

On the Relation between Influenza and Post-Influenzal (Von Economo's) Encephalitis, and Implications for the Study of the Role of Infection in Epilepsy and Schizophrenia; A Review of the Historical Works and Perspective of E.C. Rosenow (1875-1966), longtime head of Experimental Bacteriology (1915-44) for the Mayo Foundation, Rochester, Minnesota.

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Many of the component research pathways supporting and comprising the growing modern consensus that infection is involved in the cause of schizophrenia and related conditions find independent support in the historical record of the Mayo Foundation's former head of Experimental Bacteriology, the late E.C. Rosenow, MD (1875-1966). In particular, Rosenow's extensive, multi-decade experience while at the Mayo Foundation (1915-44) with influenza and encephalitis, respectively, and the relation between them, provided the requisite foundation for his later extension of studies, over the decade following his departure from Mayo in 1944, into epilepsy, schizophrenia and other associated conditions.

It may be noted at the outset that the scope of Rosenow's microbiology was far more comprehensive than that which might be strictly-defined by the term "bacteriology", incorporating as essential components transmutations among microbial species, as well as considerations of reversibly dissociative, filter-passing forms, and their toxins, and comparisons with natural filter-passing (viral) forms.

The backdrop for Rosenow's role at the Mayo Foundation in the 1918-9 influenza pandemic, and indeed for his monumental body of work spanning more than a half-century of publication in the medical literature, dates back more than a decade earlier to his works with pneumonia, wherein he presented evidence from blood cultures that lobar pneumonia may be a "secondary localization of a primary blood invasion and not a local disease ... " [1,2], and to 1912 studies of the relation of a peculiar streptococcus to epidemic sore throat [3,4]. Over the ensuing years he investigated the potential role of microbes, particularly pneumococci and streptococci, in these and other conditions.

Special studies of the streptococcus-pneumococcus group were reported in 1914 [5], based on prior works by himself and others since 1906, whereby variations in oxygen tensions and salt concentration, growth in symbiosis with other bacteria, and injections into cavities in animals were found to commonly call forth mutational forms in streptococci. Virulence and fermentative powers were found to be diminished in vitro, and increased in vivo. To assure that the claimed mutations were not the result of mixed cultures from the start, cultures of each main variety were initiated with single organisms obtained by the Barber method; and all tests available were incorporated to demonstrate that these were indeed complete transformations, including, morphology, presence of capsule, fermentative powers, solubility or

insolubility in NaCl solution, and behavior toward the respective broth culture filtrates (Marmorek's test).

Table 1. Transmutations; Streptococci to/from Pneumococci [5]

Original strain	Mutation	(number of strains mutated)
S.hemolytic to	S.rheumatism	( 1)
	S.viridans	(21)
	pneumococci	( 3)
	S.mucosis	( 1)
S viridans to	pneumococci	(17)
	S.mucosus	( 2)
	S.hemolytic	(10)
pneumococci to	S.hemolytic	(11)
	S.rheumatism	( 3)
	S.viridans	( 7)
S.mucosis to	hemolytic S.	( 5)
	S.viridans	( 2)

Also in 1914 he published details of his evolving methodology for making cultures from excised tissues, blood and other fluids through the use of tall tubes affording an oxygen pressure gradient, from aerobic at the top to anaerobic at the bottom, aided by a sterile piece of tissue at the bottom if strictly anaerobic conditions are required. [6] Rosenow would continue to use fundamentally the same methodology for the next four decades, using calf or beef brain tissue to assure anaerobism at the bottom of the tubes as early as 1919 [7]; and modifying the method of isolating streptococci through the use of serial dilution cultures as early as 1935, associated with the finding that growth at higher dilutions often occurred despite absence at lower dilutions presumably due to inhibiting substances rendered inactive by dilution. [8]

The finding that relatively avirulent strains might be made virulent by successive animal passage, and the reverse by cultivation, along with other studies suggested to Rosenow that diseases of widely different symptomatology might be associated with microbes of related species but with differing infecting powers. Accordingly he undertook associated studies of other conditions of uncertain etiology, including conditions of the nervous system. In 1916 he reported that intravenous injections of cultures from multiple sclerosis, neuralgia, and multiple neuritis resulted in production of characteristic lesions in the spinal cord, dorsal nerve roots, and peripheral nerves, respectively, of experimental animals. [9]

Table 2. Intravenous Injection of Bacteria (Mixed, Primarily Streptococci) [9]

Source of Bacteria	<u>% of Animals with Lesions in:</u>			
	Spinal Cord	Dorsal Roots	Nerve Trunks	Muscles
multiple sclerosis	58	0	0	29
neuralgia	6	83	28	33
multiple neuritis	5	0	79	27
"Myalgia"	3	0	7	93

These results were to be revisited five years later as the basis of detailed studies of post-influenzal encephalitis, this as a sequel to his major involvement on behalf of the Mayo Foundation with the 1918-9 influenza pandemic.

