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Meningococcal infection

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MENINGOCOCCUS INFECTION

This disease has appeared in the literature under many names, and it is well that a considerable number of the synonyms be collected so that they will not be misleading.

1. Brain fever
2. Black fever
3. Spotted fever
4. Petechial fever
5. Cerebrospinal fever
6. Malignant purpuric fever
7. Febris nigra
8. Typhoid meningitis
9. Epidemic meningitis
10. Cerebrospinal meningitis
11. Malignant meningitis
12. Posterior basic meningitis
13. Meningococcus sepsis
14. Spotted Typhus
15. Pestilential purpura
16. Malignant purpura
17. Black death

The best definition that I have been able to locate is that of W.W. Herrick's. "An acute infection by the diplococcus intracellularis occurring sporadically or in epidemics, having a very variable course, characterized by a primary local involvement of the upper air passages, a secondary invasion of the blood stream and a usual metastatic inflammatory process in other parts of the body."

HISTORY

The first description of the disease was made by Vieusseux of Geneva in 1806 when an epidemic occurred in 1805 in which thirty-three persons died. The first book was entitled, "A Treatise on a Malignant Epidemic Commonly Called Spotted Fever" by Elisha North of Goshen, Conn., in 1811. The meningococcus was discovered by Marchiafava and Celli in 1884. Anton Weichselbaum identified the organism as the cause of meningitis and named it the diplo-coccus intra-cellularis meningitidis in 1887. The first epidemic in the United States occurred at Medfield, Mass., in 1806 and was published under the title of "A Singular and Very Fatal Disease which Lately Made Its Appearance in Medfield, Mass.", by Danielson and Mann. In 1891 Heinrich Quincke of Kiel showed that it was possible to puncture the dura mater and withdraw cerebrospinal fluid. Domenico Cotugno in 1774 had already discovered the cerebrospinal fluid. In 1906 von Lingelsheim described 3 groups of yellow cocci of this genus. In 1906 Kolle and Wassermann

announced that they had produced a curative serum. They recommended that it be given subcutaneously. The results were not very gratifying. Simon Flexner in 1908 produced a curative serum and after careful work, recommended intraspinal treatment. There was no longer doubt as to its therapeutic result. Elser and Huntoon in 1909 described three chromogenic groups. In 1915 M.H.Gordon and E.G. Murray divided the meningococcus strains into four groups. During the World War puncture of the cisterna magna was worked out in the Army Neurological Laboratory under L.H.Weed's direction. About this same time (1918), W.W.Herrick described the intravenous serum treatment of the disease and presented additional evidence that a meningococcus sepsis exists in most cases before a meningitis. J.E.Gordon in 1921 described several strains from colds and influenza which produced a yellow pigment and fermented no carbohydrates. During 1928 and 1929 in Chicago unsatisfactory results from serum led the United States Public Health Department to study 155 strains which had been received. In 1930 Sara E. Branham, Bacteriologist of the United States Public Health Service, reported the finding of 14 new strains and recommended the recognition of a new species named, *Neisseria flavescens*.

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EPIDEMIOLOGY

There are two articles which are of extreme importance in the understanding of disease as a whole and they must be read entirely in order to give an adequate conception. The articles will be found in volume 36, 1921 of the Transactions of the Association of American Physicians----Parasitism as a Factor in Disease by Theobald Smith page 172 and The Role of the Parasite in Infectious Diseases by A.R.Dochez.

SEASONAL INCIDENCE

When all the cases occurring during the year are plotted by the month, a graph is obtained which shows that the greatest number of cases occur about from January to June. This is the usual type of graph obtained. Chart / is an illustration showing this seasonal distribution of meningococcus meningitis in the series of cases of Josephine B. Neal from the department of Health of New York City, covering a 20 year period. There are so few exceptions in the type of seasonal incidence curve, that one does not profit any by introducing others.

If all the yearly totals for meningococcus meningitis cases are plotted for the corresponding year, a cycle appears in the graph about every 10 to 15 years, but it does not appear regularly, and is therefore of no definite value in predicting the incidence of the disease for the coming year, except, that in a crude way comparison of the general form of the curve to the previous curves, gives some idea what to expect. One should not lose sight of the many errors involved in any prediction for incidence of this disease.

There appears to be a relation between an increase in case incidence and a lowering of the temperature of the air of that community where an epidemic of this disease occurred. During the spring of 1918 a severe epidemic of 1040 known cases occurred at Hong Kong, China. A. M. Gale in reporting this epidemic states, "In Hong Kong, owing to the size and localized nature of the epidemic and the existence of an observatory from which accurate meteorological data could be obtained, an excellent opportunity was afforded for obtaining material on which reliable conclusions could be based." "It is evident from this analysis that:

1. Temperature showed the most influence. A drop in the temperature being invariably followed after a lag of a few days, by a rise in the number of cases. This lag tends to increase from 3 to 4 days at the beginning to 6 to 7 days at the end of the epidemic.
2. This fall in temperature was found to be associated with the following conditions:
 - (a) Steady maintenance of the low temperature as shown by the low range of temperature.
 - (b) Saturated condition of the air as shown by the approximation to each other of the wet and dry bulb temperatures.
 - (c) Absence of or diminution in the amount of sunshine.

3. That rainfall showed no appreciable effect."

Although it is seldom wise to draw conclusions by analogy, that what is true of one disease is true of another, at least consideration must be given here, to a study made by J.J. Van Logheim, Professor of Hygiene in the University of Amsterdam, of colds based on nearly 7,000 persons from September 20, 1925 till June 5, 1926. He states, "--- increase and the decrease of these colds ran parallel to the falling and rising of the temperature of the air." Also reference should be made to chapter 20 page 645 on Weather and Disease in volume 1 of Epidemiology and Public Health by Victor C. Vaughan 1922.

GEOGRAPHICAL DISTRIBUTION

Meningococcus infection is found where ever there are human beings. It is pandemic, and small localized epidemics occur every year in many countries and especially in the United States. Sporadic cases occur all the time.

MORTALITY

(Chart shows the number of cases of meningococcus meningitis that occurred in the registration area of the United States for the corresponding years.) In 1929 two cases were reported for each death registered. In the Public Health Reports for November 7, 1930 the statement is made that, "The death rate from all causes per 100,000 population decreased from 1,207.1 in 1928 to 1,192.3 in 1929. This net decrease was almost entirely balanced by increases in influenza (from 45.3 to 55.5), diseases of the heart (208.3 to 210.9), and meningococcus meningitis (2.6 to 4.5). Deaths from these 3 diseases alone caused 21.2% of all deaths in 1928 and 22.7% in 1929." *omit.*

R.C. Williams, U.S. Public Health Service, reports, "For the U.S. as a whole during the first 2 months of the year 1930 more cases of meningococcus meningitis were reported than were reported for the same period of 1929, but early in March the graph representing the 1930 incidence fell below the graph for last year, although it is still above the incidence for any other year." The latest available report shows that the graph for 1931 is below the 1930 level up to this time.

1. MORTALITY BEFORE THE INTRODUCTION OF SERUM.

Since the book by Alfred Stillé on meningococcus meningitis was published in 1867, forty years before Simon Flexner published his article on the serum treatment, the mortality at this period helps to formulate some definite idea of the possibilities of this disease unhampered by any effective treatment. He states on page

102, "----the mortality at the Hardwicke Hospital, Dublin, in 1866, was not less than 80%." On page 72, "Hirsch has published a table exhibiting the mortality of the greater number of epidemics of meningitis between 1838 and 1865, from which it appears that the death rate varied between 75% and 20%. So, while the percentage of mortality was a little over 61% (170 deaths in 278 cases) during the recent epidemic in Massachusetts, it was but 33% (43 deaths in 130 cases) in the Philadelphia Hospital. It is to be observed, moreover, that while 10 epidemics, in various places, occurring between 1838 and 1848 presented an average mortality of 70%, a similar number occurring during the decade from 1855 to 1865 gave an average mortality of about 30%. This remarkable fact would seem to indicate a gradual decline in power in the epidemic cause."

2. MORTALITY IN AN EPIDEMIC OF 1918.

In an epidemic which occurred at Hong Kong, China from February 9, to June 1, 1918, 1040 known cases occurred with a mortality of 85.5%. Peter K. Olitsky of the Rockefeller Institute for Medical Research, reported 417 Chinese patients treated at a local hospital during this epidemic with the following observations:

104 patients received neither serum treatment nor lumbar puncture--- mortality 84.6%.

346 patients received no serum but lumbar puncture 1 to 5 times---mortality 54.1%.

71 patients lumbar puncture with spinal injection of antimeningococcus serum having a low antibody content---mortality 45%.

3. MORTALITY AS IT EXISTS TODAY WITH SERUM.

I want to consider the mortality from meningococcus meningitis in a general way first. P. T. Patel reported on 55 cases from January to July 1921 at the Municipal Hospitals at Bombay, India with a mortality of 82%. Later on, 96 cases treated by lumbar puncture and serum gave a mortality of 54.2%. During 1929 an epidemic of 203 cases occurred in Glasgow, Scotland with an average mortality of 83.5%. At the Cook County Hospital of Chicago from January 1, to April 30, 1930 fifty-seven cases occurred with an average mortality of 56%. At Detroit, Michigan from January 1 to July 31, 1929 a total of 657 cases occurred with an average mortality of 53.2%. The state of Oregon reported 44 cases during January to September 1929 with a mortality of 81%. During this same period of time the state of

Washington reported 243 cases with 27% mortality and the state of California reported 610 cases with 46% mortality.

Enough data has been presented to show that even today with serum treatment in general use, the average mortality rate when compared to the rates given by Alfred Stillé in 1867, quoted above, certainly show remarkable similarity.

This mortality deserves a more intensive study. The mortality of Meningococcus meningitis in Detroit, Michigan shows a marked variation as a study of the following chart shows.

