the cells surrounding the central vein. The line between the tumor cells and the liver cells was marked by a thin zone of scattered round cells with an occasional polymorphonuclear. Usually this line was cleancut and distinct. Occasionally tumor cells extended beyond it. The tumor cells were identical in appearance and arrangement to those in the tumor of the pleura. There was, however, very little connective tissue in the liver tumors.

Metastatic Nodules in Left Pleura: The cells were identical to those described above. Those in advance filled the alveoli of the lung, and in many cases were limited to a given alveolus. Deeper in the tumor, however, the alveolar wall was represented only by a thin line of connective tissue.

Right Suprarenal: The tumor was identical in every way to those just described. Its extending margins were clear and distinct.

Metastasis into Brain: Here the cells were arranged in a more orderly manner. Many definite papillae were present. The margin invading the brain substance was somewhat more irregular, and frequently the cells extended deeply into the brain. However, the general characteristics of the tumor cells were the same as those of the pleura.

The microscopic diagnosis was endothelioma of the right pleura with metastasis into the liver, left pleura, suprarenal, peritoneum and brain.

COMMENT

Most likely the first symptoms in this case were produced by the metastases in the brain, as no history of the chest condition was obtained until later. The diarrhea, noted at first as incontinence of feces, the stupor, and the psychosis were the outstanding signs and the ones that caused the patient to come under medical observation. The growth proper was not detected early because it produced no painful symptoms and invaded no tissue that gave any local reaction. The pleural effusion was the first sign noticed in the chest, and this was some time after the mental symptoms had appeared. The metastases were doubtless of a blood vessel type, and those in the brain were probably the first given off. Neither the motor nor the sensory areas were attacked, but apparently the parts associated with thought activity were greatly disturbed. The nodules in the intestine may have produced the diarrhea. The liver was invaded directly through the diaphragm. The latter lost its identity on the right side and was replaced by the advancing growth. The necropsy findings in no way explained the consistently and extremely high increase in white blood cells. The metastatic areas in the brain were sterile and showed no inflammatory reaction. The fever was no doubt due to toxic resorption. The growth began in the right pleura at the mediastinum and extended along the diaphragmatic and later the costal portions, compressing the lung upward in its course. Death was the result of asthenia.

The Geographic Distribution of Diseases.—L. R. Grote declares that not enough statistics and other data have been accumulated as yet for what he calls nosogeography. This is a science of the future, to be based on geographic, climatic influences, racial differences, social and economic conditions, the biology of the causative agents, and the effect of human efforts at prophylaxis. He reiterates that there is no part of the world absolutely free from any of the constitutional diseases, or where the infectious diseases cannot get a foothold when the causal agent is imported. In discussing these five elements of nosogeography in the *Geographische Zeitschrift* 25, No. 7, 1919, he cites a number of puzzling facts, such, as the high tuberculosis death rate and the low cancer death rate—only 4 per ten thousand—in the Münster region, while the reverse prevails in the East Sea provinces, the cancer rate being 14 while the tuberculosis rate is among the lowest.

THE PRODUCTION OF AN ACUTE RESPIRATORY DISEASE IN MONKEYS BY INOCULATION WITH *BACILLUS INFLUENZAE*

A PRELIMINARY REPORT *

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Many attempts have been made to produce influenza in animals, or to transmit it experimentally from man to man by inoculation of the secretions, both filtered and unfiltered, from the respiratory tract in cases of influenza, by direct exposure of the subject to patients with influenza, and by inoculation with cultures of *Bacillus influenzae* isolated from patients with the disease. In large part, the results obtained have been entirely negative. In the few instances in which successful transmission of the disease has been reported, the methods employed and results obtained by different observers have been to a considerable extent inconsistent.

During the course of an investigation of experimental pneumonia in monkeys produced by the intratracheal injection of pneumococcus and *Streptococcus hemolyticus*, a further series of experiments with *B. influenzae* was undertaken in the hope of throwing some light on the relation which this organism bears to epidemic influenza and to the pneumonia which so frequently complicates it. The results obtained have been of such interest that it seems desirable to present a brief preliminary report at this time. The work will subsequently be reported in detail with full protocols.

