

Erasmus Wilson Lecture

ON

THE PYOGENETIC ACTIVITIES OF THE PNEUMOCOCCUS.

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By J. W. H. EYRE, M.D., M.S. DURH.,
M.R.C.S. ENG., D.P.H. CAMB.,

BACTERIOLOGIST TO GUY'S HOSPITAL AND TO ST. MARY'S CHILDREN'S HOSPITAL, PLAISTOW; LECTURER ON BACTERIOLOGY AT THE MEDICAL AND DENTAL SCHOOLS OF GUY'S HOSPITAL.

INTRODUCTION.

GENTLEMEN,—In 1881 Ogston of Aberdeen published an account of his observations upon the microscopical constituents of surgical pus which enabled him to state that minute spherical bodies, "micrococci," were usually present in this pathological product of infected wounds. Moreover, he differentiated these cocci into those occurring in irregular masses—"grouped micrococci"—which were usually associated with circumscribed abscess formation, and those which occurred in rows like strings of beads—"chain micrococci"—which were usually found in connexion with the spreading "cellulitis" type of suppuration. Three years later Rosenbach published the results of his investigations which fully confirmed the earlier observations of Ogston. This second worker succeeded in isolating staphylococci and streptococci, as they were now termed, cultivated them upon artificial media in the laboratory, and differentiated some of the several varieties included in this first general morphological classification. For the next decade, no matter in what situation or association it presented itself, pus was pretty generally regarded as the outcome of infection by members of the staphylococcus and streptococcus "pyogenes" groups—a result largely due to a too literal interpretation of Koch's dicta, which laid it down that in order to establish a claim for the specificity of any newly discovered bacterium, that organism must be shown to be constantly present in some particular and definite lesion; must be capable of isolation and cultivation outside the animal body; and on its reintroduction into a suitable host must reproduce the original lesion. Hence as the specific etiological factors of the various bacterial infections were recognised and isolated attention was invariably first directed to the reproduction of the original lesions in their entirety, and subsidiary phenomena such as the provocation of pus formation were entirely disregarded, or, again instancing the formation of pus, regarded merely as the result of accidental and preventable contamination with the so-called "pyogenic" cocci already referred to. And it is only within recent years, since, in fact, the inter-reactions of seed and soil, of bacterial irritant and tissue cell, have been the subjects of extended study that the principle has been generally recognised that practically any and every pathogenic bacterium possesses the power, under some certain combination of factors, of initiating purely pyogenic processes in place of, or in addition to, its particular specific lesion.

Perhaps the most striking illustration of the above statements that can be adduced is afforded by a study of that organism which forms the subject for our present consideration. First studied in its association with one form of inflammatory reaction in pulmonary tissue—viz., acute croupous or lobar pneumonia—its specificity in this connexion was conclusively established before its potentialities in other directions received any but the scantiest consideration. Indeed, it is not so many years ago that the definite statement was made—in all sincerity and as representing the established conviction of a large body of observers—that the pneumococcus was of itself never responsible for the formation of pus, and despite the fact that the presence of the pneumococcus could so readily be demonstrated in those purulent collections within the pleural cavity that are frequently associated with pneumonia, such empyemata were invariably regarded as the direct result of secondary infection with some one or more of the ordinary pyogenic staphylococci or streptococci. The pyogenetic activities of the pneumococcus itself have, however, now been demonstrated experimentally in so complete a manner that the

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present seems a fitting opportunity to review our knowledge of the subject upon which present-day opinions are based.

HISTORICAL SUMMARY.

The micro-organism I have chosen for the subject of my lecture was first discovered by Sternberg in September, 1880, in the course of some investigations on malarial fever. By means of inoculation experiments he found that his own saliva was pathogenic for rabbits and he isolated a definite diplococcus, which he considered the cause of such pathogenicity, and to it gave the name "micrococcus Pasteuri." This he described in a report to the National Board of Health (U.S.A.), which, however, was not then published but to which he refers in the National Board of Health Bulletin of April, 1881.

In January, 1881, during a discussion following the reading of a paper ("Recherches Expérimentales sur la Transmission du Virus Rabique de l'Homme au Lapin," par MM. Raynaud et Lannelogue, Jan. 18th, 1881) before the Paris Academy of Medicine, Pasteur stated that in December, 1880, he inoculated two rabbits with saliva from a fatal case of hydrophobia, that of a boy, four hours after death. The rabbits died in 36 hours and a new bacterium was discovered in their blood shaped like the figure 8 and surrounded by a gelatinous capsule. It was virulent in broth cultures where it often formed chains. He expressed his ignorance of its relation to rabies but distinguished between the new organism and his "vibron septique"—i.e., the bacillus of malignant oedema. For the next few months communications were made to the Academy in rapid succession confirming these observations, and a commission was appointed to investigate the subject. Pasteur reported to this commission in April, 1881, that he had found the new organism in the saliva of one more fatal case of rabies and three fatal cases of broncho-pneumonia, and had failed to find it in the saliva of three persons dead from other diseases.

Vulpian (1881) stated that he had found the micro-organism in a virulent condition in the saliva of healthy individuals.

In 1881 also Ebert and Koch and in the following year Friedländer, Leyden, and Günther demonstrated microscopically the constant presence of a diplococcus in the lungs in cases of lobar pneumonia. The two latter, moreover, described the surrounding capsule as being present in specimens made from the fluid drawn from the hepatised lung itself during life by means of a sterile syringe, but they were unsuccessful in obtaining pure cultures of the organism.

In 1883 Matray and Ziehl studied cases of pneumonia and fully confirmed these observations.

In the meantime, and on the experimental side Griffini and Cambray inoculated rabbits with pneumonic sputum and regularly produced a fatal septicæmia; continuing their experiments they were equally successful in reproducing the septicæmia in other rabbits by using for the purpose of inoculation blood taken from the original rabbits after death.

In November, 1883, Friedländer described cultures upon solid media of what he considered to be the pneumococcus. He stated that his organism was an oval coccus, surrounded by a gelatinous capsule, which readily grew on gelatin at the ordinary room temperature. These observations gave a great impetus to the bacteriological study of croupous pneumonia by the modern methods, although we are now aware that Friedländer's "oval coccus" was in truth a bacillus and in no way concerned in the causation of the disease.

Two months later (1884) before the Société Anatomique Talamon described cultivations in bouillon of the genuine diplococcus and showed cultures grown at the body temperature from pneumonic exudates. Two of these cultivations were absolutely pure. Of 20 rabbits inoculated into the chest cavity with these cultures 16 died from septicæmia, often accompanied by fibrinous pleurisy and pericarditis, and sometimes by a true lobar pneumonia. The blood and exudates of these fatal cases always contained cocci, and yielded pure cultures capable of producing similar inoculation results. Guinea-pigs and dogs, he stated, were immune. He had also found the coccus in fluid drawn during life from the hepatised lung—in man—in eight cases. In one fatal case it occurred in the general circulation at the moment of death.

As Friedländer and Talamon were working with two distinct organisms a good deal of confusion resulted from their conflicting statements. As an example of this Sternberg in April, 1885, read a paper before the Pathological Society of Philadelphia, pointing out the identity of the coccus

which he had discovered in 1880 in his own saliva with the coccus which he had more recently isolated in cases of lobar pneumonia, but fell into the error of supposing it to be identical also with Friedländer's micro-organism. All this confusion and misunderstanding was, however, cleared up by the researches of Fraenkel, who in April (before the Congress für Innere Medizin, Berlin) and July, 1885, independently recognised the identity of Sternberg's coccus of sputum septicæmia with the pneumococcus, and quoted three cases of lobar pneumonia from which he had cultivated it on *solid media*. In communications during the course of the following year he published fuller accounts of his observations and gave differential descriptions of the pneumococcus and Friedländer's pneumobacillus.

In May, 1886, Weichselbaum communicated to the Gesellschaft für Aerzte (Vienna) a report to the effect that he had examined the exudate from 129 cases of pulmonary inflammation, of which 94 were undoubted lobar pneumonia and from which he cultivated the pneumococcus. In 21 of the same series he isolated a streptococcus and from nine cases only did he obtain Friedländer's pneumobacillus.

Early observers, as I have previously remarked, adhered rigidly to the postulates of Koch and attempted to prove that the action of the pneumococcus was special and specific and that its pathogenic properties were always, and solely, directed to the production of a special form of pulmonary inflammation which resulted in the consolidation of considerable areas of the lung tissue. When, however, they attempted to reproduce this lesion in laboratory animals it was found that the experimental animals rapidly succumbed to a general septicæmia, unaccompanied by lobar pneumonia, and it was necessary to continue the investigations until a combination of conditions sufficiently comparable to that obtaining in man was discovered, when the experimental infection resulted in the production of lobar pneumonia. This combination of conditions was finally obtained by Gamaleia (1888) working in the Pasteur Institute, for by employing sheep and dogs for his inoculation experiments he was successful in reproducing the typical pathological lesions of acute lobar pneumonia.

