar to those of known infectious diseases.

We believe that the cases we describe, together with most of the so-called atypical pneumonias, are in fact

due to aspiration of products from the associated upper respiratory infections. Ramsay and Scadding (1939) held a similar view of a series of cases which appear to resemble the syndrome of "primary atypical pneumonia." The following points are put forward in favour of this concept:

1. The cases followed some upper respiratory infection. This infection was usually a nasopharyngitis or common cold, but similar lesions followed such other conditions as tonsillitis, sinusitis, tracheo-bronchitis, and true influenza.

2. All lesions occurred in dependent broncho-pulmonary segments or subsegments.

3. Symptoms often first arose when severe physical exercise had been undertaken in the presence of an upper respiratory infection; this is considered to be of great significance from three points of view: (a) Aspiration will more readily occur under conditions of rapid and gasping respiration, when the nasal passages are blocked and mucus is present in the posterior nasopharynx. (b) Such patients were naturally ambulant at the time and therefore lesions occurred most frequently in the lower lobes. (c) It offers some explanation for the high attack rate amongst new recruits undergoing their initial training, whilst permanent administrative staff not undertaking such activity were very rarely affected.

4. Occasionally pulmonary lesions developed in patients already in hospital with upper respiratory infection. A group of five right middle lobe cases were all noted to occur in patients who usually sat or lay leaning towards the right side in order to observe the entrance to the ward. Radiological changes indistinguishable from those of primary atypical pneumonia have been seen in the surgical wards and would normally be termed post-operative aspiration pneumonias. In two instances in which lesions followed dental extraction with prolonged haemorrhage no upper respiratory infection was present.

These points appear to emphasize the unlikelihood of a pneumotropic virus being the cause of "primary atypical pneumonia." Why should a virus select isolated dependent broncho-pulmonary segments or subsegments? Why should a virus produce a segmental collapse? Why should a virus be suspected when identical lesions can follow aspiration of blood or other non-septic material? Why should it be possible to watch spread from a basal segment to the opposite upper lobe; the so-called migrating pneumonia? A similar "migration" of lipiodol after unilateral bronchography may often be observed. Why should there be no evidence of an acquired immunity? Recurrence in the same or in other segments has frequently been seen; such recurrence of a virus disease would be uncommon. Why should a specific pneumotropic virus produce such great variation in clinical course and degree of illness? The aspiration mechanism offers an explanation of this variation, as it is evident that the material aspirated may range from non-infected mucus to grossly infected pus.

Significance of this Point of View

The acceptance of an aspiration basis for "primary atypical pneumonia" greatly simplifies the understanding of the condition. It provides an explanation for its apparently obscure epidemiology, showing that its infectivity and method of spread are merely those of the upper respiratory infection. It shows that such pulmonary lesions are not fundamentally different from the pulmonary complications of childhood infections such as pertussis (Lees, 1950). It indicates that the condition will not be restricted to military sources; indeed, we have seen many cases among civilian patients both

in adults and in children, but these have not been included in the present survey. It offers a pointer to useful therapeutic measures to be adopted and we have extensively used such measures in the treatment of our cases.

Recognition of such radiological change as an aspiration segmental lesion has led us to perform further detailed investigations, and in this connexion over 200 cases have been examined by bronchography in order to study the changes in local bronchial pattern at the time of illness. The wide range of bronchial abnormality which may occur, some of which may be serious and irreversible, draws attention to the need for careful supervision and treatment of the original illness. These findings also contradict the usual view that "primary atypical pneumonia" is an essentially benign condition which resolves without serious sequelae.

This latter section of our work will form the subject of a separate publication.

Treatment

In the past no therapeutic measures were described as influencing the course of a "primary atypical pneumonia." More recently chloramphenicol and aureomycin have been widely advocated (Meiklejohn and Shragg, 1949).

When the aspiration basis for the lesions is appreciated it becomes evident that more simple measures may assist in the resolution of the pulmonary disease. Thus percussion postural drainage has been extensively used and has frequently assisted in the re-aeration and drainage of an infected segment. On occasion additional agents such as steam inhalations and short-wave diathermy, have been employed.

The widely varying bacterial flora of such aspiration lesions gives some explanation for the varying response to chemotherapy and penicillin. Chloramphenicol and aureomycin can be regarded only as of use in those cases in which there is a considerable infective element due to organisms insensitive to penicillin. Their indiscriminate use as agents to combat the "virus of atypical pneumonia" must be regarded as unjustified; in any case no antibiotic can have significant effect upon the mechanical element of such segmental lesions.

Summary and Conclusion

The general features of a condition believed to be segmental aspiration pneumonia are described and a review of previous descriptions of primary atypical pneumonia is given. Comparison of the two conditions reveals no significant difference between them.

Reasons are given for doubting the viral origin of the pulmonary lesions. It is considered that they result from aspiration of products from an associated upper respiratory tract infection.

The significance of such a point of view is discussed and mention is made of possible complications and treatment.

Our experiences with this series of cases has led us to believe that the name and diagnosis "primary atypical pneumonia" is meaningless, as it is not a specific condition but merely represents a segmental aspiration pneumonia.

Without the co-operation of the medical authorities of the Royal Air Force and, in particular, Group Captain Rumball, the consultant in medicine, this work would not have been possible. We are grateful to the Director-General for permission to publish our findings. Dr. Robert Coope and Dr. P. H. Whitaker, whose clinical assistants we are, have given us every encouragement and placed the full facilities of their departments at our disposal. We are also grateful for much material assistance from the University of Liverpool.

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SERUM POTASSIUM DEFICIENCY DURING TREATMENT WITH SODIUM P.A.S. AND LIQUORICE EXTRACT

BY

J. A. STRONG, M.B., M.R.C.P.

Senior Lecturer, Department of Medicine, University of
Edinburgh; Assistant Physician, Western General
Hospital, Edinburgh

Cayley (1950) reported the occurrence of serum potassium deficiency in the course of treatment of three patients with pulmonary tuberculosis using *p*-aminosalicylic acid (P.A.S.). Heard, Campbell, Hurley, and Ferguson (1950) found evidence of this complication in 12 patients undergoing treatment with the drug.

Two patients with pulmonary tuberculosis have recently shown marked myasthenia while being treated with sodium P.A.S., and in view of the apparent rarity of the complication, judging from its absence in the numerous reports of the use of the drug, an account of it may be of interest. The implications of the metabolic changes found are examined.

Case 1

A girl aged 18 suffering from a breaking-down primary tuberculous lesion in the left upper lobe was receiving streptomycin, 0.5 g. twice daily intramuscularly, and sodium P.A.S., 4 g. five times daily by mouth, each dose containing 20 min. (1.2 ml.) of ext. glycyrrhiz. liq. B.P. as a flavouring agent. After 11 days' treatment and for the succeeding five days she suffered from intermittent pyrexia. She had previously been afebrile.

The tonsils showed a follicular exudate; the right tonsillar gland was found to be enlarged, and an erythematous rash appeared over the shoulders. Treatment was continued, and these signs disappeared. By the thirtieth day of treatment she complained of generalized stiffness in all limbs and of weakness and cramping pains in her legs. She remained