ORIGINAL ARTICLES

Scientific and General

RECENT OBSERVATIONS ON VIRUS PNEUMONIA*

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WHEN the etiology of the group of diseases called virus pneumonia was discussed before the California Medical Association three years ago[1] a causative virus was demonstrable in not more than 10 per cent of cases. Since then a new virus, which is believed to be the etiologic agent in the prevalent form of primary atypical pneumonia, has been isolated,[2] and several other agents have been described as possibly associated with pneumonia in man, among them two viruses causing pneumonia in cats,[3,4] an agent infectious for guinea pigs,[5] and an indifferent streptococcus.[6] It is not possible to evaluate, on the basis of present evidence, the importance of the latter agents as a primary cause of pneumonia in man, and time does not permit a detailed discussion of the claims advanced for them by the various investigators.

CLASSIFICATION

A preliminary classification of virus pneumonias based on etiology is presented in Table 1. Those most thoroughly studied include primary atypical pneumonia caused by a virus transmitted in our laboratory to chick embryos. cotton rats, and hamsters, virus pneumonias caused by the psittacosis group of agents, and influenzal pneumonias due to influenza virus type A or B. There are important epidemiological and clinical differences between these three diseases.

Evidence to be presented later indicates that about 60 per cent of the cases of virus pneumonia are caused by the new virus. It is suggested that the term "primary atypical pneumonia" be reserved for this prevalent form of the disease or etiologic entity caused by a single virus. The diagnosis of psittacosis virus pneumonia, influenza virus pneumonia, or bronchopneumonia of unknown etiology should be applied to distinguish these diseases from primary atypical pneumonia. The disease called primary atypical pneumonia may occur as sporadic cases, in family or institutional outbreaks, or as small epidemics. Presumably the agent is transmitted from person to person by contact or droplet infection, as no reservoir other than man has been found. Primary atypical pneumonia is usually a mild illness, although severe or fatal cases are sometimes caused by the same virus. The mortality is generally stated to be less than 1 per cent.

Viruses of the psittacosis group are distinct from the agent which causes primary atypical pneumonia and are responsible for only a small proportion, probably less than 10 per cent, of all cases of virus pneumonia.[1] The psittacosis-like viruses are carried by birds of the parrot family, chickens, and pigeons, and have also been found in cats, mice, and ferrets. Pneumonia of the psittacosis group is usually produced in man by inhalation of the dried excreta of birds or by contact with infected tissues. Transmission from human cases is relatively rare, but may occur in nursing contacts. The disease is more severe than the prevalent form of atypical pneumonia, and the case fatality is high. The virus is quite readily isolated from the sputum or lung tissue by direct inoculation of mice or cotton rats.

The term "influenzal pneumonia" includes not only all degrees of pulmonary involvement from mild bronchiolitis to severe fulminating pneumonia caused by type A or B influenza virus, but also secondary bacterial pneumonias following influenza. This disease occurs only during influenza epidemics. The influenza virus has never been isolated from sporadic cases of virus pneumonia. The case fatality is variable, depending in part on the virulence of the virus causing the epidemic, but in recent years the mortality among patients with influenzal pneumonia can be placed with some certainty below 10 per cent.

The virus of lymphocytic choriomeningitis and the rickettsiae of Q-fever are known to produce a disease which sometimes resembles virus pneumonia,[7,8] but there is at present no evidence that these agents cause many cases of this illness. In 30 per cent or more of patients with the clinical signs and symptoms of virus pneumonia no etiologic agent has been demonstrated. Possibly some of these illnesses are bronchopneumonias caused by bacteria, and it should be remembered that in the early phases of coccidioidomycosis a disease resembling primary atypical pneumonia may occur. It is also possible that some of the other viruses which have been described may cause these pneumonias, which are at present of unknown etiology.

