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A SHORT HISTORY OF THE PNEUMOCOCCUS WITH SPECIAL REFERENCE TO LOBAR PNEUMONIA

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THE clinical entity—pneumonia—has been known since the days of Hippocrates and the old Greek physicians, *i.e. circa* 2300 years, but there can be no doubt that its origin goes back to uncharted medical history. On the other hand, the rôle of the pneumococcus as the *causa morbi* was definitely established just over sixty years ago. Prior to this it had been generally held that the condition was due to exposure, unavoidable or imprudent, to climatic conditions associated with a low temperature, but from the clinical behaviour of the disease and the occurrence of epidemics, it was gradually being realised that it might be due to an infectious process. Two strong advocates of an infectious theory were Jürgensen and Flindt, but even Jürgensen, while believing that pneumonia was an infection, said that a chill was a rare occasional cause. Flindt said that in over 90 per cent. of his cases a chill could with certainty be excluded.

Klebs, in 1875, was the first to investigate the bronchial secretion of a case of pneumonia for pathogenic schizomycetes. Many different organisms were found, which he called monadinen. The monad he thought responsible for the pneumonia he termed monas pulmonale. With only white of egg as a culture medium, Klebs can only be regarded as a pioneer in this particular instance. What were subsequently found to be pneumococci were recovered from an extra-pulmonary source, first by Sternberg, and shortly afterwards by Pasteur, the latter's observations being published first. It was in 1880 that Sternberg infected some of his saliva under the skin of a rabbit and found, fortuitously, that a fatal septicæmia ensued, the blood containing great numbers of oval micrococci. Repetitions of this experiment always produced the same result. His paper, published in 1881, was accompanied by a photomicrograph showing capsulated diplococci and short chains.

Pasteur, a few months later, while investigating rabies, produced a similar septicæmia by infecting rabbits subcutaneously with a little buccal mucus from a child just dead from hydrophobia. The organisms in the rabbit blood were mostly in figures of 8 and were surrounded by

an aureole. The infection could be transmitted from rabbit to rabbit always with the production of a septicæmia. He cultured the organisms in veal broth. For the time being Pasteur was nonplussed, not knowing whether he was dealing with a new disease or one that had some connection with hydrophobia. At any rate he thought it would be rash to say that they were absolutely independent. Early in 1881 his results were intimated to the French Academy of Medicine in Paris. It required five or six meetings of the Academy to clear up the position, when it was shown that a similar condition had been produced by normal saliva and also by that from the mouths of three children dead of bronchopneumonia. The organisms causing this septicæmia were later called the organisms of sputum-septicæmia by Fränkel and found by him to be identical with those causing lobar pneumonia.

In the same year (1881) Eberth examined a case of croupous pneumonia associated with a metastatic meningitis. By the use of methyl-violet he demonstrated microscopically the presence of cocci, in twin form, both in the lung and in the brain ventricles. There can be little doubt that these organisms were pneumococci, but in those inchoate days of bacteriology, his observations were not supported either by culture or animal inoculations. Also in 1881 Koch made sections of the lungs and kidneys from a case of pneumonia. The accompanying photograms showed cocci in pairs. Friedländer, in 1882, published the first of his papers, which were to lead to much controversy. His work will be referred to anon.

The following year Talamon produced an important contribution on the "coccus of pneumonia." Examining 25 cases of lobar pneumonia, he found most often a characteristic ellipsoid diplococcus, which he aptly described as lancet-shaped or lanceolate. In his researches he was hampered by having only a fluid medium (Liebig extract of beef broth) at his disposal, so that he rarely got pure cultures. Thus during life he punctured the consolidated lungs in 8 cases of pneumonia, but was able to obtain only one pure culture of the diplococci. Talamon also carried out a number of animal inoculations, chiefly on rabbits. Sixteen out of 20 died, lanceolate cocci being present in the blood of some of these. Culture of the blood from his 25 cases yielded oval cocci in 2 cases. One curiosity about his work was that he did not observe, or at least did not mention, that the organisms were capsulated. From his investigations Talamon concluded that fibrinous lobar pneumonia was an infectious disease produced by a special microbe of characteristic form, *lanceolée au grain d'orge ou de blé*. Limited to fluid culture his researches were valuable, but not complete.