During the early inquiries into the life-history of the pneumococcus each worker, almost, applied to the organism a different title. The chief of these were as follows:—

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| 1. Micrococcus Pasteuri | | Sternberg. |
| 2. Micrococcus pneumoniae croupose | | " |
| 3. Microbe septicémique de salive | | Pasteur. |
| 4. Coccus lanceolatus | | Talamon. |
| 5. Coccus of sputum septicæmia | | Fraenkel. |
| 6. Bacillus septicus sputigenus | | Flügge. |
| 7. Bacillus salivarius septicus | | Biondi. |
| 8. Diplococcus pneumoniae | | Weichselbaum. |
| 9. Diplobacillus pneumoniae | | { Fraenkel and Weichselbaum. |
| 10. Pneumococcus | | " |
| 11. Pneumonia coccus | | " |
| 12. Meningococcus | | { Foà and Bordoni-Uffreduzzi. |
| 13. Micrococcus lanceolatus capsulatus | | " |
| 14. Diplococcus lanceolatus capsulatus | | " |
| 15. Diplococcus lanceolatus fibrinogenicus | | " |
| 16. Diplococcus lanceolatus œdematogenicus | | " |
| 17. Gleococcus of Fraenkel | | Klebs. |
| 18. Streptococcus lanceolatus Pasteuri | | Gamaleia. |

Of this formidable list only three have obtained any vogue—viz., pneumococcus, diplococcus pneumoniae, and streptococcus lanceolatus. The last-named has the advantage of accurately describing the organism and is the title preferred by the purist. The first possesses the virtue of brevity, is the one in commonest colloquial use, and is the one that will be adhered to throughout the present paper.

So far all the investigations had been directed to the association of the pneumococcus with lobar pneumonia, but now that the causal nature of the association of the organism with this disease had been firmly established clinical observations concerning manifestations of the pathogenetic properties of the pneumococcus other than, but frequently associated with or following, lobar pneumonia gradually accumulated. For instance, Foà and Carbone (1894) encountered lesions in the human subject which, although apparently all due to invasion of the tissues by the pneumococcus, varied so widely in their histological characters that they felt compelled to recognise two distinct varieties or strains of this organism, which they designated respectively

"œdematogenic" and "fibrinogenic"—descriptive adjuncts which sufficiently indicate the main histological characters of the lesions produced. The first they named the meningococcus and the second the pneumococcus.

As the numbers of workers increased, however, and animal experiments were multiplied it was found that—as in the case of other pathogenic bacteria—one and the same strain of pneumococcus could, by varying the conditions of experiments, be induced to produce widely varying lesions, while clinical observations showed the presence of the pneumococcus, obviously in a causal capacity, in very different pathological conditions.

SOME OF THE LESIONS DUE TO PNEUMOCOCCUS INFECTION.

Meningitis.—Foà and Bordoni-Uffreduzzi reported to the Royal Academy of Medicine, Turin, their observations on lanceolate diplococci which they had discovered in the exudation of cases of epidemic cerebro-spinal meningitis. They further identified this organism with Fraenkel's pneumococcus and published a most valuable study of its biological properties and cultural varieties. Many cases of meningitis associated with or following upon pneumonia have since been recorded by Weichselbaum, Netter, and others, and the disease has been frequently reproduced in the laboratory by means of subdural inoculations of the pneumococcus. At the same time, instances of primary infection of the central nervous system by the pneumococcus have accumulated, and when Wolff in 1897 carefully analysed the literature dealing with meningitis he found that the pneumococcus was recorded as the causative factor in over 40 per cent. of the total number of cases. Osler records a series of 93 cases of meningitis, of which over 22 per cent. were due to the pneumococcus. Brodie, Rogers, and Hamilton (1898), too, have described cerebro-spinal meningitis due to the pneumococcus consecutive to an epidemic form of rhinitis in African natives; and Turner, in a still more recent (1907) article notes the presence of 17 cases of pneumococcal meningitis (out of a series of 70 which were investigated bacteriologically) in natives employed in the Rand mines.

Ulcerative endocarditis.—Endocarditis usually affecting the aortic valve is frequently due to the pneumococcus. Both the vegetative and ulcerative varieties have been produced experimentally by Kruse, Pansini, Vanni, Netter, and others who, however, noted that unless some injury of the valve already existed an endocarditis could rarely be set up. The method usually adopted, therefore, was to pass a sterile probe down the carotid artery into the left ventricle and injure the valve, then to inject virulent broth cultures of the pneumococcus either directly into the heart or subcutaneously.

Suppurative pericarditis.—This is practically always consecutive to lobar pneumonia and pleurisy. Sometimes the exudation is sero-pus or serum containing large flakes of fibrin rather than ordinary pus. At other times the heart is enveloped in a thick membranous layer of fibrin-entangled pus cells and the visceral layer of the pericardium lined with a similar exudation, the two surfaces being separated by a perfectly clear serous fluid.

Pleurisy.—An exudation of clear serous fluid into the pleural cavity resulting from the extension of the pneumococcus through the lung to the visceral layer of the pleura is the commonest sequel of pneumonia, and at the same time, as it is usually readily reabsorbed and the pleura rarely requires opening, is the least important. Frequently, however, the pneumococcus multiplies rapidly in this fluid which then has a sero-purulent character and contains numerous large flakes of fibrin or may gradually merge into a fluid having all the appearance of ordinary pus. The pneumococcus, however, is often able to give rise to a serous or sero-purulent pleurisy quite apart from any antecedent of pneumonia, and this observation is of frequent occurrence in experimental inoculations into the trachea of the rabbit (through a catheter passed through the larynx). Under these conditions the pneumococcus may actually enter the lung, pass through the pulmonary tissues without leaving behind it any trace of inflammatory reaction, pass through the pleura, and reaching the pleural cavity produce a marked pleurisy which often extends to the enveloping membrane of the heart and causes a large collection of serous exudation within that sac. The frequency of the pneumococcus as the exciting cause of serous pleurisy is well shown in the following table, which includes those cases investigated bacteriologically in Guy's Hospital during the past five years—24 out of a total of 82, or a percentage of 29, being the result of the analysis.

TABLE I.—*Clear Fluid from the Pleural Cavity.*

—	1903.	1904.	1905.	1906.	1907.
Pneumococcus (pure).	2	5	10	3	4
Other organisms (excluding bacillus tuberculosis).	10	2	4	9	8
No growth (some certainly and some possibly due to bacillus tuberculosis and others probably due to pneumococcus).	6	2	6	15	20

Empyema.—Pus due to the activities of the pneumococcus is perhaps most familiar to the surgeon in the shape of empyemata. An analysis of the cases of empyema in Guy's Hospital investigated bacteriologically during the past five years shows that 77 per cent. are due to this organism alone.

TABLE II.—*Pus from the Pleural Cavity.*

—	1903.	1904.	1905.	1906.	1907.
Pneumococcus (pure).	10	20	28	16	21
Pneumococcus associated with other bacteria.	3	—	—	1	2
Other organisms (excluding bacillus tuberculosis).	2	4	3	3	8
No growth (some certainly and others probably due to bacillus tuberculosis).	2	2	1	2	3

The naked-eye characters of the purulent fluid are sometimes practically diagnostic. While the pus from cases of pneumococcic empyema or pneumococcic peritonitis may present the greenish yellow colour and creamy consistence of what used to be called laudable pus, it is more often a yellowish fluid of somewhat thinner consistence, which, although quite homogeneous when removed from the body, if collected in a test tube and allowed to stand soon undergoes auto-sedimentation and separates into two layers of about equal bulk, the lower yellow layer consisting of pus cells and the upper a translucent, opalescent fluid quite clear except, perhaps, for the presence of a few flakes of fibrin. The microscopical examination of the fluid is often very characteristic, showing in addition to the pneumococcus itself many involution forms, empty capsules, dead cocci, and deeply staining particles. The contention of the clinician that a pneumococcic empyema is always primarily purulent and that the serous pleurisy due to this organism never becomes purulent obtains very little support either from direct observation or from inoculation experiment. If in a series of intrapleural or intraperitoneal inoculations of the rabbit the conditions are so arranged that the experimental animals shall die at varying periods it will be found at the post-mortem inspection that where death has rapidly followed on the injection the exudation is clear serum teeming with pneumococci. If death is delayed to three, four, five, or more days every gradation in the character of the exudation, from clear serum, sero-pus to creamy pus, will be met with. In the same way the gradual change in the character of the fluid can be noted clinically in many cases if exploration of the chest is repeated from day to day.

Otitis media.—The pneumococcus has been frequently isolated from, and in many cases found in pure culture in, the pus of otitis media. Zufal (1888), who recorded many cases, was able to produce this disease experimentally by means of inoculations into the tympanic cavity.

Arthritis.—The pneumococcus has also been isolated from the serous or purulent exudation in mono- and poly-arthritis occurring either as a primary manifestation of pneumococcic septicæmia or during the course of a lobar pneumonia, the earliest cases being those described by Vogelius (1897). The sterno-clavicular joint, shoulder, hip, and knee are those most commonly affected. Gabbi produced arthritis experimentally by injuring joints, either by traumatism or the use of chemical irritants, and then inoculating virulent cultures of the pneumococcus subcutaneously.