ETIOLOGY OF PRIMARY ATYPICAL PNEUMONIA

Isolation of virus.—Two methods of isolating the causative virus of the prevalent form of atypical pneumonia are outlined in Table 2. The "orthodox" method shown in the upper part of the table was unsuccessful. Although definite pulmonary lesions were obtained in cotton rats and hamsters after primary intranasal inoculation of sputum, only small or irregular lesions or none at all appeared on further passage. In certain series, lesions were obtained consistently in the later passages, indicating an adaptation of the virus, but these differed grossly and microscopically from the pulmonary infiltration obtained with the original sputum. The agent producing these lesions was not neutralizable by human convalescent serum, and further investigation showed that the lesions were probably due to a contaminating virus from the cotton rats. A new procedure, as shown in the lower part of Table 2, was then adopted and this method was more successful for isolation of the virus. Suspensions of sputums were filtered through bacteria-retaining collodion membranes, and the sterile filtrates were inoculated into the amnion of 12-day-old chick embryos. On serial passage in chick embryos adaptation of the virus from human material was accomplished in 5 of 10 trials. One strain was isolated from a bacteriologically sterile sample of human lung. As the chick embryos showed little significant pathology it was necessary to inoculate hamsters and cotton rats intranasally with the chick embryo material to demonstrate the presence of the virus. This procedure produced in 25 to 75 per cent of the animals pulmonary lesions which appeared, on gross and microscopic examination, to be almost identical with those resulting from inoculation of sputum.

Serological reactions.—Clinical and laboratory data on four cases of atypical pneumonia are presented in Table 3. These cases were relatively mild, and the white blood cell counts were normal or low. Two cotton rats inoculated with sputum from patients 1 and 2 respectively, both developed pulmonary lesions; and lesions were found in one of four animals inoculated with sputum from the fourth patient.

In a certain proportion of cases of primary atypical

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TABLE 1.—*Classification of Virus Pneumonias*

	Estimated proportion of all cases	Epidemicity	Source	Clinical course	Case fatality	Virus isolation in
	Per Cent				Per Cent	
Primary atypical	60	sporadic or epidemic	man	usually mild	less than 1	chick embryos cotton rats hamsters
Psittacosis group	<10	usually sporadic	birds animals?	very severe	over 20	mice cotton rats
Influenza A or B	<10	epidemic	man	moderately severe	less than 10	chick embryos ferrets hamsters
Lymph. chorio-meningitis	?	sporadic	rodents	severe	—	guinea pigs mice
Q-fever	?	—	ticks	moderately severe	about 5*	guinea pigs
Unknown etiology	30	sporadic ?epidemic	(resemble other virus pneumonias)			—

* Based on 15 laboratory infections at the National Institute of Health.[8]