1924	52 cases	10 deaths	Mortality of 19%
1925	42 cases	6 deaths	Mortality of 14%
1926	41 cases	17 deaths	Mortality of 41%
1927	50 cases	23 deaths	Mortality of 46%
1928	153 "	100 "	" of 65%
1929	867 "	430 "	" of 49%

Josephine B. Neal in an article published in February 1931, states, "Our mortality has varied considerably in different years. From July 1, 1917 to July 1, 1918 112 patients were treated with a mortality of 19%. From July 1, 1918 to July 1, 1919, 78 patients received treatment with a mortality of 20.5%. Our average mortality has been higher than this. The last 100 cases that were treated under our supervision showed a mortality of 23%." As pointed out above Alfred Stillé in 1867 showed that the decade of 1855-1865 gave a mortality of 30%. He brought out too, that in 1867 the mortality in one city was 61% while in another city it was only 33%.

One arrives at the important and definite conclusion, that to use mortality statistics as a method of evaluating the effectiveness of treatment in such a variable disease as meningococcus meningitis, is a fertile source of error, unless the statistics cover the same epidemic, at the same time, with the variation coming only in the method of treatment or in the make of serum.

Important facts come to light when we consider the mortality of any epidemic in relation to the various ages. In 1927 J.B. Neal and Henry W. Jackson of the Department of Health of New York City, reported 23 cases of meningococcus meningitis occurring in the first 3 months of life with the mortality of 47.8%, during 16 years. The mortality of all the cases during the first year was 46%, and the mortality of the second year was 29.2%. The mortality distribution according to age for the Detroit epidemic of 1928-1929 is given in the following chart.

Age in Years	Cases	Deaths	Case Fatality per cent
0----1	45	38	84.4
1----4	177	92	52.0
5----9	113	41	36.3
10--14	68	23	33.8
15--19	62	32	51.6
over20	192	124	64.6
Totals	657	350	53.2

In the Glasgow epidemic of 1929 the mortality for 42 cases under one year of age was 92%, 39 cases from 1---5 years, the mortality was 89% and of 53 cases over 5 years, the mortality was 71%.

The case fatality for the Infant's and Children's hospital of Boston from September 1, 1923 to November 1, 1929 is given in the following chart of Charles F. Mc Khann.

Age	Cases	Deaths	Fatality
Under 1 year	39	25	64%
1-----2 years	10	3	30%
2-----12 years	25	6	24%
Total	74	34	Average 45%

Not every epidemic shows the greatest mortality in children under 1 year of age, but since this fact has been watched and known for many years, it becomes a matter of caution in prognosis, a matter of caution in diagnosis, and a matter to which scrupulous attention must be paid in arriving at any conclusion relating to the effect of treatment on mortality.

Another important factor in mortality was brought out again in the study made by G.W. Anderson and G.H. Bigelow of the cases at the Infant's and Children's Hospital of Boston during September 1, 1923 to November 1, 1929. The chart below gives their findings of the duration of the disease before treatment and its relation to mortality.

Age group	Duration of the Disease before Treatment	Cases	Death
Under 1 year	under 1 week	16	4
	1-----2 "	4	3
	2-----4 "	10	9
	4-----8 "	7	7
	Over 8 "	2	2
1-----2 years	under 1 week	4	1 Fulminating
	1-----2 "	0	0
	2-----4 "	2	0
	4-----8 "	3	1
	over 8 "	1	1
2-----12 years	under 1 week	19	4 (Fulminating)
	1-----2 "	1	0
	2-----4 "	4	2
	Over 4 "	1	0

The authors make the following observations, "The results in the cases treated within the first week of the disease show almost the same percentage of recoveries in all three age groups. In infants, the mortality rises rapidly with increasing duration prior to treatment, and the outcome is uniformly fatal in prolonged cases." "In view of the high mortality in infants not treated until late in the disease, it is disturbing to find that of the patients under 1 year of age 19 or 48% had been sick over two weeks and 9 or 23% had been sick over four weeks before the diagnosis was made and serum treatment begun. Of the 23 patients who had been sick more than one week prior to the institution of treatment only two recovered." The responsibility these facts place upon the matter of diagnosis is self evident.

In a letter to the Editor of the Lancet in the February 28, 1931 issue page 497 M.H.Gordon makes the following statement, "The mortality of type 1 cases in military outbreaks from 1915-19 is put by Drs. C. Worster-Drought and A.Mills Kennedy in their valuable monograph on cerebro-spinal fever at 60%. When monotypical serum, proved before issue to contain a definite amount of anti-endotoxin to type 1, was employed in the treatment of such cases a careful and critical analysis of the results was made by Dr. T.G.M.Hine in two papers. The first, a white

paper printed by order of the Medical Research Committee, and dated January 28th 1919, states that out of 34 type 1 cases reported on up to that date, many of them severe, no less than 33 had recovered under treatment with the monotypical serum. After demobilisation of the Central laboratory a final survey of the results was made by Dr. Hine and contributed to "Special Report No.50, on Cerebrospinal Fever" published by the Medical Research Council in 1920. Out of an aggregate of 65 type 1 cases treated with the monotypical serum 59 recovered and six died, a mortality of 9.23%.

As expressly stated by Dr. Hine, however, in the papers referred to, cases considered as moribund when the treatment was first applied were included in these figures, partly because their exclusion did not appear to be justifiable, and also because when given the monotypical serum some of them recovered."

In The Lancet for February 21, 1931 page 419 these statements are made, "A disquieting feature of the present epidemic is that recently serum treatment appears to have been of little avail and the mortality has been exceptionally high. Experience during the war showed that therapeutic serum varied remarkably in potency, and that while the best sera reduced the case mortality to under 20%, many were apparently useless. The serum treatment of the disease in Denmark in recent years has given such poor results that it has been discontinued, and medical opinion is not favorable to it in Sweden." "M.H.Gordon is of the opinion that the power of neutralising the endotoxin of the meningococcus is probably the best laboratory index of therapeutic potency, since a serum may possess high agglutinin and opsonin content and yet have not therapeutic potency."

AGE INCIDENCE

Chart 2 is taken from the article of Josephine B. Neal published in February 1931 together with the following explanation, "---shows the distribution by age and etiology of more than 2,000 cases of meningitis. During the period in which these cases have been collected, nearly 20 years, there has been no severe epidemic in New York City. In 1917 and 1918, there was a sharp increase in the number of cases, and in 1928-1929, there was an epidemic of rather mild proportions. It shows also that meningitis of all forms is essentially a disease of childhood, and in the case of meningococcus meningitis, by far the largest number of cases occur in the first year of life. Of course in times of war there are epidemics of meningitis among the young adults collected in the army camps.

SEASONAL DISTRIBUTION
MENINGOCOCCIC MENINGITIS

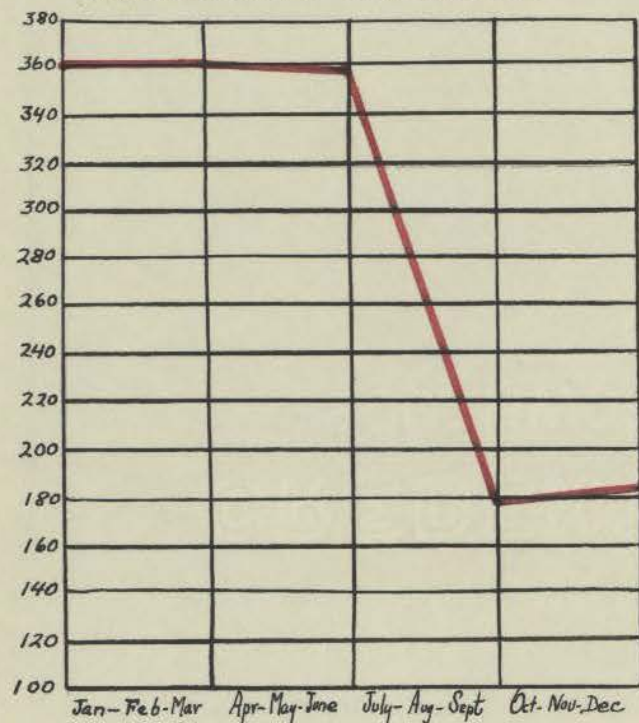
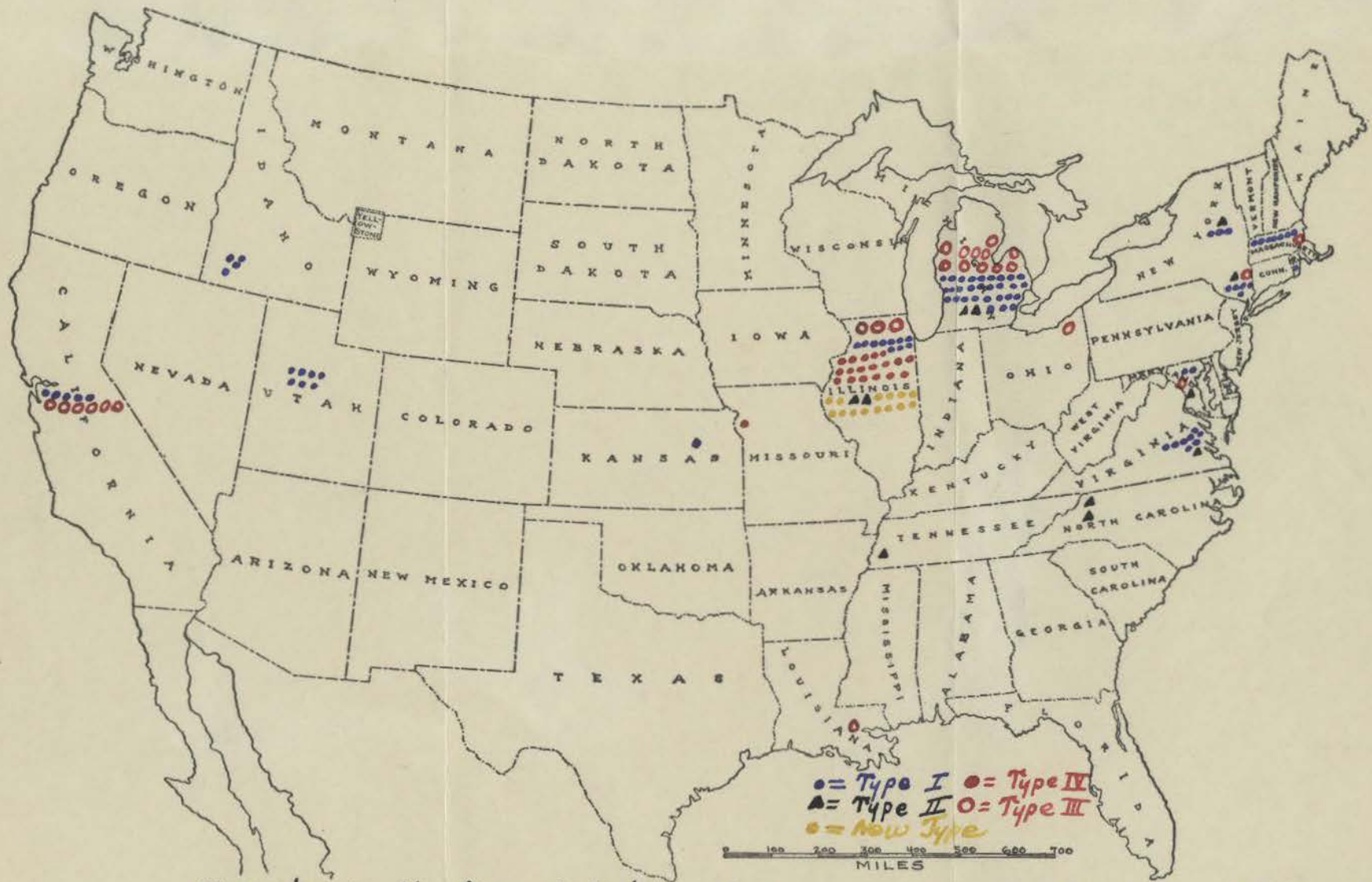
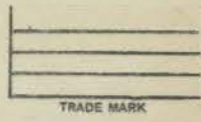