Pneumococcic peritonitis.—Peritonitis due to the pneumococcus differs in character according to whether it occurs in adults or in children. In the former it is usually diffuse and observations are now accumulating which show that the

appendix is not an uncommon point of departure. In children, on the other hand, the peritonitis is very frequently local in its distribution, being early shut off from the general cavity by fibrinous adhesions. Pneumococcic peritonitis was first noted (1890) by Sevestre. Dieulafoy collected a number of cases; and Bryant (1901) contributed a further series. Marchaux (1899) recorded vaginitis and peritonitis as common complications of pneumonia amongst natives in Africa.

Localised abscess formation.—Circumscribed collections of pus, subcutaneous, intramuscular or within some viscus, have often been described (e.g., Batten and Foulerton, 1901), and can readily be produced experimentally in laboratory animals.

Conjunctivitis, &c.—On the continent the pneumococcus is said to infect frequently the conjunctival sac, producing an acute conjunctivitis—often in epidemic form—but is not so commonly found in this situation in England. Gasparini has also recorded the pneumococcus as giving rise to keratohypopion.

Varia.—Finally, the pneumococcus has been recorded as causing, among other lesions, epiphysitis, osteomyelitis, periostitis and necrosis, thyreoiditis, parotitis, tonsillitis, follicular and membranous, gastritis, nephritis and perinephritis, endocervitis, &c.

Enough has been said to show the protean character of the lesions for which the pneumococcus has been recorded as the responsible cause. In order to explain the presence of the pneumococcus in the widely separated situations indicated by the foregoing summary it is necessary to consider for a moment how the organism gains access to the body tissues in the first instance. I have already mentioned that the pneumococcus was first discovered as the result of the examination of the saliva of a healthy individual. Sternberg records the organism as present in the same situation in 20 per cent. of the healthy persons examined; Netter in 15 per cent.; Washbourn and myself, in a limited number of individuals (20), in 30 per cent.; in a more extended series I have found it present in 18 per cent. It is also commonly found in the normal nose, its presence being recorded by Netter, Kurth and von Besser, and others—its percentage incidence being nearly 30 and the tonsillar crypts frequently harbour the coccus. In many instances the pneumococci isolated from these situations are of low virulence; indeed, sometimes they are avirulent, and at other times of a high degree of virulence. Washbourn and I carefully studied a number of them and found that even if the original virulence was low it could readily be exalted. A few varieties, however, were only exalted in virulence with great difficulty and then soon returned to their original condition. Hence the portal of entry is in the vast majority the respiratory tract and the cells of the upper air passages form the first line of defence. The pulmonary tissues constitute the second line of defence. Once arrived at the lung alveoli the pneumococcus readily enters the blood capillaries and so reaches the general circulation. In this situation if antibodies in sufficient quantity are available the invader is destroyed; short of this the cocci become deposited in areas of lowered bacterioscopic pressure and so give rise to localised infections, or multiplying in the blood stream produce a general septicæmia. Thus pneumonia may be regarded as a defensive process designed to prevent metastases or septicæmia. At its best, however, it is not absolutely efficient. Banti, Prochaska, and others maintain that pneumococci are invariably present in the blood in pneumonia and although years ago both Washbourn and myself were of opinion that the cocci only arrived at the peripheral circulation immediately prior to the fatal termination improved methods for the examination of the blood for the presence of micro-organisms lead me to believe that the cocci are present during the first two or three days of the disease even in the least severe cases of pneumonia. Next to the respiratory system the alimentary tract is probably the most common channel of entrance. Foulerton's case of gastritis and the numerous recorded cases of pneumococcic appendicitis place this method of infection beyond doubt. It is therefore easy to see how any organ or tissue may become the seat of pneumococcic infection. Finally, as affording a possible explanation of pneumococcic peritonitis occurring more commonly in the female than the male, Doyen records the presence of non-virulent pneumococci in the healthy vagina and cervix, and I have isolated the coccus from these situations in three instances—in two the organism

being of considerable virulence and in the third of very low virulence.

In order to gain some idea of the frequency with which the pneumococcus is met with in situations other than pulmonary tissue and of the frequency with which its presence provokes the formation of pus, I have examined the records of the bacteriological department of Guy's Hospital for the past five years. Arranged in tabular form, the results conclusively demonstrate the validity of the claim of the pneumococcus to be considered, potentially at any rate, a pyogenic coccus, for after subtracting seven cases of septicaemia, two of infective endocarditis, and 24 of pleurisy with clear fluid, we have no less than 168 instances—rather more than 1 per cent. of the total number of bacteriological specimens for the five-year period—where the presence of the pneumococcus had led to the formation of exudations possessing all the physical attributes of pus.

TABLE III.—*Pneumococcic Lesions other than Pneumonia.*

	1903	1904	1905	1906	1907	Totals.
Septicaemia	1	2	1	1	2	7
Infective endocarditis	—	—	1	—	1	2
Purulent pericarditis	3	1	4	—	1	9
Purulent peritonitis (pure)	1	1	2	2	4	10
„ „ (mixed)	—	1	—	—	—	1
Appendicular abscess (pure)	—	1	—	—	—	1
„ „ (mixed)	—	1	2	1	—	4
Purulent meningitis	1	2	—	3	8	14
Empyema (pure)	10	20	28	16	21	95
„ (mixed)	3	—	—	1	2	6
Pleurisy	2	5	10	3	4	24
Osteomyelitis... ..	—	—	—	—	1	1
Periostitis (femur)	—	1	—	—	—	1
Necrosis (rib)	—	—	1	—	—	1
Purulent arthritis, knee	—	—	1	—	4	5
„ „ shoulder	—	—	1	—	1	2
„ „ hip	—	—	—	—	1	1
Abscess, cerebrum	—	—	1	1	—	2
„ cerebellum	—	—	1	—	—	1
„ mastoid	—	—	2	—	3	5
„ liver... ..	—	—	—	1	—	1
„ pelvis	—	—	—	—	1	1
„ lacrymal sac... ..	—	—	—	—	1	1
„ (subcutaneous), thigh	—	—	1	—	1	2
„ „ back	—	—	—	—	1	1
„ „ scalp	—	1	—	—	—	1
„ „ sacrum	1	—	—	—	—	1
Conjunctivitis	—	—	1	—	—	1
Total	22	36	57	29	57	201
Total specimens examined	1065	1083	1933	4050	6301	14432

I have carefully excluded from the above table all cases in which the identity of the pneumococcus isolated from the pus was not completely established by methods above criticism, and in this connexion I would deprecate the diagnosis of "pneumococcic" suppuration by microscopical examination of stained films alone. It is far from rare when inquiring as to the attributes of the strain of pneumococcus implicated to find that the diagnosis rests on the slender foundation of the observation of "diplococci" in the pus, regardless of the fact that the pneumococcus is not by any means the only organism which assumes this morphological character in morbid exudates. The streptococcus very frequently, and the staphylococcus aureus and also staphylococcus albus by no means rarely, assume this type of division under similar conditions. Nor is the term "capsulated" as applied by observers who are satisfied with such cursory examination any more convincing, for often the note that this anatomical peculiarity of the pneumococcus is present will be found to depend solely on the "negative" evidence of an unstained halo—such as is so frequently due to the contraction of rapidly dried serum from the periphery of the paired coccus—around the organism, which halo,

be it noted, will probably be found surrounding nearly every particle of dirt on the same slide.

ATTRIBUTES OF THE PNEUMOCOCCUS.

Consequently it will be well to recapitulate briefly now those essential characteristics of the pneumococcus which are deemed necessary by the bacteriologist to establish its identity—although I may at once say I have no intention of entering minutely here into the laboratory habits of this micro-organism. Incidentally it must be mentioned that for convenience of reference the particular pneumococcus isolated from each individual is designated by a name, letter, or number prefixed by the word "race," or better "strain," and when a number of strains are found to possess similar characteristics they are grouped together under the heading of "Type."

Characteristics of the *Pneumococcus*.

Technically described the pneumococcus is an aerobic, facultative anaerobic, non-motile, highly parasitic coccus occurring in body fluids as pairs, of which the individual members are lanceolate or "candle-flame" shaped, with the rounded bases in apposition, and surrounded by a mucinous capsule which can be positively demonstrated by MacConkey's, Muir's, or one of Hiss's staining methods; or as short chains, also capsulated; occurring in artificial cultivations as more nearly spherical bodies in pairs or short or long chains; staining with the ordinary aniline dyes and not decolourised by Gram's method; growing upon artificial nutrient media at the temperature of the body only, but not upon gelatin at 20° C. (Certain saprophytic forms devoid of virulence, or practically so, are capable of multiplication at temperatures approximating to what is spoken of as room temperature—i.e., 20° to 22° C.—but with these races we are not at present concerned.) Multiplying in broth of reaction varying from +12 to +6 with the production of a uniform turbidity; in litmus milk with the production of an acid reaction, occasionally accompanied by clotting; upon agar and inspissated serum as translucent discrete circular, hemispherical or slightly flattened colonies; upon agar over the surface of which sterile rabbits' or human blood has been smeared, in similar manner but more freely than upon ordinary agar, and accompanied by a discolouration of the blood due to the transformation of the oxyhaemoglobin to methaemoglobin, which is an almost pathognomonic feature of the growth of this coccus; and in the serum of animals that have been immunised to the pneumococcus in the form of a flocculent deposit in an otherwise clear fluid, the flocculi being composed of felted masses of long and convoluted chains of pneumococci.