TABLE 2.—*Methods of Isolating the Virus of Atypical Pneumonia*

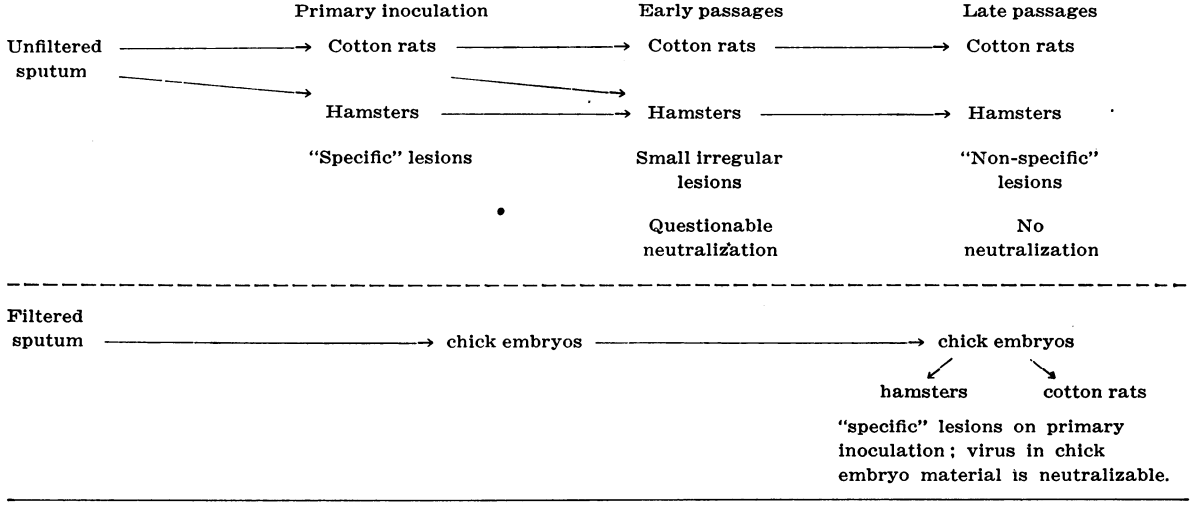

TABLE 3.—*Clinical and Laboratory Data in Four Mild Cases of Primary Atypical Pneumonia*

	Fever maximum duration	Pulmonary lesion	Day of illness	White blood cell count	Sputum (cotton rat)	Serological titers: Cold agglutination	Serological titers: Streptococcal agglutination	Serological titers: Neutralization
Ir	104. 9 days	RLL	4 32 92	5,800 9,600 —	2/2 — —	— — —	0 10 0	<2 8 <4
Sn	104. 10 days	RLL	4 8 14	4,950 — —	2/2 — —	10 80 320	0 0 0	<4 <8 16
So	102. 8 days	LLL (min.)	5 10 17 25	11,800 8,200 — —	— — — —	20 320 160 80	— 0 0 0	<2 8 32 32
McN	101. 7 days	RUL	3 17	7,500 10,400	1/4 —	10 10	0 0	4 128

pneumonia the serum develops between the 10th and 20th day the property of agglutinating type O human erythrocytes at low temperatures.[9] This cold agglutination reaction disappears in the patient after convalescence and also after storage of the serum itself for periods of a month or more. Cold agglutination has been observed in other diseases, and we have found it in three cases of influenzal pneumonia. Although this reaction is not entirely specific for primary atypical pneumonia, the presence of the cold agglutinins in titers above 20 associated with pneumonia offers a simple presumptive diagnostic test for the disease.

Virus neutralization tests were performed by mixing 20 per cent suspensions of infected chick embryo tissues with dilutions of human serum in normal horse serum, incubating at 20 degrees centrigrade for 20 minutes, and inoculating hamsters or cotton rats intranasally. In cases of primary atypical pneumonia the titers of the serums taken early in the disease were low, and an increase in antibodies to high titers was observed during con-

TABLE 4.—*Clinical and Laboratory Data in Three Relatively Severe Cases of Primary Atypical Pneumonia*

	Fever maximum duration	Pulmonary lesion	Day of illness	White blood cell count	Sputum (cotton rat)	Serological titers: Cold agglutination	Streptococcal agglutination	Neutralization
Bu	104.8	RLL	4	7,500	2/7	10	0	<2
	24 days	RUL	12-15	37,600	1/2	80	—	<16
		LLL	25-30	9,200	—	160	0	16
		LUL	46	—	—	20	—	>4
Yo	104.	RUL	4-8	7,650	7/12	8	—	<2
	9 days	RLL	16	7,800	—	1024	—	>16
			26	—	—	320	40	64
			80	—	—	160	20	64
Do	101.8	LLL	5	10,000	—	10	0	<4
	16 days	RLL	11	7,900	—	40	10	8
			16	—	—	160	20	8
			25	—	—	160	—	16

TABLE 5.—*Results of Neutralization Tests with the Virus of Atypical Pneumonia*

	Antibody increase by virus neutralization: fourfold or over	twofold	none
Atypical pneumonia	12	4	1
Streptococcal agglutination positive			
Atypical pneumonia	19	6	8
Streptococcal agglutination negative			
Total atypical pneumonia (50)	31 (62%)	10 (20%)	9 (18%)
Other pneumonias (14)	0	1 (7%)	13 (93%)
Bacterial and Influenzal			