Chart 1

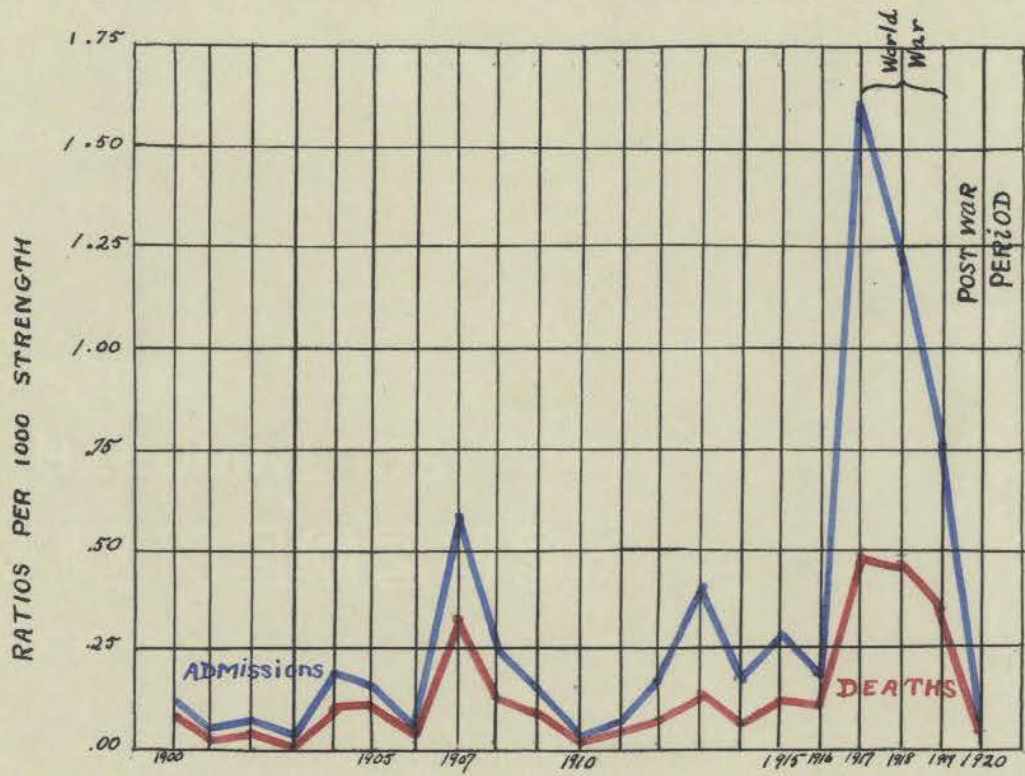
MENINGITIS-AGE-ETIOLOGY

Age	M.M.	T.B.	Pneumo.	Strep.	Inf.	Staph.	B.coli	Misc.	Total
1-2-3 Mo.	28	5	9	13	3	0	2	4	62
4-5-6 Mo.	75	29	7	9	12	0	0	2	134
7-12 Mo.	92	102	14	3	13	2	1	8	235
TOTAL	195	136	28	25	28	2	3	14	431
under 1 Yr.						1			
1-2 Yr.	86	183	13	5	19	1	1	4	312
2-3 Yr.	51	107	8	11	9	1	0	5	192
3-5 Yr.	118	150	14	11	7	4	0	6	310
5-10 Yr.	204	135	29	48	5	0	1	9	430
10-20 Yr.	198	87	18	22	3	6	0	14	348
Over 20	168	73	51	23	1	5	0	13	344
Age Unknown	0	12	1	2	2	0	0	2	19
Total	1020	893	162	147	74	19	5	66	2386

Chart 2



Map showing the type distribution of meningococci in the U.S. during 1928 and 1929.



Admissions and deaths for cerebrospinal meningitis, U.S. Army, 1900-1920. Ratios per 1000 strength.

chart 3

Meningococcus meningitis: cases and deaths by age groups, Detroit, January 1 to July 31, 1929.

Age in Years	Cases	Deaths	Case Fatality
0-1	45	38	84.4
1-4	177	92	52.0
5-9	113	41	36.3
10-14	68	23	33.8
15-19	62	32	51.6
Over 20	192	124	64.6
Totals	657	350	53.2

Meningococcus meningitis—sex incidence by age group—Chicago.

Age Group	Cases		Ratio Male to Female
	Male	Female	
Under 1 Year	3	7	0.4
1-4	19	19	1.0
5-9	23	17	1.4
10-14	17	12	1.4
15-24	36	10	3.6
25-34	13	3	4.3
35-44	7	3	2.3
45-54	6	2	3.0
55-69	2	1	2.0
Total	126	74	1.7

In tuberculous meningitis the greatest number of cases occurs in the second year of life. In most instances of the other forms of purulent meningitis, the disease is probably secondary to a focus of infection elsewhere in the body, but it is sometimes difficult or impossible to locate it by clinical examination."

In the following table from the study made by G.W.Anderson and G.H.Bigelow published in 1930 a comparison is made of the incidence in Mass. with that of New York City.

Distribution of Cases by Age Groups		
	Mass 1919-1928	N.Y.C. 1910-1925
Less than 1 year	16%	25%
1----4	27%	30%
5---9	16%	16%
10--14	9%)	15%
15--19	7%)	
20--29	8%	8%
30--39	3%	3%
40--49	4%	2%
50--Up	3%	02%
Unknown	7%	-

Reference to the charts under mortality, together with the evidence presented above, makes it evident that the child of 5 and under, is the most susceptible individual to infection.

SEX INCIDENCE

It has been known for many years that males were attacked more often than females. Alfred Stillé on page 95 of his book states, "It has in many places been noticed that the proportion of males attacked is much greater than of females, and such is probably the general rule." More facts are accumulating which substantiate these findings. The chart below taken from the study of the Detroit epidemic in 1928-1929 made by J.F.Norton and J.E.Gordon shows there is a slight but definite increased incidence among males.

Meningococcus meningitis: Cases and Deaths by Color and Sex, Detroit, January 1 to July 31, 1929			
	Cases	Deaths	Case Fatality PER CENT
White Total	542	281	51.8
males	337	182	54.0
females	205	99	48.2
Colored Total	115	69	60.0
males	64	35	54.7
females	51	34	66.7
Total Both Sexes	657	350	53.2
males	401	217	54.2
females	256	133	52.0

The study by Alton S. Pope and J.L. White of 200 cases occurring from January 1 to July 17, 1928 in Chicago, reveals the different ratios at the different age periods, as the accompanying chart shows.

Age Group	Cases		Ratio male to female
	male	female	
Under 1 year	3	7	0.4
1----4	19	19	1.0
5----9	23	17	1.4
10--14	17	12	1.4
15--24	36	10	3.6
25--34	13	3	4.3
35--44	7	3	2.3
45--54	6	2	3.0
55--69	2	1	2.0
TOTAL	126	74	1.7

RACE INCIDENCE

After the study on meningitis in the United States Army during the World War became available in 1928 it was revealed that during the period of April 1917 to December 1919 there was a difference in the white and Colored enlisted men. This difference has been known before and is given in this chart.

ADMISSIONS		DEATHS	
	Ratios per 1,000		Ratios per 1,000
White	1.25	White	.42
Colored	2.35	Colored	.91
CASE FATALITY			
	Ratios per 1,000		
White	33.41		
Colored	38.78		

Reference again to chart shows the same increased fatality for the colored individual. There appears to be no available data on the other races in comparison to the white race, covering sufficient cases and during the same epidemic, to be of any reliability.