Returning to the papers of Friedländer, his first dealt with 8 *successive* cases of acute genuine pneumonia. As a pathologist, he examined the bronchial effusion and sections of lung and pleura, describing the presence in all of ellipsoid cocci, mostly as diplococci and some chains of diplococci. In his second paper the number of his cases

of pneumonia had risen to more than 50, in only a few of which were the micrococci missing and these were old cases. Unfortunately, Friedländer goes on to cloud the situation by saying that he had obtained a characteristic growth by stab culture of gelatine. He described it as a nail-form growth, the head of the nail being heaped up on the surface of the gelatine. Another confusing statement was that rabbits were completely refractory to his organism.

Friedländer's results were equivocal. His description of the organisms was homomorphic of pneumococci, and the high incidence of positive cases was unquestionably pneumococcal. On the other hand, the strong growth on the surface of the gelatine, together with the refractoriness of rabbits, suggested that he was not dealing with the pneumococcus in this instance, but what was later called the pneumobacillus. It may be noted that Friedländer was the first to obtain a growth from croupous pneumonia by the use of solid medium.

The spotlight now turns on Fränkel, whose name is definitely linked with the pneumococcus. He first promulgated his views at a Berlin Congress in 1884, when the other main speaker was Jürgensen, the advocate of the infectious theory of pneumonia. His researches were carried out on a comparatively few cases of pneumonia, but he made numerous cultural experiments and animal inoculations. The organism he obtained was a capsule bearing diplococcus of lancet or spindle form. At first he was not sure whether the diplococcus was different from that of Friedländer or a modification differing in virulence. With his eye on two of Friedländer's results, viz. the growth on gelatine and the refractoriness of rabbits, he was at first hesitant when he obtained inconstant results with rabbits and when in one case he got a nail-form growth on gelatine in the first generation. His main work appeared in 1886. By that time he was quite satisfied that his organism was quite different from that grown by Friedländer. He reported that his diplococcus did not grow at room temperature, its growth was more delicate and died out readily unless frequently transferred to fresh media, it rapidly lost its virulence and that it was generally lethal to rabbits, and that it was the real cause of lobar pneumonia.

When confronted with Fränkel's results, Friedländer at once said that there might be different kinds of pneumonia caused by different organisms. For a time Fränkel was influenced by this conception, but at length he came round to the idea of the unity of pneumonia, that is to say, that it was due to only one organism, viz. the pneumococcus. In support of the pneumococcus being the cause of lobar pneumonia, he instanced two cases of empyema following pneumonia from which he had obtained the same organisms as from the lung, and also a case of meningitis complicating a pneumonia from which he had isolated the pneumococcus.

Another important part of Fränkel's work was to prove that the

organisms of the so-called sputum-septicæmia were similar to those found in the lungs in pneumonia. To show that they were inconstantly present in the normal mouth, he instanced his own case. One year his saliva produced regularly a septicæmia in a rabbit, whereas the following year it was quite ineffective. Fränkel knew about the Gram stain, but evidently not as a means of differentiation, and in one of his later papers he acknowledged with gratitude that Weigert had drawn his attention to it as a means of distinguishing his organism from that of Friedländer. He then quotes the original article of Gram. It might be instructive to refer to it here.

We find that the stain was primarily introduced for staining the pneumoniekokken, leaving the background of cells and tissue elements unstained, so that the organisms stood out clearly. Later it was used as a general stain for the organisms of other diseases, and still later a counterstain, such as Bismarck Brown, was employed. As Friedländer's colleague, Gram had investigated 21 cases of pneumonia, the organisms in 19 of which had retained the violet stain, while in the other two they had become decolorised. He mentions the very interesting fact that it was from one of these decolorised organisms that Friedländer had made most of his cultures and animal inoculations. This would certainly account for the growth on gelatine obtained by Friedländer and which so disturbed Fränkel.