Two species of monkeys were used: *Macacus syrichtus* from the Philippine Islands, and *Cebus capucinus* from Central America. All were fresh stock and had not previously been kept in captivity in this country. No preliminary procedures to lower resistance or to injure the respiratory tract before inoculation were resorted to. The strain of *B. influenzae*¹ employed was originally isolated from a case of influenzal pneumonia in a child. When received it had been in subculture on blood agar for a period of six weeks, and was found to possess no virulence for white mice. Since it was well known that the pathogenicity and virulence of *B. influenzae* are extraordinarily labile and very rapidly lost on subculture on artificial mediums, it was deemed necessary to raise the virulence of the strain to a considerable extent if successful results were to be obtained. This was accomplished, in brief, by successive animal passages, first through a series of eleven white mice, and then through a series of thirteen monkeys. These animals were inoculated intraperitoneally, the attempt being made always to give a sufficiently large dose to kill the animal within from twenty-four to forty-eight hours. Presumably because of individual variation in resistance, the desired result was not always obtained. In order, therefore, to avoid delay and possible loss of virulence because of this circumstance, fluid was withdrawn from the peritoneal cavity of the inoculated animals from eight to ten hours after injection, when the bacteria were still

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1. We are indebted to Dr. T. M. Rivers of the Johns Hopkins Medical School, Baltimore, for the strain of *B. influenzae* used.

actively growing in the peritoneum, and cultures were prepared to be used for inoculation of a fresh animal on the next day in case the previously inoculated animal failed to succumb. By this means the virulence of the strain of *B. influenzae* employed was sufficiently raised so that 0.01 c.c. of a sixteen-hour blood broth culture injected intraperitoneally killed a white mouse within forty-eight hours.

It was then considered probable that the organism had attained sufficient virulence to warrant testing the effect of inoculating monkeys in the respiratory tract. Accordingly, a series of twenty-two monkeys were so inoculated. The material used for inoculation may be divided into three groups: (1) first or second subculture on blood agar or in blood broth of *B. influenzae* recovered from the peritoneal exudate or heart's blood of monkeys dying of *B. influenzae* peritonitis and septicemia; (2) first or second subculture of *B. influenzae* recovered from the respiratory tract of monkeys killed during the acute stage of the pneumonia produced by intratracheal injection of the organism, and (3) the peritoneal exudate of monkeys dying of *B. influenzae* peritonitis, the exudate being controlled as to its purity by microscopic examination of stained films and by culture on blood agar plates.

Two modes of inoculation were employed, and for convenience the experiments may be divided into two groups according to the method used. In one group, in order to determine whether *B. influenzae* would initiate an infection of the upper respiratory tract, and if so, what the characteristics of the disease produced might be, the material to be inoculated was introduced into the nose and mouth either by application with a sterile cotton swab or by instillation with a pipet. In the second group, the material was introduced into the lower respiratory tract by direct intratracheal injection with a Luer syringe, the needle of which was inserted into the lumen of the trachea between the tracheal cartilages just below the larynx, the special purpose of this series of experiments being to determine if possible the pathologic characteristics of *B. influenzae* pneumonia.

In the majority of the experiments, the monkeys were held under preliminary observation for a period of from three to seven days before inoculation, during which time morning and evening temperatures (rectal) were taken, and daily total and differential leukocyte counts were made. The methods of study after inoculation consisted in the observation and recording of clinical symptoms, in the taking of morning and evening temperatures (rectal), daily total and differential counts of the leukocytes, and blood cultures at irregular intervals. Since the disease produced did not prove fatal, most of the animals were killed and necropsies performed at varying intervals during the acute stage of the disease or immediately after recovery.

THE EFFECT OF INOCULATING MONKEYS IN THE NOSE AND MOUTH WITH BACILLUS INFLUENZAE

Twelve monkeys received inoculations of *B. influenzae* in the nose or in the nose and mouth, with the successful production in every instance of an acute respiratory disease which appeared to be identical with influenza in man. The amount of culture or peritoneal exudate inoculated varied from what could be introduced by the single application of a cotton swab previously dipped in the culture up to 1 c.c. in each nostril and in the mouth.