INCIDENCE IN RELATION TO MOBILIZATION OF TROOPS

The first recorded epidemics were among young military recruits. Chart 3 is taken from the 1928 published report of The Medical Department of the United States Army in The World War. The following explanation is attended, "Since the Spanish-American War the diagnosis of cerebrospinal meningitis in the Army has been more exact, and the records have included only cases in which the clinical diagnosis was confirmed by bacteriological examination. During this time, as indicated graphically in Chart 26, the annual admission rate per 1,000 strength has been almost negligible, except during the mobilization of unseasoned troops; for example, the rate increased noticeably in 1907 at the time of the Cuban occupation, and again in 1917 when the United States entered the World War. It is noteworthy that the concentration of Regular Army Troops on the Mexican border in 1911 was not attended by any remarkable increase in the meningitis admission rate."

TYPE DISTRIBUTION OF THE MENINGOCOCCUS

Sara E. Branham, Clara E. Taft, and Sadie A. Carlin reported in May 1930 the results of their work in typing 155 strains of meningococcus isolated during 1928 to 1929. The spot map is taken from this report, and it well repays careful study. They also made a comparison as to percentage of the different groups for four different years. "The accompanying table shows the distribution of our 155 strains according to type, expressed in percentage. The first column shows the type distribution in the epidemic years of 1918-19 as determined by Butterfield and Neill. Columns 2 and 3 show the distribution of types in 2 non-epidemic years as determined by Evans. Column 4 shows the distribution among the types during the epidemic years of 1928-29 as determined ourselves. These typings are interesting to compare, because they were done with practically the same technique, and the same four standard type strains of meningococci were used to prepare the type sera."

*Grouping of meningococcus meningitis in the U.S.
according to Gordon's Types.*

Type	1918-19 128 Strains	1921 16 Strains	1922 15 Strains	1928-29 155 Strains
	Percent	Percent	Percent	Percent
I	37.5	18.7	6.7	52.9
II	25.8	18.7	-----	7.0
III	21.1	12.6	-----	18.7
IV	2.3	6.3	13.3	12.2
Not in the Above	13.3	43.7	80.	9.2

Grouping of Meningococcus in the United States
According to Gordon's Types.

Type	1918-19	1921	1922	1928-29
1	37.5	18.7	6.7	52.9
2	25.8	18.7	---	7.0
3	21.1	12.6	---	18.7
4	2.3	6.3	13.3	12.2
Not in the above	13.3	43.7	80.0	9.2
	(128 strains)	16 st.	15 st.	155 strains
	per cent	per cent		per cent

MULTIPLE CASES IN THE SAME FAMILY

Since the first epidemics it was noticed that more than one case of meningococcus meningitis in a family seldom occurs in any epidemic. In fact, the occurrence of multiple cases usually becomes a matter for a publication in some journal. Alfred Stillé on page 102 of his book states, "If there is one point in its history which is established by the concurrent testimony of American and European writers, it is the extreme rarity of its attacking the physicians and the nurses in attendance upon the sick, and those patients affected with other diseases, who occupy the adjoining beds in the Hospital wards." On page 99 he says, "In the present instance it may be affirmed that epidemic meningitis has been pronounced non-contagious by almost the unanimous verdict of competent judges." D.M. Angevine in May 1930 reported the deaths of two children in the same family occurring about 8 months apart. The mother was found to be a carrier of the meningococcus.

Archibald Hoyne and E.T. McEnery reported in November 1929 the occurrence of meningococcus meningitis in a 10 year old girl, followed by the disease in a sister after admission, and a brother 9 days after the second sister. Only the boy recovered. They also report the example of a mother and three children in the same family who came down with the disease within a period of 3 days. The mother and one child recovered.

M.R. French in an article published in February 1931 in a study of meningococcus meningitis in Milwaukee, Wisconsin during the period of 1927-1928 and 1929, has the following to say, "----; while in 17 different families there were 2 or more cases in each, or a total of 37 multiple cases.

In 3 of these families, Nos. 4, 15, and 16, where multiple cases occurred, there were 3 cases each, while in the other 14 there were only 2 cases. In all of the homes with the exception of the first 3 there was an interval of a few days between the onset of the first

case and the others. In the first 3 the dates of onset of the 1st and 2d cases were the same."

"As a rule the older persons in the family developed the disease first, with the exception of families, Nos. 14, 16, and 17 (unknown). This was especially noticeable in family No. 5 where the mother, the 1st case, developed the disease 3 days before her 19 months old baby came down. Also, in family No. 6 where the father, 36 years old, developed the disease 7 days before his 10 year old son, both slept together just prior to the onset of their illness. In family No. 7 the 25 year old uncle developed the disease 3 days before his 10 year old niece.

The interval between the onset of these multiple cases in the homes varied from the same day to $8\frac{1}{2}$ months. Eight multiple cases developed the disease on the same day in their respective families, indicating a common source of infection in the home; 20 developed within 1 to 8 days; 3 developed within $2\frac{1}{2}$ months; 2 cases in $8\frac{1}{2}$ months; and the interval for 2 was unknown."

William H. Pickett in reporting an epidemic in Saginaw, Michigan for 1929, the article written in February 1931, out of 264 cases 2 families had 3 cases in the same family and 9 families had 2 cases in the family.

Maxwell P. Borovsky reported that only 5 instances of multiple cases were noted from April 1927 to September 1928 in 190 cases at the Cook County Hospital Chicago.

Josephine B. Neal reports in February 1931 that, "In our experience, there have been only 24 instances in which there was more than 1 case in a family, or a clear history of exposure. Of these, 10 occurred in 1916, 1917, 1918 and 1919, and 10 in 1928-1929."

S. Mirsky reported in the Canadian Medical Journal of 1930 the occurrence of 3 cases of meningococcus meningitis in Stonecliffe, a small village in Ontario. There were 5 children and 2 adults in the house. Three children developed meningitis and made good recoveries. "No other cases to our knowledge occurred in that district at that time nor did any subsequently develop."

RECRUDESCENCE, RELAPSE AND RECURRENCE

A recrudescence is a return of the symptoms before the patient has really recovered from the disease. Defined again as increased severity of a disease after a remission.

A relapse is a return of symptoms after the patient has been well for a month. Defined in another way as a return of the symptoms after a period of convalescence of 6 weeks.

A recurrence is a second attack of the disease occurring after many months. In another manner it is

defined as the disease occurring again as the result of a new infection after an intervening symptomless period of many months.

The definitions are very crude and the practical application of them is very inaccurate. This comes about because of the lack of any worth-while definition of "remission," "convalescence," "disease," etc. The above definitions take into consideration only the interval between apparent recovery and the actual manifestations of the disease. That is, if the patient still has manifestations of the disease when the symptoms flare-up again, it is a recrudescence; if there are no manifest symptoms and the disease returns, it is a relapse, some making the symptomless interval a period of one month and others over 6 weeks. Just what period of time is the division between relapse and recurrence is not definitely indicated, so that among different articles there is more or less overlapping. The definitions are also inaccurate in another way, no consideration is taken of the fact that the organism causing the recurring symptoms may be the original one or that the organism may be a new species, and that the individual may be a carrier of the original organism for years before a recurrence of the disease is manifest.

At this stage of our knowledge, it is evident that if the differentiating points are widely separated, it is probably one or the other, but in those cases falling in either one, it becomes a confusing classification.

The following articles are given without making any definite evaluation. Stillé in 1867 wrote, "Relapses are very far from being uncommon. Jackson, &c. state that they occur "in many instances;" Gallup speaks of them as "very common;" Hale notices "several cases;" and in numerous examples referred to by Parks, they were met with." Foster and Gaskell in 1916 state, "That genuine relapses occur is beyond question, but their frequency is doubtful." W.W.Herrick says, "It is difficult to draw a distinction between recrudescences and relapses. The former occur in perhaps 20% of cases. If the criterion of relapses is made an arbitrary period of 6 weeks during which there is freedom from active symptoms, relapses occurred in but 1½% of the writers cases." I.P.Bronstein reported a study in 1929 of the recurrent cases of meningococcus meningitis cases since 1866 and reported the case of a man 42 years of age who developed meningitis 4 times. The attacks occurred 4 and 6 months after the first. The last and fatal attack occurred after a period of 7 years.

Sir Humphry Rolleston and F.W.Andrewes state, "Recrudescences, or return of the symptoms before the patient has really recovered from the disease, are common, and several may occur." "True relapses, or

return of symptoms after the patient has been well for a month are rare." "Relapses after many months cannot be distinguished from second attacks which, though most exceptional, undoubtedly occur."

THE PROBLEM OF THE CARRIER

A "carrier" is an individual harboring a pathogenic organism in his body, clinically not suffering from this particular infection and capable of transmitting this organism to other individuals either directly or indirectly.

Before the year 1901, when Albrecht and Ghon first discovered the meningococcus in the throat of an apparently healthy man whose child died of meningitis, nothing was known about the carrier and the great importance in transmission. It is no wonder that Stillé states, "In the epidemic which we observed in the Philadelphia Hospital, no evidence whatever of contagion was afforded."

Since that time a tremendous amount of time and study has been devoted to the detection, isolation and elimination of carriers of meningococcus, but so far, it is of slight practical significance in the prevention of disease.

All those individuals who are members of the same family, or who have taken meals in the same room or who have slept in the same room or an adjoining room, with a case of meningococcus meningitis, are called "Contact carriers." The Lancet for February 21, 1931 gives this definition. "By the term "contacts" is meant those individuals living in the same house, taking meals or working in the same room as the patient at the time of and during the week preceding his development of the disease." The inadequacy of this definition is apparent.