In Rosenow's words, "The epidemic was severe, and the need and the demand for vaccination were great; a large number of cases were available for bacteriologic study, and to supply the proper strains for the vaccine. ... Owing to the foresight of the founders of the Mayo Foundation, necessary funds to meet the emergency were available. A large amount of the vaccine has been prepared and sent gratis on request to numerous physicians on condition that reports of the results be returned." [10]

On the basis of responses involving nearly a half-million persons, it was reported that unvaccinated persons were more than three times as likely to contract influenza, and six times as likely to die, as compared to persons receiving three prophylactic inoculations.

Table 3. Results reported in questionnaires from all sources [10]

	Number of Persons	<u>Incidence per thousand of:</u>		
		Influenza	Pneumonia	Deaths
One inoculation	26,936	118.2	8.7	3.0
Two inoculations	23,348	97.0	3.04	2.62
Three inoculations	93,476	87.9	4.4	1.43
Not vaccinated	345,133	281.8	21	8.55
	488,893			

Whereas Rosenow's initial vaccine used in 1918 had contained a small portion of influenza bacilli, these were rarely found later in the epidemic and thus were omitted from the vaccines used in this report; for the most part these reported vaccines were comprised of mixed cultures of fixed types of pneumococci (30%), pneumococci group IV and allied green-producing diplostreptococci (40%), hemolytic streptococci (20%) and staphylococcus aureus (10%). Of these, Rosenow suggested "that of all the bacteria isolated, the somewhat peculiar green-producing streptococcus or diplostreptococcus is the most important. This organism is present in large numbers at the very outset of symptoms of influenza and of the accompanying pneumonia; it is commonly present after death." Further, intraperitoneal injections of sputum or mass cultures in animals resulted in death, usually from invasion of the green-producing streptococci or pneumococci; and intratracheal injections closely simulated influenzal pneumonia.

In 1924 Rosenow discussed the extreme specificity of the characteristic green-producing streptococci, particularly in the case of nervous system diseases. In addition to the 1916 results for nervous system diseases discussed above, he cited the reproduction of characteristic lesions in intervertebral ganglions in rabbits and dogs by IV injection of green-producing streptococci from herpes zoster; in the posterior or sensory roots of rabbits, in the case of intercostal neuralgia; in the sheaths of large nerve trunks, in the case of sciatica; and paralysis with hemorrhagic lesions in the cord, in a series of animals, from infectious transverse myelitis.

These results had prompted him to apply these same methods, over a four-year period from 1921 to 1924, to the study of epidemic encephalitis, and encephalitis contacts, epidemic hiccup, spasmodic torticollis and respiratory arrhythmia (plus normal controls). In these conditions, he noted a constant finding of a low grade pharyngitis, and, as in his earlier experiments with other nervous system diseases, was able to isolate a similar streptococcus using methods affording a gradient of oxygen pressure.

Whereas intravenous injections had been found to yield striking results in the case of some nervous system conditions such as MS, neuralgia and multiple neuritis, it was found that intracerebral injections of small amounts of suspensions (in NaCl solution) were more likely to produce characteristic symptoms in the case of encephalitis. This method enabled the production of "profound lethargy never before seen or described in rabbits" from a fatal case of epidemic encephalitis, and similar results from eighty-one additional cases of various forms of encephalitis. [11]

It was noted that in sharp contrast to the production of epidemic or other forms of encephalitis by intracerebral injection of a strain from epidemic encephalitis, intratracheal injection of this strain produced little or no effect. However, following a series of rapid animal passages the virulence increased whereby intracerebral injection produced acute encephalitis associated with meningitis, and intratracheal injection produced marked hemorrhagic edema of the lungs associated with leukopenia. Rosenow stated at the time that these were "experimental facts in accord with the observation that epidemics of encephalitis usually follow, or occur coincidental with, influenzal outbreaks." [12]

In 1928 Rosenow followed up on his earlier results, noting that they had been recently confirmed by Evans and Freeman [13].