TABLE 6.—*Laboratory Differentiation of Primary Atypical Pneumonia from Virus Pneumonias of Psittacosis Group*

Case No.	Virus isolated sputum	Serum days after onset	Complement fixation psittacosis group	Neutralization virus of atypical pneumonia	Streptococcal agglutination	Cold agglutination
1	Atypical pneumonia	4	0	< 2	0	0
		25	0	>16	0	160
2	Atypical pneumonia	4	—	< 2	—	0
		25	4	64	40	640
3	—	5	0	< 2	0	10
		17	0	8	80	80
4	—	6	0	0	0	0
		30	32	0	0	0
5	Psittacosis group	1	0	4	—	—
		30	32	4	0	—
6	Psittacosis group	Pre-	4	—	—	—
		21	32	0	0	—

valescence. The antibodies had decreased or disappeared at periods of several months to two years after the illness. The neutralization was found to be specific in that no increase in antibodies was observed when serums from persons with atypical pneumonia were tested against influenza or rodent pneumonia viruses, and serums from human cases of psittacosis, influenza, or bacteral pneumonia showed no significant increase in antibodies against the atypical pneumonia virus. The occurrence of these neutralization reactions is good evidence for an etiologic connection between the virus isolated in the laboratory and primary atypical pneumonia in man.

Three cases of greater severity are shown in Table 4. Serums from certain cases of atypical pneumonia develop agglutinins for an indifferent streptococcus isolated by Thomas and his associates at the Rockefeller Institute Hospital[6] from a fatal case. The relation of this organism to the disease is at present uncertain, but the observations that the lungs in certain fatal cases are bacteriologically sterile[2,10] and that atypical pneumonia may be produced in man with bacteria-free filtrates of throat washings or sputum[11] seem to exclude the streptococcus as the primary cause. This organism might in some cases produce secondary infection and a more severe illness.

The results of neutralization and streptococcal agglutination tests on 50 patients with a clinical diagnosis of primary atypical pneumonia are summarized in Table 5. Thirty-one, or 62 per cent, of the patients had definite increases in virus-neutralizing antibodies for the new virus of atypical pneumonia; and of these, 12 also showed positive agglutination of the indifferent streptococcus. If the streptococcus were the primary cause of atypical pneumonia we should expect to find streptococcal agglutination without virus neutralization in these cases. Of the 9 patients who had no increase in neutralizing antibodies, only one had streptococcal agglutinins. In 14 patients with bacterial or type A influenzal pneumonia no significant change in neutralization titer was found.

In another series of 87 patients, cold agglutinins were found in about 70 per cent, and among those with cold agglutinins the streptococcal agglutination was positive in 60 per cent. Only 3 patients had streptococcal agglutinins in the absence of cold agglutinins.[12] This suggests that streptococcal agglutinins and cold agglutinins tend to occur in parallel. The serological reactions with the indifferent streptococcus are somewhat analogous to the Weil-Felix reaction with certain strains of proteus bacilli in rickettsial diseases.

DIFFERENTIATION OF PSITTACOSIS FROM PRIMARY ATYPICAL PNEUMONIA

The differentiation of virus pneumonia of the psittac-

osis group from the severe form of primary atypical pneumonia is important on clinical and epidemiological grounds, and this can be done by laboratory tests as illustrated in Table 6. In the first three cases the causative agent was the virus of atypical pneumonia and this was isolated from the sputum of two patients. These patients showed no significant complement-fixation titer with the psittacosis-group antigen, but neutralizing antibodies for the virus of atypical pneumonia, cold agglutinins, and streptococcal agglutinins appeared in the sera during convalescence. In the three other cases a virus of the psittacosis group was the causative agent as judged from the presence of this virus in the sputum and the appearance of complement-fixing antibodies in the serum. No significant titers of neutralizing antibodies for the virus of atypical pneumonia, no cold agglutinins, or no streptococcal agglutinins were found in these patients.