Individuals found harboring the meningococcus and not coming under the above definition are called "non-contact carriers." Extensive carrier surveys made in many camps showed that from 1 to 3% of apparently normal individuals, who presumably had not been associated with meningitis cases harbored meningococci in the upper respiratory tract. These persons were called "casual" or "non-contact carriers." Temporary or casual carriers are defined by Victor C. Vaughan as ---"those in whose nasopharynx the meningococcus is found at one examination and is absent a week or ten days later and in all subsequent examinations;" chronic carriers or permanent carriers as ---"those in whom the results are positive at two or more examinations a week or ten days apart."

W.W.Herrick has a slightly different idea of the casual and chronic carrier. He states, "The casual or secondary, carrier is usually such for only a short time, but may become a chronic carrier. The average length of time during which the meningococcus can be found in the

nasopharynx of these secondary carriers is 3-4 weeks, about 90% of carriers belong to this group. A small per cent may continue as carriers for 12 or even 20 months and then become free from the organism. The third or chronic carrier group is the most dangerous of all. Harboring meningococcus usually in large numbers in the nasopharynx, tonsils or accessory sinuses of the nose, these individuals, innocent of their power to harm, keep alive the organism during non-epidemic periods and, when conditions of association, of atmosphere or other less well understood factors are favorable, transmit to others the infection to which they themselves are immune. Not more than 2% belong to this group." The percentage of carriers among contacts is greater than among non-contacts, depending upon the degree of intimacy.

R. D. Herrold in 1918 showed that out of 93 carriers 54.6% had a negative nasopharyngeal culture while the culture from the tonsils, anterior superior nares or the sputum, was positive. His study revealed also that the individual with a wide distribution of the organism was a carrier for a longer period of time than the individual with a more restricted area of infection.

W.M.Scott in 1916 was able to study 16 cases of meningococcus meningitis and in 8 of these the nasopharynx culture gave positive results even after complete convalescence. Three were still positive 3 weeks after discharge; one for 9 weeks and one was still positive after 3 months. He was able to study 150 individuals---38 males and 112 females, presumably non-contacts, who came in to the dispensary for treatment for coughs, rheumatism, etc. The period of time was June 1st to July 15th, 1915. The final results were that 22% gave positive nasopharyngeal cultures identified by microscopical and cultural characteristics. It is interesting to note too, that the colonies are reported "almost pure culture" in 2 cases, "numerous" in 15 cases, "few" in 8 cases, and in 10 cases only one colony occurred.

In 1917 W.M.Scott made a further study of the meningococci by comparing the meningococci found in the nasopharynx of 71 apparently normal individuals with the meningococci from 60 cases of meningococcus meningitis. The organisms were carefully studied for morphology, culture, agglutination, and absorption of agglutinin and he arrives at the following conclusion, "The conclusion in my first report is therefore maintained that any strain possessing the admitted morphological and cultural characters of the meningococcus should be regarded as potentially pathogenic without considering its serological reactions."

Constant Ponder in 1917 studied the results of nasopharyngeal cultures from 400 individuals. At Addenbrooke's Hospital during June and July 1917 thirty strains were obtained from 200 practically normal individuals. At the Norfolk and Norwich Hospital during August 27 strains were obtained from 100 individuals mostly in impaired health. At Cambridge during October 37 strains were obtained from 100 cultures from factory employes in good health and comfortable circumstances.

He states, "Such strains were found more often in males of every age group than in females, and in adults more often than in children." "In examining the employes at a factory, I obtained the strains in a higher proportion from the men working in those shops where air space was more restricted and ventilation less perfectly effected." He comes to the same conclusion as W.M.Scott when he states in the conclusion, "With regard to those naso-pharyngeal strains which were not identified with cerebro-spinal strains by serological tests (agglutination and absorption), I consider that in view of the great variation in the serological reactions shown by different ~~strains of~~ ~~undoubted~~ ~~meningococci~~ ~~and~~ ~~very~~ even by different emulsions of the same strain, it is very difficult, if not impossible, to exclude any such microscopically and culturally typical organisms from the meningococcus group on the basis of serological tests."

In an article by M. H. Gordon he states, "The report of Captain Martin Flack on cerebro-spinal fever in the London District during 1916 demonstrates in a convincing manner the value of the agglutination test in actual practice, both for detecting cases of the disease, and also for identifying carriers. With regard to cases he found (1) that not more than a single type of meningococcus could be obtained from the cerebro-spinal fluid of a patient, (2) on examination of the nasopharynx of the patient he confirmed the later observation of von Lingelsheim as to the constant presence of the meningococcus there at the onset of the disease, and he showed further that this meningococcus in the nasopharynx was always of the same type as that present in the cerebro-spinal fluid of the patient when this was positive. A similar observation as to the identity of type between the meningococcus in the nasopharynx and cerebro-spinal fluid of the same case has also been reported by Major F.W.Andrewes. This constant presence of the meningococcus was found by Captain Flack to have a direct clinical application in facilitating a correct diagnosis of cerebro-spinal fever in the very cases where help of this kind was most needed, namely in cases where the symptoms of the patient were atypical, or where the cerebro-spinal fluid failed to yield a growth of the meningococcus. The importance of early diagnosis cannot be over-emphasised from the point of view of successful serum treatment. Captain Flack also found that the same type of meningococcus was most prevalent both in cases and in carriers during the period that he was in charge of the London District C.S.F. Laboratory.

Another observation made by him was that, like the cases, chronic carriers are remarkably mono-typical in the sense that the great majority of them carry one and the same type of meningococcus throughout the whole period of their carrying. This was confirmed by Captain Tulloch."

A. Eastwood in an article published in 1916 stated, "There is an obvious difference between diagnosing the meningococcus in cerebro-spinal fluid withdrawn from a patient with symptoms of meningitis and identifying this organism in a culture from the nasopharynx of a person not clinically affected with the disease. Assuming the two organisms to be alike in cultural characters, with the former the confirmatory evidence of specific pathogenicity is supplied by the condition of the patient; with the latter organism, this confirmatory proof is lacking. In the case of such organisms as the bacilli of plague, tuberculosis, or anthrax, the proof could readily be proved by animal experiment; but for the meningococcus, as for the typhoid bacillus, there is not laboratory animal available for routine demonstration of specific pathogenicity. It is therefore necessary to be content with indirect evidence that an organism isolated from the naso-pharynx is capable of producing cerebro-spinal fever."

A. Eastwood made a study of 480 outpatients beginning on March 29th, 1915 and terminated on July 22nd of the same year. The first 100 (completed April 19th) gave 20 positives; the second hundred (completed May 6th) gave 7; the third 100 (completed June 7th) gave 6; the fourth 100 (completed June 24th) gave 7; the last 80 (completed July 22nd) gave 9.

Eastwood arrives at the following conclusion. "How far do the above considerations provide an answer to the question: is a naso-pharyngeal strain, found identical with true meningococci in culture and fermentation tests, to be regarded, ipso facto, as capable of producing cerebro-spinal fever in a suitable soil? It is impossible to reply by a categorical "Yes" or "No", because the evidence is incomplete. The balance of available evidence is on the side of "Yes." Is future work likely to reverse that balance? It might, if it can be shown that serum reactions or animal experiments place the great majority of non-contact strains into a distinct class. But this evidence is not yet forthcoming. If it is provided in the future, it will be necessary for me to reconsider my present opinion, which is that all naso-pharyngeal strains, as defined above, should be regarded as possibly capable of producing cerebro-spinal fever."

J.A. Glover in 1917 stated, "It would appear that estimations of the carrier-rate by means of large sample swabbings afford a reliable warning of the imminence or danger of an epidemic." "During the epidemic, the carrier-rate among non-contacts was substantially the same as amongst the actual contacts of cases, averaging 34% for the period, in each case." "Sever overcrowding (i.e. when beds are less than 1 foot apart) is usually accompanied by a carrier-rate (serological) of at least 20%. (Twenty per cent, is the danger line indicated in the War Office Memorandum on Cerebro-spinal Fever, March 1917.)

In Arthur Eastwood's second report in 1917 we find the following:

"With reference to the work of the Board's investigators on the carrier problem it will be useful to clear up certain ambiguities attaching to the significance of the convenient terms "contact" and "non-contact."

There is, I believe, general agreement on the following matters:-

- (1) Cerebro-spinal fever develops in persons who, prior to the onset of the disease, have "carried" the meningococcus in their nasopharynges.
- (2) The number of persons who develop the disease is very small in proportion to the number of carriers.
- (3) The meningococcus is disseminated amongst the population by contact with carriers.
- (4) When a person develops cerebro-spinal fever, some of the persons who have been in intimate contact with him will also, in all probability, be found to be carriers. Such carriers may be termed, collectively, Group 1.
- (5) It cannot be assumed that each member of Group 1 became a carrier owing to contact with the person who developed the disease; it is quite possible that the patient derived his infection from one of these healthy carriers.
- (6) Persons not in contact with the patient may have been in contact with one or other of the persons A, B, C, etc., who constitute Group 1, and may have become carriers in consequence, thus forming groups A, B, C, etc.
- (7) Similarly each individual in Groups A, B, C, etc. may be the focus of another group; and so the process may go on indefinitely.
- (8) Carriers may retain the meningococcus in their throats for a long time, though not, as a rule, for more than two or three weeks.

It is thus evident that a case of cerebro-spinal fever can usually be regarded as associated, directly and indirectly, with an indefinitely large number of carriers, of whom (a) some are known to have been in contact with the patient; (b) a larger number can be found on enquiry to have been associated, directly or intermediately, with (a); and (c) a still larger number are intermediately connected with (a), but the connecting links cannot be traced. Then the rest of the population would comprise (d), all the persons, whether carriers or not, who have no connecting links, however remote or obscure, with (a).