At this time he reported results of further experiments involving encephalitis and other nervous system diseases. He noted as particularly striking, among rabbits injected with organisms from epidemic encephalitis, a high percentage exhibiting lethargic behavior, 54%, compared to much lower percentages of such behavior in rabbits injected with organisms from other strains. In those rabbits exhibiting lethargy, "It varied in intensity and duration from slight somnolence lasting for a day or two to deep sleep continuing for a number of days, from which the animal could be aroused only with difficulty." It was noted that certain symptoms such as ataxia, tremors, hyperpnea and paralysis are relatively common in most of the conditions in this study, particularly in fatal cases; and in the case of parkinsonian encephalitis,

that ataxia and tremors were "often pronounced", despite a lack of particularly high incidence among symptoms listed.

Table 4. Symptoms in Rabbits from Intracerebral Injection of Streptococci [11]

Source of strains	Number Injected	<u>Percent Incidence in Rabbits:</u>		
		% Spasms of Diaphragm	% Lethargic	% Ataxia
Epidemic Hiccup	15	33	7	33
Epidemic encephalitis	50	2	54	20
Myoclonic encephalitis	31	3	9	23
Parkinsonian encephalitis	128	2	2	38
Respiratory arrhythmia	20	0	5	45
Spasmodic torticollis	52	0	0	44
Chorea	52	0	0	57

Over the years numerous investigators were able to replicate Rosenow's results through strict adherence to his protocols. [14] The extreme specificity noted by Rosenow in the case of nervous system diseases was independently and dramatically characterized by others who witnessed his results. For example, Jarlov and Brinch described how "Rosenow ... demonstrated in his laboratory an experiment on a single rabbit which was infected with material from a patient who had died under violent encephalitic hiccoughs. Already 48 hours after the injection, the animal died in front of the visitors' eyes after having hiccoughed violently for several hours." [15]

And Rowntree had related how Rosenow was able to "repeatedly by intracerebral injections ... set off syndromes in rabbits the exact counterparts of the clinical manifestations observed in the patients - especially tics of one kind or another. When the patient and the rabbit were placed side by side the resemblance of syndromes [was] often unbelievable and at times almost ludicrous and suggestive of plagiarism. ... he prepared autogenous vaccines that worked miracles in innumerable patients." [16]

In 1929 Rosenow reported that viability and specific properties of streptococci could be preserved for long periods of time in dense suspensions in two parts glycerol to one part saturated NaCl solution. [17] Use of such suspensions was retained as a tool throughout the remainder of Rosenow's career. He would later report that heat-killed vaccines prepared from dilutions of these suspensions were much less toxic and more antigenic than vaccines prepared directly from cultures and elicited a more rapid and more favorable, response." [18]

In 1933 Rosenow recorded seasonal changes in cataphoretic measurements as well as similarities between organisms isolated during convalescence from influenza and those from remote cases of chronic encephalitis. He also noted a "striking parallelism" between measurements of streptococci from ill persons and those from the raw milk supply during epidemics, and the return to normal patterns of both after the epidemics. These results were cited as further evidence of a role for these organisms in both influenza and encephalitis. [19]

In 1935 he reported on a new medium for cultivation of the streptococcus, autoclaved chick mash; intracerebral inoculation of streptococci cultured in this medium enabled the replication of typical lesions of encephalitis, both in type and distribution, as well as symptoms; whereas the streptococcus from encephalitis that had been derived from dextrose-brain broth had enabled replication of symptoms, but lesions induced had often been atypical both in type and distribution. Added attributes of this chick mash medium were that it was highly favorable for rapid growth and long-term maintenance of viability of streptococci, and it did not turn acid from growth of streptococci. [20]

But its two most remarkable attributes were that (a) on prolonged storage of streptococci in the chick mash medium, changes in agglutinative titer and virulence occurred seasonally in accord with current epidemics of encephalitis and respiratory infection, and (b) as cultures in the chick mash medium became old, very small and filtrable forms appeared, which were found to behave "quite like the 'natural' viruses of these diseases." [21] Thus, with this new medium Rosenow was able over the next two decades to more fully explore prospective relations of the streptococcus to seasonal epidemics; as well as the relation between the streptococcus and dissociative filtrable forms, and between these "artificial" filtrable forms and the natural virus.