The conclusion one comes to is that Friedländer had found pneumococci in most of his cases and the Gram-negative organisms (pneumobacilli) in only a few. White gives support to this view, as had Muir and Ritchie in 1907. There seemed to be an *odium medicum* between Fränkel and Friedländer, especially on the part of Fränkel. Friedländer refers to Fränkel's personal attacks and reproaches. It is only right to point out that independently of Fränkel, Sternberg in 1885 had already come to the conclusion that his salivary coccus was also the same as that causing lobar pneumonia, but his proof was not so conclusive.

In 1886 there appeared the equally important paper of Weichselbaum on acute lung inflammations. His work entailed the examination of 94 cases of lobar pneumonia and 35 other types of pneumonia, and extended over a period of more than two years. Influenced by Friedländer having obtained a growth on gelatine, Weichselbaum had used this medium at first, but always unsuccessfully. He afterwards resorted to agar and blood serum with satisfactory results. His organisms were oval and lancet formed, usually in pairs, but sometimes also round and in chains, and he gave them the name diplococcus pneumoniæ, a name they still retain. They were obtained from the great majority of his cases, and he concluded that they were the main cause of lobar pneumonia. Streptococci were found in a few cases of both lobar and lobular pneumonia, while Friedländer's organisms (bacillus pneumoniæ) were obtained pure in 4 cases of lobar pneumonia. Staphylococci were the cause of secondary pneumonias

only. Weichselbaum's results therefore supported Friedländer's contention that pneumonia may be of various forms caused by different organisms.

Serology

Immunity problems soon began to engage the attention of research workers. Already, in 1886, Fränkel had made the observation that when a rabbit had recovered from a subcutaneous inoculation of his diplococcus, it became refractory to further infections of the organism. About the same time Foá and Uffreduzzi had had a somewhat similar experience. Foá, along with different colleagues, continued to take a keen interest in the subject. Thus in 1888, with Bonome, rabbits were immunised with the soluble products of the diplococcus, and later with Scabia a high-grade immunity was obtained with a glycerine extract of the pneumococci. Foá and Carbone reported in 1891 that immune serum had a protective influence in infected mice.

In the same year G. and F. Klemperer carried out immunisation experiments on rabbits, using sputa (pre-critical and post-critical) pleural exudate, glycerine extracts of pneumococci and broth cultures. Both subcutaneous and intravenous routes were employed. The post-critical serum from pneumonia cases proved capable of curing pneumococcal infection in rabbits. Having tested immune serum on themselves and found it harmless, they tried its curative properties on 6 cases of pneumonia, with encouraging results. This was the genesis of serum therapy in the treatment of pneumonia.

Emmerich and Fowitzky also immunised rabbits and found that the degree of immunity obtained varied with the method employed. Thus immunity was incomplete if attenuated cultures of pneumococci were introduced subcutaneously, whereas complete immunity was obtained by the intravenous inoculation of a fully virulent culture. Emmerich, in 1894, prophesied that the serum of immunised animals would undoubtedly in future be used as an ideal healing method in human disease.

The *modus operandi* of an immune serum was given various interpretations by the immunologists of that time. Thus the brothers Klemperer explained it on a toxin-antitoxin basis. In this they were doubtless influenced by the lately published important results of Behring and Kitasato on the toxins and antitoxins of the diphtheria and tetanus bacilli. Emmerich thought it depended on a bactericidal substance in the blood, and Mosny a toxicidal. On the other hand, Issaeff found that phagocytosis played the most important rôle in the acquired immunity. This was a significant finding, but, coming from the Metchnikoff laboratory, not a surprising one. Kruse and Pansini, while admitting phagocytosis, thought it of secondary importance. Later Neufeld thought that the diplococci were rendered more susceptible to phagocytosis by the production of bacteriotropins (opsonins).