To avoid ambiguity, therefore, the distinction between "contacts" and "non-contacts" should be expanded into a distinction between (a) direct contacts (known), (b) indirect contacts (known), (c) unknown contacts (direct or indirect) and (d) persons who have not been contacts either directly or indirectly.

Fred. Griffith in his second report in 1917 after a study of 66 strains of meningococci from the cerebro-spinal fluid and 86 strains from the naso-pharynx of non-contacts states in the summary:

"The naso-pharyngeal strains are not serologically separate and distinct from the cerebro-spinal strains, and moreover have not been found to exhibit among themselves such serological differences as would justify the separation of any number of them into a class or classes, identical with each other and distinct from meningococci of cerebro-spinal origin. Consequently I can find no justification for the view that nasopharyngeal meningococci of the non-contact differ as a class from strains which might be found within the immediate environment of cases of the disease. The occurrence of such organisms in considerable numbers among the on-contact population, though unexpected, is in accordance with epidemiological experience that the majority of cases of the disease cannot be traced to a previous focus."

In volume 9 of the Medical Department of the United States Army in The World War published 1928 the following statements are made:

"The results of attempts to immunize normal individuals against meningococcus infections by means of specific vaccines were inconclusive." "Contact carriers isolated until their naso-pharyngeal cultures indicated that they were free from meningococci. Various antiseptics and anti-meningococcus sera were used locally, and vaccines were administered subcutaneously in attempts to eradicate meningococci from the upper respiratory tract. The results of such treatment were not of obvious value, but fortunately the carrier state in contacts was usually temporary and even without treatment over two-thirds of them cleared up in a short time. Many observers thought that, except in carriers with diseased tonsils, sinuses, or pharynx where surgical removal of the focus was indicated, it was best to rely chiefly on exercise, fresh air, and sunlight for treatment of the carrier state." "The isolation and treatment of these large numbers of meningococcus carriers proved to be a very difficult problem. They were kept in special wards, hospitals, or in segregation camps. Many antiseptics, including dichloromine T, tincture of iodine, silver nitrate solution, and others were used locally in the nose and throat. The injection of meningococcus vaccines or local applications of serum apparently had no specific effect upon meningococci in the respiratory passages. Although some observers claimed that certain antiseptics were effective, it can be stated that no generally satisfactory specific cure for the carrier state was found. Apparently, outdoor exercise and exposure to sunshine was about as effective as the use of drugs in the treatment of meningococcus carriers."

The results of attempts to immunize normal individuals against meningococcus infections by means of specific vaccines were inconclusive.

Theoretically, it should be possible to prevent the occurrence of meningitis by the isolation of all cases and carriers, but the experience of the World War demonstrated the futility of such a course in large, active military organizations. As a result, during the latter part of the war it was considered advisable to limit isolation and treatment to actual cases of meningitis and contact carriers and to attempt to keep down infection by paying particular attention to the improvement of the general living conditions."

G. A. McCoy, Director, Hygienic Laboratory, of the United States Public Health Service, in an article published in July 1929 has this to say of carriers, "Most carriers clear up within a few days regardless of what one does or does not do, and it remains to be shown that the process of recovery from the carrier condition can be hastened by any means now at our disposal."

"During the prevalence of infection carriers are very numerous. In a study made in Detroit recently it was reported that 46% of household contacts were found to be carriers, while as high as 6% of unexposed persons showed meningococci in the nasopharynx. Data of this sort lead one to realize the well-nigh hopeless nature of any attempt to control the carrier."

Frederick L. Gates in 1918 showed that the chronic meningococcus carriers may be relatively immune to epidemic meningitis because of the presence of specific antibodies in the blood. He found that the blood serum of the carriers would agglutinate meningococci.

In a letter to the Editor of the Lancet for February 24th, 1931 J. A. Glover has this to say about isolation of the carriers. "There are however many reasons to regard this procedure not only as not ideal but even as a vain endeavour. First it has been shown that, in an infected community in which multiple cases of cerebro-spinal fever are occurring, the carrier-rate will almost certainly be high. Secondly it may be assumed that there will be hundreds of carriers to every case, and that in large collections of individuals (in barracks, schools, etc.) living under similar conditions and circumstances (mainly of intimate contact if not of crowding) the carrier rate of so-called "non-contacts" will be equal to that of so-called "contacts". Thirdly, even if the necessary bacteriological facilities are available for determining whether the organism is a true meningococcus, it takes time to get the result of a swab, and all this time rapid transference of meningococci is taking place, so that, when the result is known, some carriers will have cleared up, whilst others will have become infected. Fourthly, one swab is not a conclusive test.

While therefore there may be some justification for isolating the infected institution or community as a whole from the outside world, it is not desirable to isolate those individual carriers who as "contacts" have been found positive. A procedure more useful than such isolation is to diminish the mass-infection in the community by (a) "spacing-out" of beds; (b) improving the ventilation; (c) prevention of any indoor crowding in canteens, etc, and possibly, but much less certainly, (d) by exposure of all the individuals of the community to an antiseptic vapour spray as was done on the large scale during the war. The only case in which any benefit is likely to accrue from the isolation of the individual carrier is one where there are special circumstances of contact, which enable the "casual carrier" to be identified."

"Another point in which my experience leads me to disagree is with regard to the utility of sniffing up liquid disinfectants whether a solution of chloramine T or other fluids. Such a procedure is not without risk, and I have never been able to satisfy myself that it had any beneficial effect upon the carrier state in chronic carriers. Temporary carriers in good hygienic conditions clear up so rapidly (even without treatment) that observations upon them are deceptive. A fine vapour spray using a solution of zinc sulphate 1.5 to 2% seems sometimes to have a beneficial effect, and at any rate to be without risk. If any other form of medication is used for the nose it is probably safest to administer it in the form of a finely divided oily spray."

During the World War A.J.Eagleton came to the following conclusions from a number of valuable experiments and states, "Experiments 1-8 show therefore that in the type of army hut investigated the bacterial content of the air during sleeping hours is very high and that the air throughout the hut is uniformly infected." Experiments 11 thru 16 were done with meningococcus carriers. "The conclusions to be drawn from the above experiments, limited as they are, seem to be the following:

- (1) In the ordinary infantry sleeping hut, there is a stagnant well of infected air in which the men sleep.
- (2) This dead space extends up to 8 feet above the ground level.
- (3) The wider the hut and the lower the temperature, the better the condition of the air.
- (4) More adequate ventilation is needed; probably this could be obtained by ground ventilation.
- (5) The meningococcus can be carried at night from a carrier to his neighbors unless the bed space is more than 5 feet.
- (6) The spraying capacity of a carrier varies between 5 and 15 feet, but is 5 feet during ordinary sleep.
- (7) The meningococcus is carried in the spray to a much shorter distance than many other organisms."

MODE OF INVASION

Stillé makes this statement on page 125 of his book, "All other epidemics are propagated more or less, and either directly or indirectly by contagion, however much atmospheric conditions may favor their diffusion. But epidemic meningitis and influenza appear to proceed, primarily and alone, from some unknown constituents or conditions of the atmosphere, or some conjunction of terrestrial causes, the nature of which at present eludes our comprehension altogether, and about which it is an idle waste of words to speculate."

W.C. Deming in an article in 1930 brings out the known point again that the soiled finger will convey infection into the eye. "It is asserted, and the writer believes with truth, that the hands are more massively soiled with infective agents in acute diseases of the upper respiratory tract than any other vehicle of contagion, especially in ambulatory patients.

Whether this is verified or not, the utmost stress should be laid on frequent hand washing, on avoiding contact of the hands with the mouth, nose, and eyes, and on avoiding contacts such as hand shaking, food and dish handling with unwashed hands, at any time."

The editorial department of the New England Journal of Medicine for January 2, 1930 discusses W.E. le Gros Clari's findings in his Report to the Committee on Vaccination on an Anatomical Investigation into the Routes by which Infections may pass from the Nasal Cavities into the Brain, and states, "Using Weed's solution, he injected material into the nasal cavity of live animals; examination of the brains histologically within a few hours demonstrated clearly that the granules of Prussian blue passed upwards by way of the perineural sheaths of the olfactory nerves and reached the surface of the brain within one hour. He produces evidence to show that the perineural sheaths of the olfactory nerves are continuous above with the sub-arachnoid space and extend peripherally along the fibres of the olfactory nerves to the olfactory sensory epithelium. He also postulates the existence of a current passing upward from the nasal mucous membrane. Evidence was found, moreover, to support the idea that material might pass upwards by other pathways than by the perineural sheaths of the olfactory nerves, by way for instance, of the blood vessels piercing the cribriform plate in company with the olfactory nerves and by direct propagation along the protoplasmic axis cylinders of the nerve supplying the peripheral infected areas. He found no evidence to support the old proposition of Key and Retzius that the subarachnoid space was in direct communication with the lymphatic vessels of the nasal mucous membrane."

A. Sophian in an article published in 1929 says, "It is accepted that the nose and the throat are the portals of entry of the meningococcus, and that nasopharyngitis predisposes to infection. Many consider that every case of meningitis is first a case of meningococcus pharyngitis

and this has been proven in many instances. Meningococcus tonsillitis has also been described.

Invasion by the meningococcus from the nose and throat is believed to be affected in one of two ways---by the primary invasion of the blood stream causing a meningococcus septicemia with secondary localization in the meninges, or by direct infection from the nose through the lymphatics.

It was at first suggested that the meningococcus reached the meninges by direct extension upward, through the cribriform plate of the ethmoid; later it was suggested that the course was through the sphenoid, it being shown in a study of 39 cases that only 2 had inflammation of the sphenoidal sinus. It was suggested that after the sinus became infected the suppuration might readily extend through the thin lamina of bone over it. The localization of the exudate at the base in the region of the hypophysis was considered significant, but similar localization has been found in secondary meningitis as from the ear and in tuberculous meningitis, and a like localization occurs in experimental meningitis in the monkey.