Noting that changes in cataphoretic velocity and virulence of streptococci had been induced by exposure to the high frequency field, by Rosenow and others as early as 1933, and that mutations or dissociations in bacteria and viruses had been produced by others on exposure to x-rays, ultraviolet, and other radiation, Rosenow hypothesized that the responsible agent for the observed changes may be some form of radiant energy. [21] This hypothesis was tested in three long-lasting storage experiments, in which organisms derived from "neurotropic" (poliomyelitis) and "pneumotropic" (from influenza) sources were stored (in the chick mash medium) in a mine 5000 feet under limestone and compared with samples stored (in this same medium) at ground level where they would be exposed to solar radiation and also in a lead-lined safe where they would not be so exposed. Rosenow found that the samples exposed to radiation changed properties seasonally, as indicated by measurements of cataphoretic velocity, but that samples shielded from solar radiation did not change. [22] In contrast, organisms stored at ground level for up to 7 years in glycerol-NaCl (2:1) suspensions were found to retain their original specificity regardless of season or current epidemic.

In a subsequent series of experiments, Rosenow was able to demonstrate parallel altered infectivity in the case of both non-filtrable (streptococcal) and filtrable forms in accord with seasonal occurrence of neurotropic and pneumotropic epidemics respectively. [23] The concept of a phasal nature of the involved organisms, critical to an understanding of how Rosenow's well-documented and monumental studies of the role of streptococcal forms in a range of diseases might be integrated with bodies of work implicating filtrable (viral) forms, was by no means originated by or isolated to Rosenow's works.

As precedents he prominently cited the 1927 work of Phillip Hadley and his

comprehensive discussions of the large body of earlier literature on dissociation, including numerous investigators from the 19th Century. These included Nägeli, who in 1877 advocated extreme variability, and Cohn, whose contrary views had become the accepted dogma after being adopted by Robert Koch and followers. Hadley had discussed in detail "an ever-increasing mass of evidence pointing to the instability of bacterial species [which] ... may have a more significant bearing on problems of virulence, infection and immunity than many have supposed." [24]

While results from preliminary studies of epilepsy and schizophrenia, conducted in association with studies of other conditions as early as 1935, were noted as "highly suggestive", it was not until 1943-4 that Rosenow was able to undertake a more concentrated study of cases of epilepsy and dementia precox at Rochester, Minnesota State Hospital from an infectious standpoint. Following his retirement from Mayo in 1944, he was able to resume full time studies in this area a year later at Longview Hospital in Cincinnati Ohio. Results of this work were published in a three-part series of articles in 1947-8 [25].

Part I of this series recorded (in 14 tables) results of agglutination, agglutinin absorption, and precipitation experiments between streptococci, streptococcal polysaccharides, and/or nasopharyngeal swabbings from patients; and serum of patients, thermal [26] antibody, and/or serums of and antisera prepared in horses and rabbits. [25(a)] For example, Table 5 below illustrates some results of his agglutination experiments:

Table 5. Agglutination of Alpha Streptococci Isolated in Studies of Epilepsy, Schizophrenia and Arthritis by Serums of Persons Suffering From these Respective Conditions [25(a)]

<u>Source of Streptococci</u>	<u>Number of Strains</u>	<u>Percent of Total Possible Agglutination by Serum of Persons Suffering From:</u>			
		<u>Epilepsy</u>	<u>Schizophrenia</u>	<u>Arthritis</u>	<u>Control</u>
Epilepsy	23	64	45	19	20
Schizophrenia	22	45	68	26	19
Arthritis	43	14	19	53	16

Part II of this three-part series reported on symptoms and signs in rabbits and mice following intracerebral inoculation of streptococci from persons with epilepsy and schizophrenia. [25(b)] Part III recorded cutaneous reactions in persons with schizophrenia and epilepsy to intradermal injection of antigen and natural and in vitro streptococcal antibody, comparisons of results on admission and recovery, and comparative results for relatives and married couples. Also incorporated were effects of electro-shock in relation to circulating antibody and antigen, as reflected in cutaneous reactions. He concluded that the data implicated "specific types of alpha streptococci of low general but high and specific 'neurotropic' virulence ... [which] produce neurotoxins which have predilection for certain structures in the brain and thus may play a role in pathogenesis ... " of epilepsy and schizophrenia. [25(c)] (Rosenow's antibody-antigen tests were based on and a new application of Foshay's

classic 1936 work [27].)