So far an important property of immune serum had not been mentioned. It was drawn attention to by Metchnikoff in 1891 in a paper on immunity. He found that the serum of guinea-pigs vaccinated against the vibrio metchnikovi clumped the vibrios, and he interpolated "Elle se rencontre aussi pour le microbe de la pneumonie qui forme dans le serum des lapins vaccinés des paquets de streptocoques très longs." This phenomenon of immune serum had already been reported in the case of *B. pyocyaneus* by Charrin and Roger in 1889.

Metchnikoff's observation was confirmed by Mosny (1892), Arkharow (1892), Issaeff (1893), and in this country by Washbourn in 1896. In the words of Washbourn: "When protective serum is inoculated, it appears perfectly clear at the end of 24 hours, but at the bottom a sediment is seen. This sediment consists of pneumococci staining well and grouped in masses." Was this congeries of organisms real agglutination? It would appear so, as normal serum showed only a uniform turbidity.

This phenomenon was more fully studied in 1897 by Bezançon and Griffon and definitely called by them agglutination. These workers were obviously inspired by their association with Widal, who had published his sero-diagnostic method for typhoid fever in 1896. Compared with typhoid fever, they found that the serum of pneumonia cases agglutinated only in low titre and also that some pneumococci were agglutinated and not others. They believed that they had been able to differentiate between pneumococcal races by the agglutinating reaction.

Neufeld contributed a paper on pneumococcal agglutination in 1902. He found that normal serum of both man and animal had no agglutinative effect, so that there was no risk of wrong inferences in this respect. Using broth cultures of pneumococci in his experiments, he found that the highest dilution of rabbit immune serum and convalescent serum of pneumonia cases to cause agglutination was 1 : 50. Wadsworth cast doubt on agglutination technique prior to Neufeld's experiments. Like Neufeld he used a broth culture, but this was centrifugalised and saline added to the precipitate. He claimed more accurate results from this method.

Type Differentiation

Prior to the evidence that varieties of pneumococcus could be distinguished by means of agglutination tests, it had been suspected that more than one type existed. An experience of Foá suggested this. He cultivated two organisms, one from a pneumonia, which he called a pneumococcus, and the other from a meningitis, which unfortunately was called a meningococcus. Later he referred to the latter as meningococcus or streptococcus lanceolatus, and it is generally presumed to have also been a pneumococcus. But without presuming too much, the interest lay in the fact that they were found to be serologically different. There was more satisfactory proof later.

Eyre and Washbourn acquired some anti-pneumococcal serum from Pane of Naples and carried out a series of tests on pneumococci obtained from five different sources. They found that the serum protected against four varieties, but not against the fifth.

It is interesting to note that the first type of pneumococcus to be recognised as different from all others was to become known as Type III. There was nothing dramatic about its discovery. Indeed at first no one even called it a pneumococcus, although it was sometimes described as looking like one. It was rather a case of a conjectural approach, being referred to as a pathogenic diplococcus, a pseudo-pneumococcus, streptococcus mucosus, pneumococcus mucosus and finally Type III. The outstanding feature of this organism was its peculiar mucoid growth on culture. The pathogenic diplococcus, resembling a pneumococcus, was obtained in 1897 by Atkinson from an extra-pulmonary source, while Richardson in 1900-1 reported that during the past five years he had obtained pseudo-pneumococci from 4 cases of lobar pneumonia. Although they had difficulty in giving it a name, Howard and Perkins called their organism streptococcus mucosus.

Schottmüller published papers in 1903 and 1905, but he had first obtained what he called streptococcus mucosus from a parametritis in 1896. Since then he had found it in pus at different times and also in the blood in cases of pneumonia.