Most of the evidence points to the primary blood infection as the probable channel. The clinical and laboratory evidence to be discussed later is entirely confirmatory.

Meningitis is disseminated through the medium of healthy carriers."

Harold L. Amoss and Frederick Ebersson in 1919 stated, "That the portal of entry of the meningococcus into the body is the mucosa of the nasopharynx is generally admitted. The point which has not been settled is whether the meningeal invasion is lymphatic or hematogenous. The most direct route would be along the lymphatics of the olfactory filaments to the meninges of the base of the brain; but no convincing evidence has been brought forward for that mode of invasion."

"Up to the present no satisfactory solution of the problem of the mode of infection in epidemic meningitis has been secured, and not considerable additions to our knowledge of the subject have been made since the pandemic of 1905-10."

Sir Humphry Rolleston in 1919 classified the invasion in this manner,

"The Path of Invasion.

- (1) Direct invasion via lymph.
- (2) Lymphogenous infection along spinal nerve roots.
- (3) Invasion of the bloodstream from the portal of entry in the nasopharynx. First, nasopharyngeal entry; second, general hemic infection and third, localization in the central nervous system.

CAUSE OF DEATH

The cause of death has been thought to be:

1. Toxemia.
2. Respiratory failure---due to cerebral hyperemia and edema.
3. Local cerebral sepsis.
4. Hydrocephalus.
5. Bronchopneumonia.

DAY OF DEATH

Stillé on page 103 says, "Thus Niemeyer states that life is most endangered during the first four days of the attack. Out of 38 deaths, 23 took place within that period. The conclusions drawn by Parks from his careful analysis, are, "first, the prognosis, during the first few days, at least, is grave; secondly, after four or five days have elapsed, if fatal symptoms be not present, the prospect becomes more hopeful; thirdly, the patient is not safe, even in convalescence, since there have been instances of fatal relapse."

In 1919 Sir Humphry Rolleston stated, "Out of 86 deaths among 225 naval cases during the third and fourth years of the war 17 occurred within the first two days or were fulminating cases, eight on the third and 12 on the fourth day, so that 37, or 42% of the deaths occurred within the first four days. Three deaths occurred on the fifth, 5 on the sixth, and 2 on the seventh day, so that 47, or more than half the cases, were fatal within the first week. During the second week there were 15 deaths, during the third week 12, during the fourth and fifth weeks 3 each, 2 in the sixth week, 1 in the seventh week, and isolated cases on the 57th, 67th, and 90th days of the disease."

Vaughan on page 534 of his book states, "Of 20 fatal cases reported by this author, seven died within 24 hours, 5 within 48 hours, 3 in 72 hours, and the remaining 5 from the third to the seventh day. Fish says that death took place usually between eighteen hours and seven days, but he reports instances of patients dying after 12 days. In reporting an epidemic in Vermont, Fassett states that in no case did recovery take place in less than from 3-5 weeks, and Ketchum, reporting on other patients in the same epidemic, states that several died after 5 or 6 weeks. Tourdes says that the disease is distinguished by the slowness of recovery and the rapidity of fatal issue, and Hirsch adds that its duration is between a few hours and several months. Relapses are not infrequent."

George H. Garrison in an article published in 1929 states, "A more straining reduction in mortality occurs, however, when we consider the patients surviving the first 48 hours after admission. Of the 89 deaths in the first group, 38 occurred within the first 48 hours after hospitalization, and 51 occurred later. Of the 59 deaths in the second group 34 died within 48 hours after admission to the hospital, and 25 died after that interval. In the first group this mortality is 41% and in the second group 15%. We believe that this reduction in mortality is due to the more intensive treatment received in the first 48 hours after hospitalization. Undoubtedly there has been gradual improvement in the serum during the ten years but the combined mortality rate from 1916 to 1926 inclusive is in excess of 50%, and the abrupt drop to 30% came in 1927 coincident with the more intensive treatment."

M.A.French in reporting 383 cases of Meningococcus meningitis in the city of Milwaukee says, " The first few days of illness were the ones of greatest danger for the life of the patients, for 60% of all deaths occurred during the first 6 days of illness. The largest number of deaths occurred in the 3d day, followed closely by the 1st, 6th, 3d, 4th, and 5th days. Deaths continued to occur, however, during the following days, decreasing as the number of days of illness increased.

No recoveries were reported until the 12th day of illness, and from that time on through the 35th day over 77% of all recoveries had taken place. The largest number of recoveries were from the 21st to the 26th days of illness. However, recoveries continued to be reported for as long as 60 days and over from date of onset."

DIAGNOSIS

Henry Heiman and Samuel Feldstein on page 208 of their book on Meningococcus Meningitis state, "Symptoms that speak for the presence of meningitis pure and simple are: Fever, rapid pulse and respirations, headache, vomiting, convulsions, delirium or unconsciousness, restlessness, pupillary changes, mydriasis on flexion of the head or irritation of the skin, strabismus, facial paresis, hyperaesthesia, rigidity of the neck and spine, retraction of the head, orthotonus or opisthotonus, tache cérébrale, bulging fontanelle or Macewen sign, Kernig sign, Brudzinski's signs."

The most important of these are hyperaesthesia, bulging fontanelle in infancy or Macewen sign in older children and adults, mydriasis on attempted flexion of the head or irritation of the skin, rigidity of the neck, retraction of the head, Kernig sign, and Brudzinski's signs."

"Sources of Diagnostic Error.---Failure to make a correct diagnosis of the disease is chiefly attributable to two facts: (1) Absence of one or more of the characteristic symptoms of the disease; (2) prominence of one or more symptoms that are more characteristic of some other disease. In cases belonging to the first class, we are misled by the non-appearance of one or more of the following symptoms: fever, psychic disturbances, rigidity of the neck and Kernig sign.

Cases are described in the literature in which the temperature was normal during the first few days of the disease. Indeed in the older descriptions of the disease, before clinical thermometry came into general use, there is frequent mention of the fact that fever was quite often absent. In the subacute and chronic cases prolonged periods of apyrexia are quite commonly seen.

Psychic disturbances are at times so slight that they are easily overlooked. The patients are apparently rational and answer questions quite intelligently. This is the more striking when we consider the gravity of the condition and the marked lesions which may be present in the meninges, brain, and cord."

Michael Foster and J. F. Gaskell (1916) on page 28 of their book state, "With perfection of the technique of lumbar puncture it became possible to recover the meningococcus from the cerebro-spinal fluid at an early stage of the disease. An early diagnosis and the institution of specific treatment are thus secured by one and the same procedure. The question to be determined, therefore, is what cardinal symptoms are sufficiently suggestive of the disease to justify the immediate performance of lumbar puncture. A sudden onset, probably accompanied by a rigor, headache gradually increasing in intensity, and vomiting occurring within the first 24 hours, point towards meningitis, but are common to other infections. The absence of herpes or a macular rash is of slight value: these do not appear until the third to fifth day, and to wait for confirmation

from their appearance might mean fatal delay. The presence of a petechial or purpuric rash, which may appear in the first 24 hours, leaves so little doubt as to justify immediate lumbar puncture. Haemophilia must be excluded, as lumbar puncture has been performed on a case of this disease with meningeal haemorrhage, the difficulty in arresting bleeding first calling attention to the true nature of the case. Head retraction is variable in the date at which it makes its appearance, and much stress should not be laid on its absence. The cervical muscles should be carefully examined for any tenderness or stiffness; if this is present, the probability in favour of meningitis is increased. The value of Kernig's sign in all adult cases cannot be over-estimated. This value lies firstly in the date of its appearance,---it may be only slightly marked at the end of 18 hours, but is usually fully developed at the end of 24; and secondly in the fact that it is never present in its fully-marked form in other affections liable to be mistaken for meningitis. Kernig's sign is common to all forms of meningitis of whatever origin, but its presence is a powerful factor in determining the necessity for immediate lumbar puncture. Retention of urine is an important symptom to be taken into account. It occurs in a large proportion of cases, many of which are comparatively mild ones. Further, it may make its appearance at the end of 24 hours, and is an uncommon symptom at this early stage in other febrile affections. The presence of this symptom should be given great weight in estimating the relative values of the clinical aspects of the case. Early delirium, especially when associated with the persistence or indeed aggravation of the headache, tends further to differentiate the case from other acute infections. To sum up: a patient who has been seized with sudden illness ushered in by a rigor, accompanied by severe headache rapidly growing worse and soon accompanied by vomiting, may be regarded as a suspicious case. When Kernig's sign is present, and there is some pain and stiffness of the muscles of the neck, and if retention of urine occurs, the probabilities are sufficiently great to justify lumbar puncture. Delirium going on to coma, the presence of petechial rash, or of head retraction, would merely confirm these probabilities."

Josephine B. Neal in volume 6 of Abt's Pediatrics (1925) states, "The principal symptoms and physical signs to be considered in studying meningitis are the following:

1. Temperature, pulse, respiration.
2. Headache.
3. Stiffness of neck.
4. Kernig's sign.
5. Brudzinski's sign.
6. Convulsions.
7. Paralysis or paresis.

8. Mental condition; unconsciousness, stupor, delirium, irritability.
9. Gastro-intestinal condition; vomiting, diarrhea, constipation.
10. Bladder; retention, suppression.
11. Reflexes; normal, increased, diminished, lost; equal, unequal.
12. Eyes; pupils---equal, unequal, dilated, contracted, reaction to light. Nystagmus, strabismus, ptosis, conjunctivitis, iritis, keratitis, hypopion, disturbances of vision, diplopia, loss of acuity, etc.
13. Ears; hearing, discharge.
14. MacEwen's signs or bulging fontanelle.
15. Eruption; hemorrhagic, herpetic miscellaneous."