Because of the widespread infection of pigeons with the psittacosis group of viruses, outbreaks of atypical pneumonia have often been diagnosed as ornithosis or psittacosis on rather unsound evidence. In one outbreak which came to our attention[15] a flock of pigeons was associated with many of the cases and the virus of ornithosis was demonstrated in the birds. The human contacts, however, gave no significant serological reactions for the psittacosis group, and most of them had definite increases in neutralizing antibodies for the unrelated virus of atypical pneumonia. Although the epidemiological evidence tended to incriminate the pigeons, the laboratory findings indicated that the causative agent in these cases was entirely distinct from the psittacosis group. It would seem, therefore, as regards patients with virus pneumonia who have been in contact with infected pigeons or other birds a diagnosis of ornithosis or psittacosis cannot be made with certainty unless the same strain of virus is isolated not only from the birds, but also from the sputum of the patient, or definite increases in psittacosis complement-fixing antibodies associated with the illness are demonstrated.

CHEMOTHERAPY

In the treatment of virus pneumonia, sulfa drugs have generally proved to be of little value. Possible exceptions are the secondary bacterial pneumonias following influenza A or B. Penicillin has been shown to have a definite inhibitory effect on viruses of the psittacosis group in experimental animals.[13,14] Although no clinical evidence of its effectiveness on psittacosis in man is yet available, a trial of this drug in severe cases which presumably belong to the psittacosis group would appear justified. There is no evidence at present that penicillin is effective in the more prevalent and milder primary atypical pneumonia not caused by psittacosis-like viruses.

DISCUSSION

The present evidence suggests that the majority of cases of virus pneumonia are caused by a single agent which in recent experiments has been transmitted to chick embryos, cotton rats, and hamsters. The relation of this virus to sporadic cases of undifferentiated respiratory disease without pneumonia and to epidemics of influenza-like illness not caused by the influenza virus is under investigation. It is hoped that the recent advances in knowledge of the etiology of primary atypical pneumonia and other virus pneumonias may lead to a better understanding of the epidemiology of these diseases and to the development of methods of control, immunization, or chemotherapy.

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CURRENT CONCEPTS IN VARICOSE VEIN THERAPY

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ANY clear evaluation of the methods now being employed in the treatment of varicose veins is contingent upon a knowledge of both the normal and abnormal anatomy and physiology of the peripheral venous system. Several methods of therapy regarded as definitive by their proponents fall short of their goal because basic factors are either ignored or not fully appreciated.

If an adequate solution to the problem was available, one approach would be universally recognized and no further investigative procedures would be indicated. Conversely, if the problem remained unsolved and no interest was being manifested, little would be found in the literature. That progress is being made towards an effective approach is readily borne out by the many therapeutic proposals currently being advocated in medical journals. This makes for a healthy situation which, if continued, will assuredly result in an effective means of combating a common and distressing malady.

ANATOMY

Variations in the course taken by the veins of the lower extremity are numerous, however the normal anatomic arrangement is such as to allow an unimpaired return blood flow. For practical purposes this venous system can be divided into four component parts, of which only the features pertinent to peripheral venous pathology will be discussed. To be technically correct, any description of venous anatomy should begin at its peripheral source and be carried cephalad. However, for reasons of surgical convenience a reverse order is utilized here, unless otherwise specified.

I.—The deep system, namely the femoral vein and its tributaries. Adequate descriptions of this phase of the venous return are readily available in the literature.

II.—The superficial system, which is composed of the internal saphenous vein emptying into the femoral vein, and the external saphenous vein which empties into the popliteal vein. While no specific pattern prevails for these two superficial vessels; a more or less general picture has evolved from various studies. The juncture of the internal saphenous vein with the femoral vein is a constant finding. The three main tributaries in the sapheno-femoral region, namely the superficial circumflex iliac, the external pudendal, the superficial epigastric veins are usually present although variation and duplication are not uncommon. Tributaries of variable size arising from the anterior, mesial and posterior aspect of the thigh