In 1905, Park and Williams in a study of pneumococci in normal throats and in pneumonic exudates, isolated streptococcus mucosus from 8 cases of pneumonia (twice in pure culture) and also from healthy people. After saying it should be called streptococcus lanceolatus var. mucosus or diplococcus lanceolatus var. mucosus, they themselves rather naïvely said that they gave it the *trivial* name of pneumococcus mucosus. Streptococcus mucosus was also reported from lobar pneumonia cases by Duval and Lewis, and Eng. Fraenkel, and from a case of suppurative otitis by Heim. Neufeld had reported in 1900 that pneumococci were soluble in bile, but none of the observers cited above mentioned that they had made use of this test. The organisms of Park and Williams and Howard and Perkins fermented inulin.

Still calling it streptococcus mucosus, Holman in 1914 isolated it from a case of lobar pneumonia. Hanes, in the same year, obtained it from 9 cases of lobar pneumonia, but called it pneumococcus mucosus. It fermented inulin and was soluble in sodium taurocholate. That there should exist so much confusion between a streptococcus and a pneumococcus is readily understandable, as in this instance the pneumococcus mucosus may be rounder than normal and under certain conditions there is a strong tendency to catenation.

After this hesitant approach to the pneumococcus mucosus, we are indebted to Neufeld and Haendel for further type differentiation. The foundation was laid during their researches in 1912 on pneumococcal healing sera. The most usual pneumococcus reacting with their sera was regarded as typical and named Pneum. I. The next

commonest was called Pneum. Franz—a name derived from that of the immunised horse. Non-reacting types were referred to as atypical.

It was in 1913 that Dochez and Gillespie produced their well-known classification. Using the two strains of pneumococcus most commonly causing pneumonia, they immunised rabbits, and with the sera obtained carried out protection and agglutination tests on sixty-two strains of pneumococci. The pneumococci were divided into four groups—I, II, III and IV.

I and II groups reacted with the antisera obtained from the rabbits.

Group III, or mucosus group, had distinctive growth characteristics.

Group IV a heterogeneous group.

Cole in 1915 called the four groups types, but he preferred to call Type IV Group IV. Neufeld's types were obtained from Germany and compared with the American types. His Pneum. I corresponded with their Type I, and Pneum. Franz was identified as their Type II. Dochez and Avery in 1917 made an important discovery when they found in young pneumococcal cultures a substance specifically reacting with the homologous immune serum. This suggested to them that if present *in vitro*, it would also be found in the animal body; and it was so. It was demonstrable in the blood and urine of inoculated rabbits and also in the blood and urine of a percentage of cases of lobar pneumonia in human beings. The amount present in the urine was held to be a measure of the severity of the infection and was therefore of prognostic value. The type of the infecting pneumococcus could be determined by a precipitin test. Neufeld had already shown in 1900 that pneumococci dissolved in bile yielded a precipitate when tested with homologous antiserum.

The specific soluble substance (S.S.S.) was found to be derived from the carbohydrate in the capsule. Chemically it was a complex polysaccharide, quite distinct in Types I, II, and III. The nucleo protein in the body of the coccus was common to all pneumococci, irrespective of type. It is paradoxical that the kernel of type specificity is inherent in the capsule.

Heidelberger along with Avery and other associates investigated the chemistry and immunology of the capsular polysaccharides. As originally isolated these carbohydrates were found to be non-antigenic. In 1925 Avery and Neill found that intact pneumococci acted as complete antigens, while pneumococci in solution, although retaining their type specificity, did not stimulate the formation of antibodies. On this point Avery and Heidelberger concluded that the carbohydrate in the intact cell was combined with some substance which empowered it to act as an antigen, but when this combination was broken up on dissolution of the cell, the carbohydrate could no longer act as an antigen.