Clinical Course and Symptoms.—The onset occurred from three to six hours after inoculation, the first symptom being a variable degree of prostration, often extreme, the animals in many cases lying prostrate on the floor of the cage, eyes closed and very stuporous. This was accompanied by an abrupt rise in temperature varying between 103 and 106 F. in some cases, with only moderate or no febrile reaction in others. Symptoms of upper respiratory tract infection soon followed, frequent sneezing, blinking of the eyes and rubbing of the nose being the prominent initial manifestations. The subsequent course of the disease showed some variation, but in general it was that of a self limited respiratory disease of from three to five days' duration. In most cases, by the end of from twenty-four to forty-eight hours, the infection had spread to the lower respiratory tract, as shown by the development of a racking cough. A variable amount, usually scanty, of mucoid or mucopurulent nasal secretion appeared in which *B. influenzae* might or might not be found. The temperature reaction varied greatly and showed no constant type of curve, being analogous in this respect to the variable types of febrile reaction seen in influenza in man. The leukocyte counts showed during the active stage of the disease either a definite degree of leukopenia or no significant variation from the normal, leukocytosis occurring in only three cases on the third or fourth day of the disease coincident with the development of a complicating purulent sinusitis.

Complications.—Five monkeys developed an acute purulent sinusitis of the antrum of Highmore from which *B. influenzae* in pure culture or mixed with some other organism was recovered at necropsy. Two animals developed pneumonia on the third and fourth days, respectively. The onset of pneumonia was insidious, and the presence of the disease was suspected only because of a rise in temperature and moderate acceleration of the respiratory rate. Both animals were killed during the early stage of the pneumonia, *B. influenzae* being recovered from the lungs in pure culture in both cases.

Pathology.—Nine animals were killed, and necropsies with bacteriologic examination were performed. Those killed during the active stage of the disease all showed rhinitis, with purulent sinusitis of the antrums in five cases. Cultures from the antrums showed *B. influenzae* in abundance in three cases, moderate numbers in a fourth, and none were recovered in the fifth. In two cases, *B. influenzae* was present in pure culture; in two, other bacteria also were found. Six cases showed a tracheitis or tracheobronchitis. *B. influenzae* was recovered from the trachea or bronchi in all of these: in two cases, in pure culture; in four, mixed with other bacteria (*Staphylococcus albus*, nonhemolytic streptococcus, or a gram-negative micrococcus). Two animals showed a fairly extensive bronchopneumonia involving the right upper and lower lobes, and the left upper lobe in one; the left lower, middle and upper and right upper lobes in the other. This pneumonia, in brief, was characterized by extensive hemorrhage, peribronchial areas of consolidation with an exudate of leukocytes, mononuclear cells and desquamated alveolar epithelium and thickening and infiltration of the alveolar walls, absence of pleurisy, and considerable patchy emphysema of the peripheral lobules. *B. influenzae* was recovered in pure culture from the lungs in both cases.

THE EFFECT OF INTRATRACHEAL INJECTION OF
BACILLUS INFLUENZAE IN MONKEYS

Ten monkeys received intratracheal injections of *B. influenzae*, in amounts varying from 1 to 5 c.c. of culture or peritoneal exudate, with the successful production of pneumonia in seven instances. Two monkeys showed only a tracheobronchitis; one showed no evidence of infection. The symptoms of prostration and cough, temperature and leukocyte reactions were the same as in the preceding group. In addition, the respiration was accelerated. In two cases, the infection spread to the upper respiratory tract with the development of coryza and frequent sneezing. In one case, a general infection with *B. influenzae* septicemia and pericarditis ensued. In no case did the disease prove fatal. It seems probable, however, that death would have occurred in the monkey that developed septicemia and pericarditis had it not been killed.

Pathology.—Of the seven monkeys developing pneumonia, three were killed during the active stage of the disease with the recovery of *B. influenzae* in pure culture in all; four were killed immediately after recovery, cultures made at necropsy being sterile. In the two cases in which only a tracheobronchitis developed, cultures from the trachea at necropsy yielded *B. influenzae* in pure culture in one, and no growth in the other.