Finally, and most important of all, is the fact that a pneumococcus isolated from a definite lesion in the human subject is markedly pathogenic for the rabbit. Speaking generally, if injected into the peritoneal cavity of this animal it will produce an acute septicaemia and cause the death of the animal in one, two, three, or four days, while the organism can be recovered from the blood of the general circulation and from all the organs in a state of purity. The dose usually employed for this purpose is the entire growth from the surface of one 24-hours-old blood agar tube cultivation emulsified in one cubic centimetre of broth. Usually a dose many thousand times smaller than this suffices, but I have never yet found it necessary to employ a larger one.

Interesting but of minor importance from the point of view of identity is the power possessed by the pneumococcus of splitting up certain carbohydrate substances when these are dissolved in the medium in which the organism is growing. The substances generally used in these tests are dextrose, laevulose, galactose, lactose, saccharose, maltose, mannite, dextrin, and inulin. The first six of these are always acted upon by the pneumococcus, and if the medium, originally neutral in reaction, is tinted with litmus solution, the activity of the pneumococcus is indicated by the change in colour associated with the presence of an acid reaction. The remaining three compounds are sometimes but not invariably "fermented" by the organism under discussion, hence the contention of some American observers that the fermentation of inulin by the pneumococcus is so constant a character as to be of the highest value in diagnosis is not borne out in every-day work.

Having indicated the general characters of the cocci isolated from the varied *materies morbi* already tabulated the question that next arises is how to explain the varying pathogenetic properties exhibited by the pneumococcus. Before referring to the experimental work which has been

carried out in the attempts to answer satisfactorily this question I would remind you of the essential factors that are concerned in this question of infection, or of immunity if you prefer to regard it from the standpoint of the defenders rather than that of the invaders. Briefly, those factors which we shall now deal with here are: (1) the type of the organism; (2) the virulence of the organism; (3) the numbers of the infecting organism; and (4) the defensive powers of the invaded tissues, e.g., the resistance or the susceptibility of the animal cell or of the invaded individual.

Types of Coccus.

During some of our observations upon the natural history of the pneumococcus Washbourn and I noted that although all strains of virulent pneumococci produced a rapidly fatal septicæmia when introduced into the peritoneal cavity of the rabbit, yet if the injection was made into the subcutaneous tissue the various strains frequently presented striking differences in the histological characters of the local lesions they produced. Thus in the case of strains recovered from the hepatised lung in cases of pneumonia, fibrinous exudation formed the bulk of the material at the site of inoculation; while when strains isolated from broncho-pneumonia and from suppurative lesions were injected the local reaction consisted mainly of accumulations of polymorphonuclear leucocytes. These two types of cocci which we referred to as the "fibrinous" and the "cellular" types respectively agreed in some measure with those previously described by Foà and the hope was raised that the existence of two distinct and fixed varieties of pneumococci would afford an explanation of the differing clinical phenomena provoked by the invasion of human tissues by this organism in general, and in particular of the occurrence of acute septicæmia on the one hand and of pus formation on the other. Such, however, was not the case, for it was soon found when the experiments were carried further that by varying the conditions of the experiment either type was capable of giving rise to pus formation or to septicæmia. As an example of the different results obtained by varying one factor of the experiment—viz., the resistance of the tissue cell—I may instance the infection of the subcutaneous tissue of the abdomen of the rabbit.

(a) If we select for the experiment a young rabbit we find that a small dose of either of these types of the pneumococcus will cause death within 48 hours from acute pneumococcic septicæmia. At the seat of inoculation the reaction, usually small in amount and limited in area, is practically always œdematous in character, and either of the serous, sero-hæmorrhagic, or more rarely the hæmorrhagic type.

(b) If, however, we substitute a half-grown rabbit and inject a similar dose of the same cultivation the animal survives for a much longer period, say three or four days, or even a week. Now the local reaction at the seat of infection is a much more extensive process and clearly indicates by both its macroscopical and microscopical characters the particular "type" of pneumococcus that has been employed to produce the infection. It may be either a firm gelatinous exudation consisting of fibrin and leucocytes, together with red blood discs, thrown out and occupying the subcutaneous cellular tissue for a considerable distance around the needle puncture, frequently, indeed, extending down to the peritoneum below; or else a dense, opaque, yellowish exudation consisting almost entirely of small round cells, fibrin being almost entirely absent.

(c) Finally, if a fully grown animal is infected with a similar dose of either type the local lesion at the seat of inoculation consists of a larger or smaller circumscribed œdema, usually noticed within 24 hours of infection, which enlarges slightly during the next few days, though remaining strictly localised, becomes soft, and in about ten days contains pus and can be made to fluctuate. If untreated the skin over the abscess undergoes necrosis, sloughs, and gives exit to a thick creamy yellowish pus literally teeming with pneumococci and the animal dies from exhaustion in a fortnight or so, or in some few instances completely recovers.

Again by varying the site of inoculation and introducing the organism either into the peritoneal cavity or directly into the general circulation each type of pneumococcus would produce an acute septicæmic infection irrespectively of the age of the experimental rabbits.

From the clinical aspect exceptions were numerous and it was found that the fibrinous type of pneumococcus was as often isolated from purulent collections unassociated with pneumonitis as the cellular type.

DEGREES OF VIRULENCE.

Then, too, in our early observations Washbourn and myself found that pneumococci isolated from pathological processes in man invariably possessed a certain amount of virulence for the rabbit and so constituted the virulent type of pneumococcus; on the other hand, some strains of pneumococci isolated from various situations in the healthy body were devoid of virulence for that rodent and constituted the avirulent type; whilst between these two extremes every grade of virulence could be recognised. Here again an obvious explanation for the various lesions produced in man as the result of infection by the pneumococcus seemed to be forthcoming and it was at once put to the test. Strains of pneumococci were isolated from various situations and from exudates of very different naked-eye characters and their virulence was tested. The usual rough-and-ready method of estimating virulence by observing the amount of a 24-hours-old broth culture of the organism under investigation needed to produce any given result did not appeal to us, as among other peculiarities of the highly parasitic pneumococcus it does not usually grow well in this medium and when it does it varies from time to time in its rate of growth and moreover rapidly loses its virulence. Cultivations upon blood agar which had previously been described by Washbourn and myself as particularly adapted for the purpose of maintaining the virulence were therefore employed and a more accurate method of estimating the size of the doses, in which a specially manufactured and calibrated loop was always used to remove the growth from the medium was devised. Briefly our method was as follows. One loopful of the 24-hours-old growth at 37° C. was taken from the surface of the blood-agar and thoroughly emulsified in a known quantity (10 cubic centimetres) of sterile broth or saline solution, in a suitable vessel. It was then easy to prepare dilutions, in tenths, of the original loopful by measuring the requisite fractions of this emulsion in sterile graduated pipettes, transferring them to other vessels and adding more saline solution to any desired volume. Thus a series of rabbits could be inoculated with decreasing amounts of the pneumococcus cultivation and the minimal lethal dose ascertained.

The accompanying table shows such a series of inoculations of a strain known as strain "Sudbury," which was originally isolated from the rusty sputum of a case of lobar pneumonia.

TABLE IV.—*Determination of the Minimal Lethal Dose of the Pneumococcus (Strain "Sudbury").*

Rabbit.	Dose of culture.	Method of injection.	Result.
No. 1	1 loopful.	Intraperitoneally.	Death in 18 hours.
" 2	0.1 "	"	" 24 "
" 3	0.01 "	"	" 48 "
" 4	0.001 "	"	" 3 days.
" 5	0.0001 "	"	" 3 "
" 6	0.00001 "	"	" 7 "
" 7	0.000001 "	"	" 7 "
" 8	0.0000001 "	"	Unaffected.
" 9	0.00000001 "	"	"

It was soon found that the different strains of pneumococci differed markedly in their virulence. Of some when first isolated it was necessary to inject an entire blood agar culture to kill the animal. Others, again, were fatal in doses corresponding to one-millionth part of a loop. Usually it was found that even those of comparatively slight virulence would after one or two passages through animals be so enhanced in virulence that the very minute dose just mentioned—the one-millionth part of a loop—now proved to be the minimal lethal dose. Consequently such a degree of virulence came to be regarded as the standard, and a pneumococcus which was fatal in doses of 0.000001 of a loop was spoken of as possessing "standard virulence."