A certain combination was reported by Avery and Goebel in 1933, who showed that an acetyl group was attached to the polysaccharide

of Type I pneumococcus. If the acetyl groups were removed during extraction and purification the deacetylated polysaccharide lost its antigenic properties. A contrary opinion was put forward by Felton and Prescott in 1939. In a comparative study of the Type I polysaccharide isolated by the calcium phosphate method and the method of Heidelberger, they concluded that the presence or absence of the acetyl group was of no significance for its antigenicity in white mice. Zozaya and Clark found that the polysaccharides of Types I, II and III did not lose their antigenic properties in mice if they were adsorbed on collodion particles and carbon.

While pneumococci were being investigated from the chemical side the original American classification was not allowed to remain static. At first Types I, II and III were regarded as fixed types, but only Type I has remained immutable. In 1915 Avery found that with certain strains the agglutination reaction with Type II antiserum was sometimes incomplete and less prompt. Using univalent immune sera against ten such strains, he divided them into three subgroups of Type II, viz. Subgroup II_A, Subgroup II_B and Subgroup II_X. Subgroup II_A and Subgroup II_B were later identified as Type V and Type VI respectively, while from Type III, Type VIII was hived off after Sugg *et al.* had reported atypical Type III.

The next obvious step was the disintegration of the heterogeneous Group IV. Many tentative attempts were made towards this end. Thus, in 1916-17, Olmstead investigated 94 Group IV strains and demonstrated twelve distinct groups, leaving some of the strains undifferentiated. Griffith, from forty-nine strains, distinguished twelve types including Type II, Subgroups A and B, and Robinson, in 1927, from sixty-five strains obtained eight immunological groups, but nothing of a permanent value resulted from their efforts.

It was not till 1929 that Cooper and her associates placed the segregation of Group IV organisms on a sound basis. Using monovalent antisera, 120 strains from lobar pneumonia cases were divided into ten groups, IV to XIII, leaving some unclassified. In 1932 they extended their types from XIV to XXXII. At the same time some of the types obtained by Avery, Griffith, and Robinson were correlated. Kaufmann *et al.* in 1940 reported twenty new types, sixteen of them being subtypes. These included some already described by Vamman. A new type was determined not only by capsular swelling, but by agglutination and absorption tests. The new types were all serologically distinct from those of Cooper, but as some were antigenically related, Cooper's numbers were retained and a letter added. They said that fifty types were now known, but that presumably the number of types was far beyond a hundred.

In 1941 Walter *et al.* classified a thousand cultures in seventeen new types, some of which corresponded to those of Kaufmann. They comprised nine new types and eight subtypes. Cooper's Types XXVI and XXX were replaced by new types. There were now forty types

and fifteen subtypes. Mørch (1942) said that the studies commenced by Kaufmann *et al.* had been continued and eighteen new types established. Eddy (1944), in order to avoid confusion, recommended that every type should be given a different number regardless of its antigenic relationship to other types. Seventy-five types were listed. It should be mentioned that, *pari passu* with the American classification, Lister in South Africa had commenced a system of grouping, which promised to be of equal importance, but it became subordinated to the American system. Ordman has correlated the types found in South Africa and in the U.S.A.

Addenda

It is true, as Don Quixote has said, that in the nests of the last year there are no birds of this year. It is also true to say that the past contains the germs of the future, and it is from this viewpoint that the subject of this paper has been approached.

The history of this interesting organism in modern times is, or should be, well enough known, whereas knowledge of its early beginnings is not so easy of access. Since its first recognition sixty-odd years ago, the pneumococcus has been christened a score of times. The list may be found in *The Biology of Pneumococcus* by White. The specific name is diplococcus pneumoniæ (first given to it by Weichselbaum), but the familiar name pneumococcus, that is to say lung coccus, although it takes no cognisance of its activities outside the lung, will almost certainly continue to be popular. The term pneumokokkus was used by Klein in 1884, while Fränkel employed it only sparingly, his usual nomenclature being pneumoniecoccus or pneumoniemikrococcus.