Also in 1948, in an article recapping studies of multiple sclerosis, Rosenow provided details of animal experiments indicating a great degree of specificity as among nervous system diseases, including schizophrenia, epilepsy, poliomyelitis and MS:

Table 6. ANIMAL EXPERIMENTS Schizophrenia, Epilepsy, Polio, MS [28]

Organism from:	<u>(% Symptoms in rabbits; and % positive brain cultures)</u>				
	Normal Control	Schizophrenia	Epilepsy	Polio	MS
% Died	25	87	74	46	60
% Hyperactivity	2	87	25	26	36
% Tremors	4	79	75	33	70
% Spasms	2	21	75	35	23
% Convulsions	0	3	34	2	1
% Ataxia	16	10	13	23	66
% Nystagmus	7	0	5	2	29
% Paralysis	8	9	16	70	49
% Positive Brain Cultures	25	83	93	91	62

It may also be noted that histamine was reported to decrease antigen and increase antibody.

In a subsequent article Rosenow reported production of epilepsy in mice by intracerebral injection of streptococci, recording spasms in 93% and convulsions in 69% of 130 mice inoculated, versus spasms in 7% and convulsions in 2% of 44 control mice. In this article he discussed an apparent prenatal passage of epilepsy, this in the case of a pregnant mouse intracerebrally inoculated with a streptococcus cultured from a case of epilepsy; one of four offspring died in a grand mal seizure several weeks after birth. A pure culture of streptococcus was isolated from the brain, and produced spasms in 19 and convulsions in 16 of 22 mice that were repeatedly inoculated intranasally. Notwithstanding these results and modern documentation of a higher than normal incidence of epilepsy in association with autism, there seems to have been no mention of the latter by Dr. Rosenow in this or other discussions of epilepsy. [29]

One of the most unusual sets of experiments conducted by Rosenow followed from an unexpected occurrence in a study of a prison population. Nervous prisoners with intercurrent arthritis, myositis, stomach ulcer or respiratory infection reacted not only to specific respective "thermal" (artificial) antibody, but even more strongly to antibody from streptococci isolated in studies of chronic encephalitis. This led to study of violent criminality from a bacteriologic standpoint, where it was found that streptococci isolated from incorrigible prisoners in accord with Rosenow's methodology, on intracerebral inoculation, tended to produce behavior which in some respects simulated incorrigible behavior. This included "severe tremors and excitation, hyperirritability, dashing about wildly, jumping up at the wall of the cage at repeated intervals, burying the head in bedding on the floor or under other mice



and dashing over the huddle of more normal mice. Others walked slowly about in a dazed manner." Cutaneous reactions and agglutinative titer tests substantiated specificity of infection associated with incorrigibility. [30]

In his last article specifically directed at schizophrenia and related disorders, Dr. Rosenow once again emphasized that "These highly specific results were obtained by the use of special methods. The usual methods did not suffice." Herein he reported results of numerous additional sets of tests involving cutaneous reactions and agglutinative titer, and indicating specificity of infection with organisms cultured exclusively from nasopharyngeal swabbings. These included cutaneous reactions to thermal antibody, to the implicated streptococcus before and after vaccine, and to antibody with and without chlorpromazine and before and after oral chlorpromazine.

Additional agglutinative titer tests reported involved pooled blood serum, blood and spinal fluid on admittance, A.M. urine specimens, serum by season, serum and urine in relation to chlorpromazine, serum with and without chlorpromazine, A.M. urine with and without chlorpromazine, and serum on admittance and later in relation to chlorpromazine. It may be noted that based on these tests chlorpromazine was contraindicated immunologically.

In this article Rosenow also reported positive correlations between schizophrenia and some psychoneurotic and psychophysiologic disorders in terms of agglutinative titer of blood serum, in sharp contrast to distinctly negative results for well controls and chronic brain syndromes due to syphilis. He also found surprisingly strong indications of specificity (for an infectious agent isolated from schizophrenia cases) in cases of "mental deficiency", implying that such a condition might be amenable to therapy, etc. Also noted were relatively higher agglutinative titers of patients on admission during Winter and Spring, as compared to lower levels in Summer and lowest in Autumn.

Rosenow's conclusion: "It is realized how contrary to current psychiatric tenets the concept that schizophrenia and related mental disorders can possibly be due to an infectious process, but the results of bacteriological studies by the special methods used indicate that such is nevertheless the case." [31]

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