The method already described for estimating the virulence of any given strain of pneumococcus not only enables the bulk of the dose to be measured in terms of a loop with some degree of accuracy but also gives a fairly close approximation to the actual number of cocci contained in at least the smaller doses. For example, working with a pneumococcus of standard virulence it was found that the minimal lethal

TABLE V.—Initial Virulence of Various Strains of <i>Pneumococci</i> .					
No.	Sex.	Age.	Pneumococcus isolated from—	Minimal lethal dose.	Clinical result.
1	M.	30	Peripheral blood.	0·000001 loop.	Death.
2	F.	22	" "	0·000001 "	"
3	M.	26	" "	1·0 "	"
4	M.	36	Heart blood.	0·000001 "	"
5	F.	18	" "	0·01 "	"
6	M.	26	" "	0·01 "	"
7	F.	20	" "	2·0 "	"
8	F.	18	" "	0·001 "	"
9	F.	42	Vegetations on valve.	0·01 "	"
10	F.	1½	Peritoneal pus.	0·000001 "	Recovery.
11	M.	3	" "	0·000001 "	Death.
12	F.	2	" "	0·000001 "	"
13	F.	8	" "	0·000001 "	Recovery.
14	F.	18	" "	0·001 "	"
15	M.	15	" "	0·001 "	Death.
16	M.	24	" "	0·1 "	Recovery.
17	M.	30	" "	1·0 "	"
18	F.	26	" "	2·0 "	"
19	F.	18	Cerebro-spinal pus.	0·000001 "	Death.
20	M.	6	" "	0·001 "	"
21	F.	3	" "	0·001 "	"
22	M.	1½	" "	1·0 "	"
23	M.	16	" "	1 entire culture.	"
24	M.	36	Pus from chest.	0·000001 loop.	Recovery.
25	M.	45	" "	0·000001 "	"
26	F.	22	" "	0·000001 "	"
27	M.	10	" "	0·000001 "	"
28	F.	10	" "	0·000001 "	"
29	M.	3	" "	0·000001 "	Death.
30	M.	1½	" "	0·1 "	Recovery.
31	M.	27	" "	1·0 "	"
32	F.	12	" "	1 entire culture.	"
33	M.	30	" "	1 entire culture.	"
34	M.	22	Fluid from chest.	0·000001 loop.	"
35	M.	30	" "	0·000001 "	"
36	M.	18	" "	0·000001 "	"
37	F.	19	" "	1·0 "	"
38	M.	7	Pus from knee.	0·000001 "	"
39	M.	5	" " shoulder.	0·000001 "	"
40	F.	9	" " knee.	0·000001 "	Death.
41	M.	3	" " hip.	0·01 "	Recovery.
42	F.	5	Pus from cerebral abscess.	0·000001 "	Death.
43	F.	15	Pus from subcutaneous abscess.	0·001 "	Recovery.
44	F.	3	Pus from subcutaneous abscess.	2 loops.	"
45	F.	46	Rusty sputum.	0·000001 loop.	"
46	F.	50	" "	0·000001 "	Death.
47	M.	24	" "	0·001 "	Recovery.
48	M.	36	" "	1·0 "	"
49	M.	45	Lung juice.	0·000001 "	Death.
50	F.	45	" "	0·000001 "	"
51	M.	38	" "	2·0 "	"
52	F.	28	" "	1 entire culture.	"
53	M.	1½	" "	0·000001 loop.	"
54	M.	1½	" "	0·000001 "	"
55	M.	1½	" "	0·000001 "	"
56	M.	1½	" "	0·000001 "	"
57	M.	1½	" "	0·000001 "	"
58	F.	2	" "	0·001 "	"
59	F.	1½	" "	0·01 "	"
60	M.	1½	" "	1·0 "	"
61	M.	1½	" "	1·0 "	"

dose was either 0·000001 or 0·000001 of a loopful, and control plate cultivations made with that quantity of the emulsion corresponding to 0·000001 showed that sometimes it contained 200 cocci, sometimes 20. If it contained 200 cocci the minimal lethal dose was 0·0000001 of a loop; if it only contained 20 the animal that received 0·0000001 of a loop was usually unaffected, and 0·000001 of a loop proved to be the minimal fatal dose.

Now in the experiments already quoted the introduction of the pneumococcus into the subcutaneous tissues of an animal of but feeble resisting power—i.e., the young rabbit—was followed by acute and rapidly fatal septicæmia, while the same organism similarly used to infect an animal of greater resistance—i.e., the full-grown rabbit—led to the formation of a localised collection of pus. Conversely, it seemed possible that septicæmia in the adult—I purposely specify the adult in order to avoid touching upon the question of greater susceptibility in the infant and the aged—would be the result of infection by a pneumococcus of extremely high virulence, while pus formation would be due to the inroads of attenuated pneumococci. Sometimes this does obtain. For instance, a recent case of primary peritonitis yielded a pure culture of a pneumococcus the virulence of which was so low that two loopfuls of the optimum cultivation were required to produce fatal infection in the rabbit, whilst a morphologically identical pneumococcus from a fatal case of septicæmia was of standard virulence—that is to say, was two million times as powerful. Now, supposing it were possible to apply the results of these observations without reservation to pneumococcic infections in man, it should be a simple matter, given the nature of the lesion produced, to forecast the approximate virulence of the strain of coccus isolated; or, given the virulence of the organism, to predict the characters of the lesion that would follow its introduction into human tissues. Thus the pneumococcus of high virulence should produce septicæmia and the pneumococcus of low virulence should induce the formation of pus. But, on the other hand, two strains of pneumococci of equal and standard virulence were isolated from two cases which differed widely in the clinical manifestations, the one being a chronic otitis media, the other being a fatal case of pneumonia, suppurative pericarditis, and suppurative cerebro-spinal meningitis. However, the hypothesis I have suggested was put to the test and a large number of strains isolated and the virulence of each estimated, with the result that it proved untenable, for the simple reason that no constant relationship could be shown to exist between any given pathological manifestation of pneumococcic activity and either high, low, or medium virulence. The general results obtained will be readily appreciated from the accompanying details which are arranged in tabular form.

SIZE OF DOSE.

The next point to which my attention was directed was the relationship, if any, that existed between the size of the dose of infective material—or if you prefer it the number of pneumococci injected—and the character of the resulting lesion. Under certain conditions it was found that the size of the dose exercises a direct bearing upon the subsequent lesion—a result which was arrived at in a manner illustrated by the following example. In this experiment full-grown male rabbits were injected with cocci from one and the same

TABLE VI.—Minimal Lethal Dose 0·000001 loop. Virulence Attenuated by Four Successive Subcultivations upon Ordinary Agar. (*Pneumococcus* Strain "Hunt.")

Rabbit.	Sex.	Weight in grammes.	Dose of pneumococcus.	Method of infection.	Lesion.	Result.
No. 31	M.	1230	0·00000001	Subcutaneously.	Transient local cedema.	Unaffected.
" 32	M.	1250	0·0000001	"	Localised abscess; necrosis of skin; raw, granulating surface.	Death in 18 days.
" 33	M.	1280	0·001	"	"	Death in 12 days.
" 34	M.	1300	1 loop.	"	Limited fibrinous exudation; pneumococcic septicæmia.	Death in 72 hours.

Note.—0·000001 loop contained 200 pneumococci.

cultivation of a strain of pneumococcus (which had been isolated from the lung juice of a fatal case of lobar pneumonia). The factor that was wittingly varied was the size of the dose. The first rabbit received approximately 20 cocci, the next 200, the next 200,000, and the last 200,000,000.

CELL RESISTANCE.

Having investigated the various phases of pneumococcal infection with reference to (1) the biological type and (2) the virulence of the organism concerned, and, incidentally (3), the magnitude of the infective dose without obtaining any satisfactory explanation of the disease lesions produced in man by the invasion of his tissues by the one morphological entity, the pneumococcus, it still remains to inquire into the possibility of the resistance of the cell being the most important factor, and I may say at once that in this direction undoubtedly lies the solution we are seeking. Experimental work had already pointed to the importance of this factor. Indeed, most of the instances which I have already adduced in illustration of the action of the other factors in the problem have also demonstrated to a greater or less degree the influence of this the most important factor. Thus we have seen how the pneumococcus which in the young and immature rabbit is able to produce a rapidly fatal septicæmia, in the adult and fully formed rabbit remains localised to the seat of inoculation, and is at most only able to give rise to a circumscribed collection of pus.

The rabbit forms the subject of the bulk of the pneumococcus experiments, because it is certainly the most susceptible of all the laboratory animals to infection by this organism. The young rabbit is infected with the greatest ease, half-grown animals are slightly more resistant, and fully grown and mature ones are more resistant still, but even in the normal adult rabbit the resistance offered to the pneumococcus is very slight, and that resistance varies to no appreciable degree in different individuals. Now in the process of immunisation the method that gives the most satisfactory results is the preliminary intravenous injection on two or three suitable occasions of "killed" broth cultivations of the pneumococcus. This proceeding is found to confer a certain slight degree of immunity upon the animal, which now survives the introduction of several times the minimal lethal dose of living cocci into its subcutaneous tissues, but, and this is the point I wish to emphasise, a small circumscribed abscess almost invariably forms at the seat of inoculation. If this is untreated it bursts, discharges its pus, and then the cavity closes by granulating up. When completely healed the animal is found to be highly resistant to subsequent injections of living cocci.