A chill, once held to be of prime importance in the causation of pneumonia, is now considered as only a possible contributory factor, just as any other debilitating influence, such as fatigue, alcoholism, injury, and so on. Old ideas, however, die hard, and many people still have an affecting belief in a chill as the *fons et origo* not only of pneumonia but many of their other illnesses. Thus if a doctor diagnoses a chill it serves a dual purpose, not only satisfying the patient, but at the same time affording the medical man a ready escape from all etiological difficulties.

It was at one time suggested that pneumonia might be of pythogenic origin. This meant it could be caused by inspiring emanations from foul matter, for example defective drains. It may be recalled that this was once thought to be the origin of typhoid fever. This theory has long since been forgotten. Yet is it not strange that the medical profession perpetuates a similar mistaken diagnosis in the name of a very important disease, namely malaria, a name that to those who are at all word conscious still conjures up visions of reeking swamps! Still another theory may be referred to only to be dismissed. A telluric origin was suggested by Prof. Purjesz, who rejected both the

infectious and *a frigore* theories and thought that pneumonia was due to some underground disturbance. This idea soon went *zu grunde*, as the Germans say, and appropriately so in this case.

The infectious theory did not meet with general acceptance for some time. Indecision is reflected in an article in the *Lancet* of 2nd April 1892, and remember this was six years after the apparently conclusive findings of Fränkel and Weichselbaum. There we find the following views : " The pathology of pneumonia is one of the *questiones vexatæ* of Medicine " ; " Much remains to be done before we are in a position to conclude that bacteriology has said the last word regarding pneumonia " ; and finally, " It will thus be seen that the pathology of pneumonia remains a question *sub judice*, but that the best authorities more and more incline to the specific theory of its origin."

The fact that pneumococci were not uncommon denizens of the normal oro-pharynx stuck in the throats of many. It puzzled them how such apparently harmless organisms could cause pneumonia. They did not know at that time that there were many types of pneumococci, varying greatly in virulence, and that these oral types caused only about 25 per cent. of cases of pneumonia, the disease in the main being due to infection from without. In 1900 Bezançon and Griffon during their agglutination experiments concluded, rather erroneously, that pneumonia in the majority of cases was due to these indwelling pneumococci.

Attention should be drawn here to a remarkable instance of prescience. Sternberg in 1885, after admitting that autoinfection may occur, went on to say: " A person whose vital resisting power is reduced by any of the causes mentioned may be attacked by pneumonia from external infection with material containing a pathogenic variety of this micrococcus having a potency, permanent or acquired, greater than that possessed by the same organism in normal buccal secretions." This is a prediction worthy of Nostradamus.

The serum therapy for the treatment of pneumonia, foreshadowed by the Klemperers and Emmerich, could not be put on a rational basis until the type of the infecting organism could be determined and thus had to wait over twenty years. At first it was used only for Type I and Type II pneumonias, a Type III antiserum being difficult to obtain. As time went on and the type of some of the Group IV organisms was determined, sera for the more usual types causing pneumonia were made and used especially in the U.S.A. They were not available for general use in this country. Serum treatment, if available, was the recognised rational therapy till the advent of the sulphonamide drugs in 1938, the first being sulphapyridine. This new treatment involved no type differentiation and thus could be applied equally well to any case of pneumonia. In their time they have been more or less superseded by penicillin, but they are still of use in penicillin resistant cases.

The usual method of determining the type of the infecting pneumococcus was by the intraperitoneal inoculation of a mouse with a

specimen of sputum and subsequent application of the agglutination test to the peritoneal exudate. The agglutination test gave way to Neufeld's quellung reaction, which had lain fallow for over two decades, and which was applicable either to the direct examination of the sputum or to the peritoneal exudate of the mouse.

The sluice-gates of literature have, in truth, been opened on the pneumococcus, and references have perforce had to be selective and in the hope that there has been no flagrant omission. This paper does not presume to be other than a parergon.

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