Two types of pneumonia were encountered: a widespread, patchy pneumonia with extensive hemorrhage and edema, little cellular exudate or infiltration, and patchy emphysema; or a bronchopneumonia with extensive bronchitis and bronchiolitis, thickening and infiltration of the alveolar walls with swelling, proliferation and desquamation of the epithelial lining, and areas of peribronchial consolidation in which the alveoli were filled with mononuclear cells, polymorphonuclear leukocytes, red blood corpuscles and desquamated epithelial cells in varying proportions. Fibrin was very scanty or entirely wanting, and the pleural surface was rarely involved. One animal showed bronchiectasis. These two types of pneumonia appear to be essentially identical with the types of pneumonia in man that have been ascribed to infection with *B. influenzae*, when uncomplicated by secondary invaders.

SUMMARY

Twelve monkeys inoculated in the nose or in the mouth with a strain of *B. influenzae* originally isolated from a case of influenzal pneumonia in man and subsequently raised in virulence by animal passage developed an acute, self limited respiratory disease of from three to five days' duration, characterized by sudden onset with profound prostration; the development of rhinitis and tracheobronchitis, with sneezing, cough, and the outpouring of a scanty mucoid or mucopurulent exudate; a variable febrile reaction, and either a leukopenia or no significant change in the leukocyte count. This disease was complicated in five instances by the development of a purulent sinusitis, in two by the development of a fairly extensive hemorrhagic pneumonia with areas of peribronchial consolidation. *B. influenzae* was recovered at necropsy from lesions of the disease either in pure culture or in association with organisms that are normal inhabitants of the upper respiratory tract of monkeys. The disease produced appears to be identical with influenza in man in its course, symptomatology, complications and pathology.

Of ten monkeys injected intratracheally with the same strain of *B. influenzae*, seven developed pneu-

monia, two developed tracheobronchitis without pneumonia, and one resisted infection. The general symptoms of the disease produced were the same as in the preceding group, that is, sudden onset, prostration, a variable febrile reaction, and leukopenia or no significant change in the leukocyte count. The disease was accompanied by a severe cough and accelerated respirations; and in two cases, infection of the upper respiratory tract ensued. *B. influenzae* was recovered in pure culture from the lungs, bronchi or trachea in those animals killed during the active stage of the disease. The pneumonia produced presented the same pathologic picture as that which was found in the two animals developing influenzal pneumonia following inoculation of *B. influenzae* in the upper respiratory tract, and appears to be essentially identical with that ascribed to pure influenza bacillus infection of the lungs in man.

CONCLUSIONS

1. *Bacillus influenzae* can initiate in monkeys an acute infection of the upper respiratory tract which may be complicated by acute sinusitis, tracheobronchitis and bronchopneumonia.
2. This disease appears to be identical with influenza in man.
3. *B. influenzae* when injected intratracheally will produce in monkeys a tracheobronchitis and bronchopneumonia, the pathology of which appears to be essentially identical with that which has been ascribed to pure influenza bacillus infection of the lungs in man.
4. In view of these facts and the constant association of *B. influenzae* with early uncomplicated cases of influenza, it seems reasonable to infer that *B. influenzae* is the specific cause of influenza.

SIMPLIFIED TREATMENT OF THE
ORDINARY VARICOSE ULCER

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Ulcer of the leg is by far the most common type of ulcer with which the medical practitioner has to deal, and its treatment is generally most unsatisfactory. The reasons for this lie in the fact that the patient will not consent to take the necessary time for the rest essential to successful treatment, until the ulcer becomes painful; or the physician contents himself with the application of some ointment and allows the patient to gain the impression that there is little else to be done. Many of these patients suffer for years from this extremely annoying condition, thinking that there is no help for it.

When these cases first come under observation, the surface of the ulcer is denuded, with a ragged, overhanging edge, while the base is filled with gray granulation tissue accompanied by a continuous discharge. There is usually more or less edema and a brawny condition of the surrounding skin, and if the ulcer lies over bone, there may be a secondary periostitis which stimulates the patient to seek relief. Bacterial absorption from the ulcer plays an important rôle in the causation of the local edema; usually this clears up following the healing of the ulcer, in spite of the fact that there may be more or less varicosity.

During the past few years, I have evolved a technic which seems to me very simple and applicable in most cases with the minimum loss of time to the patient.