Many experiments were undertaken in the attempt to devise some means of measuring the resistance offered by the living cell to the onslaughts of the pneumococcus, and in the course of these advantage was taken of the fact already referred to that the pneumococcus when grown in immune serum—that is to say, the serum of an immune animal—became agglomerated into masses of convoluted chains which formed flocculi in an otherwise clear fluid, in short because agglutinated. In the course of these observations the serum from the healthy individual of several varieties of mammals was examined as well as that of highly immunised animals of various species, and also serum from subjects suffering or convalescent from natural or experimental pneumococcal infections, and, speaking generally, the constancy of the phenomenon was established. Many other observers, particularly Issalf and Arkharow, also noted the peculiar features of growth in immune sera; indeed, Bezançon and Griffon endeavoured to utilise the agglutinins present in the blood of infected individuals as a method of diagnosis. Pneumococcus agglutinins, however, are only formed in small quantities and for a limited period, and rapidly disappear from the serum, so that it is difficult not only to measure their amount but also, in many instances, to demonstrate their existence, so that for clinical purposes the agglutination reaction in pneumococcal infections has but a very restricted application.

Next the bactericidal action of normal and of immune serum was carefully investigated, and while the observations of Baring and Nissen and Kruse and Pansini relating to the absence of bactericidal substances from the serum of the normal rabbit were fully confirmed it was further found that the serum of immunised animals varied considerably in this respect in that sometimes bactericidal substances were

present in considerable amount, although on the other hand they were frequently absent or present only in amounts too minute to be appreciated. Mennes, however, pursuing this line of investigation, found that while the serum of an immunised animal frequently failed to exercise any definite bactericidal action by itself, if white blood cells from either a normal or an immunised animal were added to the mixture of cocci and immune serum the serum so acted upon the cocci as to render them sensitive to the action of the leucocytes, and many of the pneumococci in the mixture were englobed and destroyed by the white cells. This property he stated was peculiar to immune serum.

Then came the epoch-marking and now widely accepted researches of Wright and Douglas, which followed on Leishman's work on phagocytosis, in the course of which the presence of certain bodies designated "opsonins" was demonstrated in human serum—substances which enabled the serum containing them to behave in a manner similar to that described by Mennes in connexion with his pneumococcus immune serum. These observers next devised a very ingenious method for measuring the amount of opsonin in a given serum, by means of which they were able to show that as compared with normal serum, the serum obtained from a recently infected individual or animal contained a diminished amount of an opsonin special and specific for the infecting bacterium. The serum of an immune animal on contrary contained as much as or more of that specific opsonin than the serum of the normal. Finally, by injecting small doses of "killed" cultivations of the bacterium into the subcutaneous tissues of the patient they were able so to stimulate the immunising machinery in the direction of the over-production of specific opsonin as beneficially to influence the course of the infection. Such in bald outline are the experimental data around which Wright and his pupils have built up a complete and extensive system of pathology, diagnosis, and vaccine-therapy. It now remains to indicate its application to pneumococcal infections in particular.

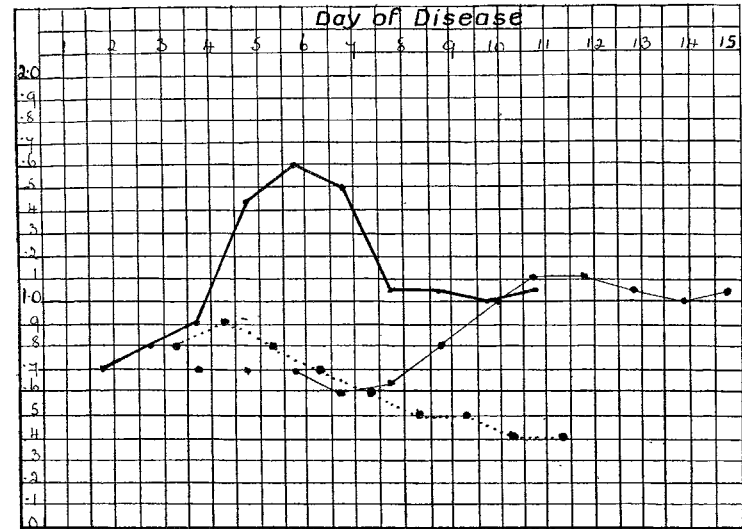
In the first place man, as compared to the adult rabbit, exhibits a very marked resistance to invasion by the pneumococcus, although this resistance varies considerably in different individuals and at different ages. These differences are, no doubt, due to many factors, of which hereditary selection may be one. Another which possibly has a bearing upon this aspect of the question is the situation of the pneumococcus in nature. Some 10 per cent. at least of the healthy population cultivate the pneumococcus in that natural incubator, the mouth and upper air passages. What is more likely than that a considerable quantity of antibodies is formed and some degree of immunity set up as a result of the continual absorption of small doses of the toxins and other metabolic products of the pneumococcus. It is not surprising to find that the opsonin content of normal human serum is on an average double that of the normal rabbit, although it must be borne in mind that opsonins probably form but one of many antibacterial substances elaborated by the body in its unceasing resistance to the attacks of external forces. Assuming the opsonin present in the normal human serum to be represented by unity, the opsonin in the normal rabbit serum only reaches half that figure. The figure expressing that ratio—viz., 0.5—is spoken of as the opsonin index. By the exercise of infinite care, however, in the process of immunisation the pneumococcus opsonin content of the rabbit's serum may be raised until it is equal to, and even greatly superior to, that of normal human serum. Under these conditions the injection of the pneumococcus of sufficient virulence and sufficient dose to cause the death of a control rabbit within 36 hours from acute septicæmia will only give rise to localised suppuration.

TABLE VII.—*Minimal Lethal Dose 0.000001 loop. (Pneumococcus Strain "Suabury.")*

Rabbit.	Sex.	Weight.	Opsonin index.	Dose.	Result.
Control a	M.	1250	0.58	0.0000001	Unaffected.
" b	M.	1260	0.62	0.000001	Death in 48 hours.
" c	M.	1250	0.50	0.00001	Death in 36 hours.
Immune	M.	1240	1.13	0.00001	Local abscess.

Macdonald, who very carefully studied the clinical aspects of pneumonia with reference to the formation of pneumococcic opsonin throughout the course of the disease, published his results in 1906 and showed that the movements of the curve representing the opsonin index afforded an exact record of the measure of resistance opposed by the patient to the inroads of the organism. My own observations fully confirm Macdonald's, and, moreover, show that the resistance of the individual so far as can be measured by his opsonin response to any given pneumococcus infection conforms to one of three main classes which are represented by the three accompanying curves. Two of these opsonin curves are compiled from estimations carried out in connexion with that clinical form of lobar pneumonia in which crisis takes place and that which recovers by lysis in order to contrast them with the curve obtained in the acute septicæmia which terminates in death; and although we are not immediately concerned with pneumococcus infection of the lung tissue I make no excuse for presenting them here, as being derived from acute cases they illustrate my point much more concisely than would be the case if they had been derived from chronic suppurations.

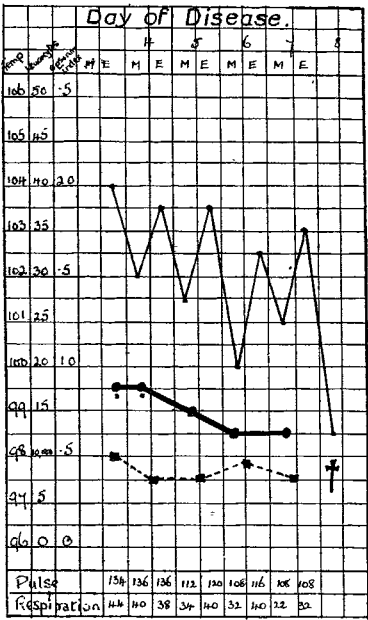
CHART 1.—The Opsonin Index in Pneumococcic Infections; Three Leading Types.



In the third, represented by the lowermost (continuous) curve, the process by which opsonins are elaborated is completely paralysed, as the result possibly of an extremely heavy dose of infective material, or of infection by an extremely virulent pneumococcus, or of infection directly into the blood stream, or more probably of a combination of all of these factors. In the second (dotted line), the production of pneumococcus opsonin is temporarily suspended, perhaps owing to the existence of, say, any two of the factors just enumerated, but after a time recovery of tone takes place, production goes on in excess of expenditure, and finally sufficient opsonin is produced and thrown out into the circulation to subdue the invader. Incidentally it may be mentioned that this type of case is most frequently the one in which the pneumonia is associated with suppurative lesion. In the first (thick continuous line) the immunising machinery promptly responds to the call made upon it, at once elaborates opsonin in excess, with the result that the pneumococcus is rapidly destroyed and recovery takes place. [Occasionally, be it noted, this type of curve after returning to the normal suffers a further fall, and some few pneumococci remaining in some far distant spot, in an almost moribund condition, take on a fresh lease of life and some small localised suppuration results. In such circumstances the opsonin curve would be expressed by tacking the beginning of the second curve in the chart on to the end of the first.] In other words, in the third instance the immunising machinery is badly overstrained, in the second understrained, and in the first severely but not unduly strained. As suggesting a possible source of the pneumococcus opsonin I have inserted in the two following charts (Charts 2 and 3) the leucocyte curve as well as the opsonin curve. In the fatal case leucocytosis is absent, the opsonin index falls gradually and continuously. In the second case the fall in the opsonin index that is practically always noted

in the early stages of an acute infection is associated with a considerable leucocytosis which becomes less marked as the amount of available opsonin increases.

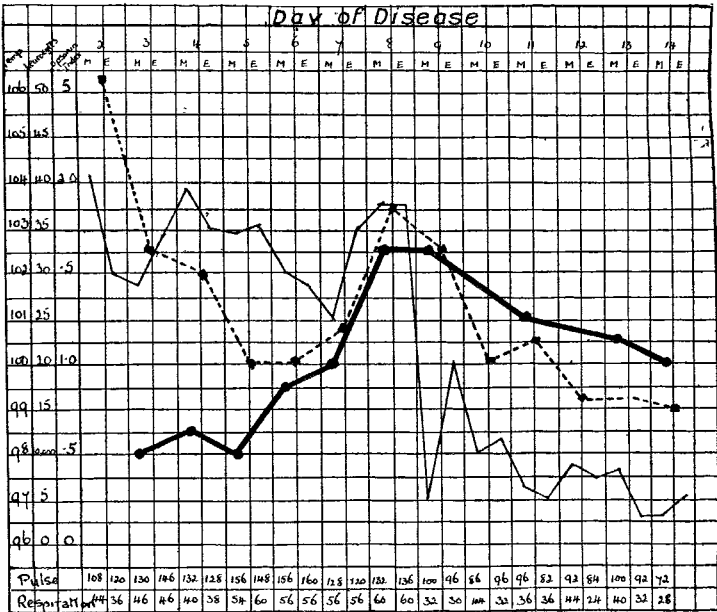
CHART 2.—Fatal Case of Pneumococcic Septicæmia.



Upper thin line = temperature; middle thick line = opsonic index; lower dotted line = leucocytes per cubic millimetre of blood.

I cannot conclude without a few remarks upon what may be termed the bacteriological therapy of pneumococcic infections. Many of the earliest students of the life-history of the pneumococcus—the Klemperer brothers, Foà and Carbone, and in this country Washbourn—showed that the

CHART 3.—Case of Pneumonia terminating by Crisis.



Thin continuous line = temperature; dotted line = leucocytes; thick continuous line = opsonic index.

blood serum of immunised animals protected other animals from the effects of pneumococcus inoculations if injected simultaneously or even subsequently. Washbourn early in 1897 immunised the horse and about the same time Pane immunised the donkey and the goat with a view to obtaining a potent serum for the treatment of cases in man. Such serum has never been really extensively tested in this country and therefore no very definite opinion can be expressed as to its value. What little evidence there is available is certainly in its favour; for instance, in a small series of six cases of pneumonia collected by Washbourn the serum in three cases exerted a powerful and beneficial effect

upon temperature and upon the pulse and respiration rates; in one case it appeared to have no effect whatever, and in the last case it was powerless to avert the fatal issue. Pane, in reporting 29 cases with two deaths and a further series of nine severe cases of epidemic pneumonia (in Naples) with one death, insists on the rapid improvement that follows the injection of serum.

Antipneumococcic serum has, however, nowhere achieved the striking results in acute infections that are associated with the serum treatment of diphtheria, and it has never obtained the confidence of the profession, while in chronic and suppurative pneumococcus infections the serum is quite useless. There are many reasons for its failure. In the first place, the pneumococcus elaborates but very feeble toxins *in vitro*, and the serum which is obtained from immunised animals is antibacterial only and not antitoxic, hence it would appear probable that its administration would only be effective during the very early

was absolutely powerless against the fifth. Finally, the various brands of serum vary considerably, even in their bactericidal power, probably owing to the fact that the bleeding of the immune animal is usually carried out at a date determined by purely clinical observation, and it is just possible that if the animal's blood was examined daily and the amount of some antibody—say, pneumococcus opsonin—estimated and the bleeding performed when that body was present in maximum quantity, vastly superior clinical results might follow the administration of such serum.

Turning now to the employment of killed cultivations or vaccines in the treatment of pneumococcus infections a much greater measure of success is obtained. The behaviour of acute infections such as septicæmia and lobar pneumonia under the influence of pneumococcus vaccine has not yet come under my own personal observation, but excellent results in this direction are reported by American observers. I am, however, firmly convinced of the value of vaccines

CHART 4.—CASE OF PNEUMOCOCCIC SEPTICÆMIA WITH VARIOUS METASTASES SHOWING THE EFFECT OF INJECTIONS OF PNEUMOCOCCUS VACCINE UPON THE PYREXIA.



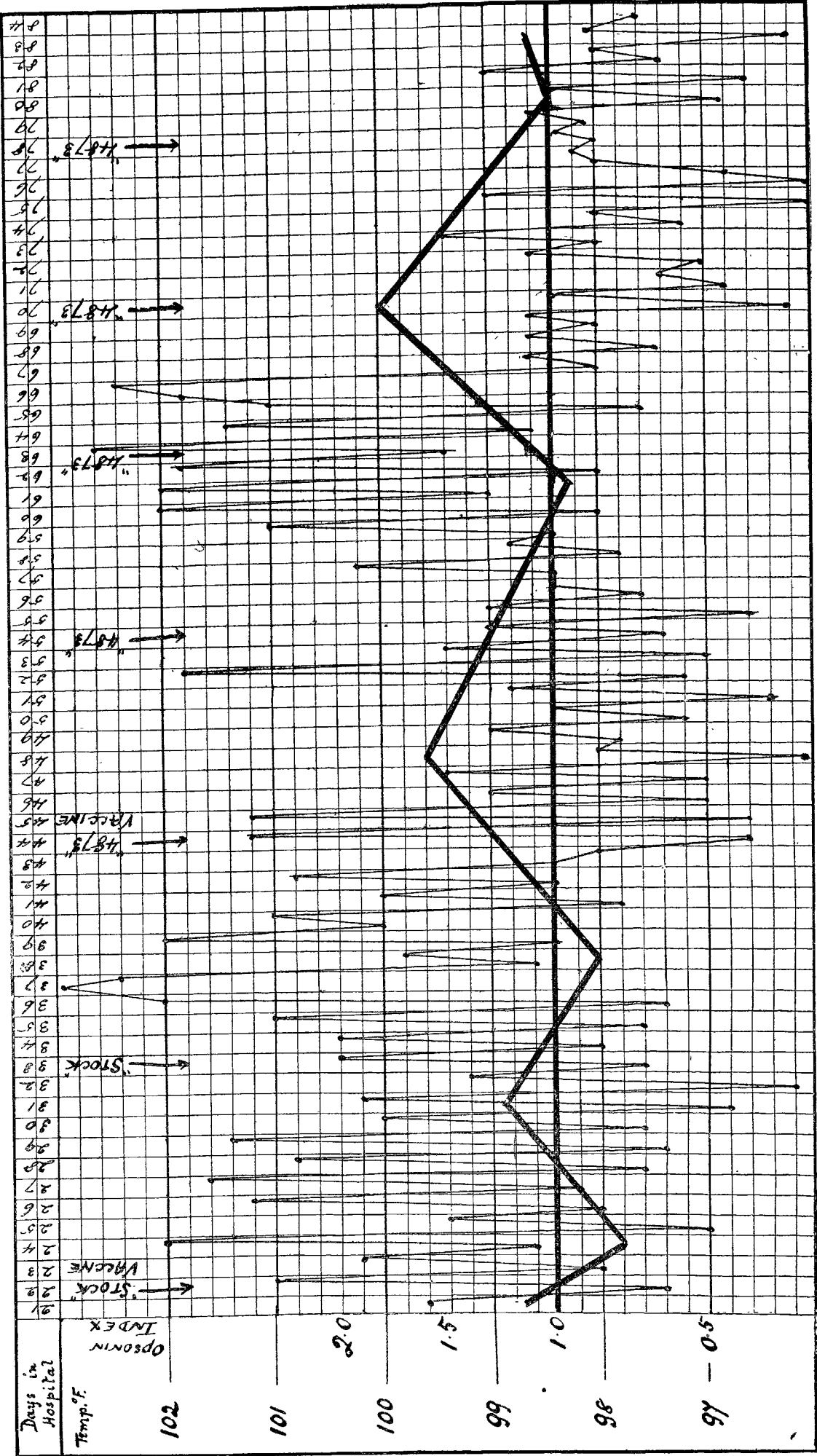
The arrows indicate the days when injections of pneumococcus vaccine were administered.

stages of infection or in cases of pneumococcic septicæmia. But the symptoms develop in man and the diagnosis is made only when the pneumococcus has obtained a firm foothold; consequently to be of value a very powerful bactericidal serum is needed and experimentally at least the capacity to protect against some 300 minimal lethal doses per cubic centimetre of serum is the most powerful yet available. Many of the symptoms observed in pneumococcic infections are, moreover, those of profound toxæmia and a purely bactericidal serum would appear to possess very little therapeutic value in such circumstances; on the other hand, Pane states that though his serum is bactericidal it does not act directly upon the pneumococcus itself but produces its beneficial effects by establishing a true active immunity. Then, again, Washbourn and I elicited the fact that varieties exist among strains of pneumococci which can only be appreciated by the failure of the serum to protect animals infected with them, for in testing Pane's serum we found that it protected against four out of five of our strains but

in the chronic suppurative lesions due to the pneumococcus.

In our early studies of experimental infections with the pneumococcus Washbourn and I had observed the fact that when immunising rabbits by the method I have already described the healing of the subcutaneous abscess which followed the inoculation of the first dose of living pneumococci could be accelerated by a subcutaneous or an intraperitoneal injection of killed broth cultivation; indeed, in some instances, if the injection was made before definite fluctuation could be detected in the local lesion, the process of tissue necrosis was arrested and resolution took place. These happy results were not always attained, the reason, of course, being that we had no reliable guide as to when and how much to inject. I have already stated that a correct appreciation of the movements of the opsonin index forms the basis of, and renders possible, the treatment of bacterial infections by means of killed cultivations of the responsible organisms, or, more shortly, "vaccines," and

CHART 5.—CASE OF SECONDARY PNEUMOCOCCIC INFECTION OF A TUBERCULOUS PERITONEUM, SHOWING THE EFFECT OF "STOCK" AND "SPECIAL" PNEUMOCOCCUS VACCINES UPON THE OPSONIN INDEX AND UPON THE TEMPERATURE.



Thin continuous line = temperature.
Thick black line = opsonin index.
The arrows indicate the days when injections of pneumococcus vaccine were administered.

this holds good in the case of infections by the pneumococcus, and particularly those which are localised and are associated with pus formation. Cases such as these have yielded most promising results and I could cite numerous instances. I have, however, selected two which will suffice to show the possibilities of this adjunct to ordinary operative procedures.

The first (Chart 4) was a small girl in whom double lobar pneumonia was followed by empyemata, that on one side being opened on the twentieth day of the disease and on the other two days later. A subcutaneous (pneumococcic) abscess of the arm was also opened on the twenty-second day. The right hip, the seat of suppurative arthritis, was operated upon on the thirtieth day and an iliac abscess also was drained. On the fifty-fourth day an abscess in the gluteal muscles, behind the trochanter, was incised. A vaccine was prepared from a pneumococcus isolated from the empyema pus and treatment was commenced on the fifty-second day. The effect of the injections upon the temperature is well seen, and the case, which had been regarded as hopeless, was discharged to a convalescent home on the eighty-second day. The next case (Chart 5) suggests the point I have already referred to concerning particular varieties of pneumococci against which certain antipneumococcic serums were powerless. The boy was under treatment for tuberculous peritonitis complicated by a secondary pneumococcic infection, and pus crowded with pneumococci was discharged freely through the ruptured umbilicus. On the twenty-second day after the patient's admission to hospital and again on the thirty-third a "stock" pneumococcus vaccine was injected but without obvious effect so far as concerned either temperature or general clinical condition. A vaccine was then prepared from the particular pneumococcus isolated from the peritoneal pus of this patient and improvement followed the injection of a dose on the forty-fourth day. The improvement was continued, the patient put on weight, the pus gradually disappeared, and the temperature came down. Tuberculin treatment was then adopted and the patient after a short stay in a convalescent home will become an out-patient.

One other application of pneumococcus vaccines to cases in which operative treatment is needed—and these remarks hold equally in the case of other bacterial infections—and I have done. Where the opsonin content of the blood is low the preliminary injection of a suitable vaccine by stimulating the manufacture of further supplies places the patient in the most favourable condition to withstand shock and resist the further spread of infection through the disturbance of the tissues involved by the necessary operative procedures. In illustration I might mention a case of empyema and peritonitis following lobar pneumonia in an adult female under the care of Dr. W. Hale White. From the pus, the fluid portion of which had an opsonic index of less than 0.2, a virulent pneumococcus was isolated, a vaccine prepared, and a dose injected. Two days later the empyema was opened, when it was found that the pleural cavity communicated with the abdominal cavity and some five or six pints of pus were removed. The index of the liquor puris was now 0.9. The patient convalesced rapidly—a few more injections of vaccine were required—and was discharged cured.

CONSIDERATIONS CONCERNING THE FUNCTIONS OF THE STOMACH AND THE OPERATION OF GASTRO-ENTEROSTOMY.

BY H. M. W. GRAY, F.R.C.S. EDIN.,

SURGEON AND LECTURER ON CLINICAL SURGERY, ABERDEEN ROYAL INFIRMARY.

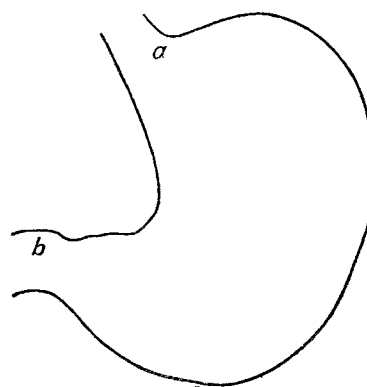
ON account of the usually immediate and striking benefit obtained, the operation of gastro-enterostomy has established itself as a very valuable and necessary procedure in many diseases involving the stomach and duodenum. Nevertheless, in spite of careful selection of cases, disappointing results, such as regurgitant biliary vomiting or formation of jejunal ulcer perhaps with perforation, occur occasionally, even when the most modern method (posterior no-loop) has been followed. Why such sequelæ should occur only occasionally, when apparently the same technique has been carried out as in perfectly successful cases, is not clear. A possible

explanation may be that sufficient care is not taken in the selection of the site of the opening in the stomach. Mayo's guide (that the opening should lie in a vertical line from the cardiac orifice) is probably a thoroughly sound one when the stomach is lying undisturbed in the abdominal cavity. When the stomach is pulled out, however, or otherwise manipulated the proper place may not be chosen, as the organ tends to swing round its lesser curvature. This, as I shall endeavour to show, *may* be the reason of untoward results.

The best operative procedure is that which most nearly preserves or restores the natural functions of any part requiring such interference. For this, of course, accurate knowledge of the natural functions of the part concerned is necessary. I venture to assert that this essential is not fulfilled in the case of the stomach, at least in so far as its motor functions are concerned.

It would seem that gastric surgery, as developed from experience gained in earlier operations on greatly dilated stomachs, has persisted in regarding the stomach as a "one compartment" organ. (Fig. 1.) Operations were

FIG. 1.



Tracing of stomach figured by W. J. Mayo in article on the Technique of Gastro-enterostomy in the *Annals of Surgery*, April, 1906 (reduced to one-third). a, Cardiac orifice; b, pyloric orifice.

planned with the object of "draining" these huge stomachs. To suit latter-day ideas some other term than "drainage" must be found. It does not convey a proper idea of the modern operation, which is executed more on the principle of a "short circuit" or, in some cases, of a "safety valve." Cannon and Blake¹ showed that gastro-enterostomy need not be a drainage operation; that, in fact, food preferred to pass through the pylorus rather than through the newly formed "stoma," unless the latter was made very large. Their observations have probably been too much emphasised in this connexion. They were made on normal healthy cats. Leggett and Maury's² more recent experiments prove little. Most of their operations, recorded in detail, seem to have resulted, more or less, in the old "vicious circle."

To procure its beneficial results gastro-enterostomy *must* be at first a drainage operation; later, when the gastric secretions and the condition of the pyloric sphincter and of the neighbouring mucous membranes have become more normal, this function of drainage is not required and food *may* again pass naturally through the pylorus. Where permanent pyloric or duodenal stenosis is present, then, of course, "drainage" is permanent. Cannon and Blake³ have shown that towards the end of digestion the pyloric end of the stomach is the lowest part, owing to the contraction of the longitudinal fibres of the stomach, and therefore that the "stoma" in gastro-enterostomy should be made as near the pylorus as possible. This seems rather at variance with their finding, that the operation is not a drainage one, and I shall endeavour to show that there are probably more potent reasons why the "stoma" should be made as near the pylorus as possible. The great reason is that by making the stoma in this situation gastric digestion is allowed to become more quickly and permanently normal again.

Professor D. J. Cunningham,⁴ the late Professor Birmingham,⁵ and others have shown very conclusively in anatomical specimens that the shape of the stomach is very different from that described until a few years ago. It is evident

¹ *Annals of Surgery*, May, 1905.

² *Ibid.*, October, 1907.

³ *Loc. cit.*

⁴ *Transactions of the Royal Society of Edinburgh*, vol. xlv., Part I., No. 2.

⁵ Cunningham's *Text-book of Anatomy*, second edition, p. 1052.