"Temperature.---The temperature curve in epidemic meningitis is characteristic, in that it is practically always irregular and has little relation to the prognosis. It varies greatly in different cases, and even in a given case it does not follow any particular course. The temperature at the onset is almost invariably elevated, from 102 to 105 degrees, and it ordinarily remains elevated usually with remissions every few hours during the course of the disease, falling by lysis as the patient improves. Rarely a case is practically afebrile throughout a long and tedious illness."

"Pulse.---The pulse is usually increased in rate, though often not in proportion to the temperature, is regular in rhythm and of good volume and tension."

"Respiration.---The respiration is often of the Biot type, showing marked variation in the rate and depth. The rate is usually increased in proportion to the temperature. In very severe cases the Cheyne-Stokes type often develops near the termination."

"Headache and Other Sensory Disturbances.---Severe headache is an almost constant symptom in patients old enough to indicate their sensations. It is often diffuse, but it may be localized in the occipital or frontal region. The pain is usually very intense. A measure of relief is afforded by lumbar puncture in most instances. Pains in the limbs, except following the injection of serum which frequently causes some pain in the legs, is not very common. There may be pains in the back, especially in the cervical region. Patients are frequently hyperesthetic and sensitive to light."

"Hypertonicity of Muscles and Motor Disturbances.---One of the most marked and characteristic symptoms of the disease is increase in muscle tone. This shows itself in various ways: First, the stiffness in muscle tone. This is almost constantly present in patients over a year old. It varies from a slight anteroposterior stiffness to retraction with almost complete fixation of the head.

The retraction may be so great that swallowing is impossible. Another manifestation of this hypertonicity is opisthotonus, which often develops in serious and prolonged cases, especially in posterior basic types. The Kernig's sign is a third manifestation." "This sign unless well marked, has seemed to us of much less value than the stiffness of the neck. It is often absent or difficult to determine in young children, and few adults who are not very athletic fail to show some resistance to complete extension. The Kernig's sign is usually equal on the two sides. To the same cause is doubtless due the Brudzinski neck and leg signs. The neck sign is the more valuable. Indeed, in young children, it is often of more value than the Kernig or the stiffness of the neck." "Convulsions are rather common in young children, but as they occur with so many other diseases they are not particularly diagnostic. In adults and older children, they occur only in the severest cases."

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"Paralyses are rare, but they may occur. They may be very fleeting." "Paralyses of the eye muscles are the most frequent."

"Mental Condition.---The mental condition is subject to the widest variations. In rather mild cases, the mentality may be practically normal throughout the course except for some irritability and restlessness. In more severe cases active delirium may develop early, sometimes clearing up with the first dose of serum. In other cases, when recovery is slower, it lasts longer and may recur at intervals. In unfavorable cases, the delirium is usually succeeded by stupor, progressing to coma."

"Gastro-intestinal Symptoms.---Vomiting almost constantly occurs early in the disease and may be very persistent for the first 24 to 48 hours. It is generally not projectile in type though it is not often associated with nausea. It usually clears up with the institution of treatment, but in untreated cases it often recurs periodically."

"Bladder Symptoms.---Retention is an occasional symptom and from it cystitis may develop."

"Reflexes.---The patellar reflex is often increased early, becomes lost as the disease progresses and returns during convalescence. It may, however, remain normal throughout the illness. The cutaneous reflexes are not of great value."

"Mac Ewen's Sign and Bulging Fontanelle.---An increased pressure in the lateral ventricles, especially in children after the closure of the fontanelle, is indicated by a change in the percussion note over the lateral ventricle." "We have not used this method." "Before the fontanelle is closed, the use of the sign is not indicated, but the absence or presence of a bulging fontanelle is an almost infallible indication of the state of pressure of the spinal fluid. It is not absolutely infallible because on several

occasions a lumbar puncture revealed increased pressure although the fontanelle did not bulge."

"Eruptions.---Herpetic and hemorrhagic eruptions are the most frequent. Herpes, while varying in different epidemics, occur more frequently than any other eruption except in the septicemic type of meningitis in which the hemorrhagic rash is nearly constant."

"Most of the conditions relating to the eye and ear seem to belong to complications rather than symptoms and are described under that heading."

"While it seems undesirable to attempt to classify the disease too closely and to assign symptoms to the various classes, it is necessary to call especial attention to the fulminating and septicemic type and to the indefinite symptoms of the disease in infants."

J.B.Neal in a recent article published in February 1931 states, "In very young children the early signs and symptoms of meningitis indicate a disturbance of the gastrointestinal rather than of the central nervous system. The disease begins rather abruptly, often with vomiting, almost invariably with greenish slimy stools, irregular fever, and irritability. The fontanelle practically always shows increased pressure. The child does not respond to the ordinary methods of treatment for gastroenteritis, but it is not until the disease is fairly well advanced that stiffness of the neck, opisthotonus and changes in the reflexes develop. The case therefore is usually diagnosed and the serum treatment is begun late in the disease. It is for this reason, I believe, that the mortality in the first year of life is so high. Our mortality has been about 45%. Debré said: "In times of epidemic think of meningitis and do a lumbar puncture on every infant sick without apparent cause." It is even more important in our opinion to do this when there is no epidemic.

Whenever a patient shows signs of meningeal irritation, there should be no delay in doing a lumbar puncture. It is only by the examination of the spinal fluid that a definite diagnosis can be made. The symptomatology of all forms of purulent meningitis are so similar that the bacteriological examination of the spinal fluid is essential for the diagnosis."

Volume 9 of The Medical Department of the United States Army in the World War (1928) states, "The specific diagnosis of cerebrospinal meningitis depends upon the isolation and identification of the meningococcus from the cerebrospinal fluid. During the World War, spinal punctures usually were performed on all patients with symptoms of meningeal irritation or inflammation; and the diagnosis was based entirely on the bacteriological examination of the spinal fluid. Wegeforth and Latham, however, warned against the indiscriminate use of spinal puncture as a diagnostic procedure in human septicemia, stating that the release of spinal fluid was an important factor in the development of meningitis. This observation was preceded by the investigations of Weed, Wegeforth, Ayer, and Felton, who showed that in

animals suffering with an experimentally produced bacteremia, spinal puncture was invariably followed by meningitis. It was therefore recommended that careful consideration be given to the bacteriological study of the blood before attempting puncture of the spinal canal. However, in spite of the fact that cases were observed in which the spinal fluid obtained at the first puncture was sterile and from later punctures infected, this was usually considered only an indication of the normal progress of the infection; and it was quite generally believed that diagnostic spinal puncture in meningitis was not attended by any serious results.

The observations of previous workers that meningococci may invade the blood stream were confirmed during the World War by Herrick. He reported that in a comparatively large percentage of the cases at Camp Jackson, S.C., the organism was isolated in cultures made of the blood before the appearance of meningeal symptoms; and, as a consequence, he advocated the more general use of blood cultures as an aid to early diagnosis, and proposed that the term "meningococcus sepsis" be used.

In most cases it is possible to isolate the meningococcus from the upper respiratory tract, and nasopharyngeal cultures may be helpful, when meningococci in a turbid spinal fluid escape detection. During the World War nasopharyngeal cultures were used mainly in the detection of carriers, but occasionally as an aid in the diagnosis of cases.

The symptomatology of cerebrospinal meningitis observed during the World War did not differ materially from that already recognized as characteristic of the disease. Naturally, differences occurred in the percentage of severe and mild cases in the various camps, resulting in variations in the predominant clinical signs and symptoms."

A. Sophian in an article published in 1929 states, "In the early stages especially, the characteristic feature of the disease is a hyperactive, hypersensitive mental state, frequently undisturbed except for occasional periods of delirium. As hydrocephalus increases in the later stages of the disease, the patient becomes stuporous and later comatose. Even when stuporous however the patient will respond upon being disturbed.

The symptoms above described include some of the more important ones of sepsis in acute meningitis. The symptoms next to be considered are those due to (1) meningeal irritation and (2) hydrocephalus (accumulation of fluid within the ventricles).

Headache is constant and a bitterly complained of symptom throughout the whole course of the disease. It is most often referred to the frontal region or vertex. Sometimes, especially in women, it is localized in the occiput. The patient protests that his head is splitting and begs for relief, even asking for lumbar puncture if relief had already been experienced by that means.

Photophobia is a common and annoying symptom from the very onset.

Convulsions are noticed most often in young children in whom they may usher in the disease. They are absent in many cases of older children and adults. Where the disease is progressing unfavorably and is accompanied by a steadily increasing hydrocephalus, general clonic and tonic spasms frequently occur. At the onset of meningitis, convulsions are usually general and clonic in character. Later in the disease local spasms lasting for hours. In children under one year of age convulsions are of very significant importance. If tetany can be excluded one should be very suspicious of meningitis.

Twitching is observed most often late in the disease and acts much the same way as the local convulsion.

General bodily pain grippal in character is quit common at the onset. With the development of more active meningeal signs, pain is referred principally to the back of the neck and along the spine.

Rigidity of the neck is one of the most important diagnostic symptoms. It is an early and constant sign, persisting throughout the entire course of the disease. In the very early accumulative stage rigidity of the neck is absent, or there may be a little anteroposterior spasm on attempting to flex the head. As active meningitis sets in, the neck becomes rigid and fixed, and attempts to move the head in any direction are resisted and cause considerable pain and spasms of the posterior group of neck muscles. A good way to test this sign, especially in young children, is to place the hand under the occiput and raise the head gently. If rigidity be present, one can usually raise the head and trunk without flexing the neck. Varying degrees of retraction of the head accompany the neck rigidity. At times, chiefly in the cases of posterior basic meningitis, there is extreme retraction of the head, the occiput almost touching the spine. The rigidity of the neck, the spasm and retraction of the head usually subside with improvement in the disease. There is a "limbering-up" of the neck muscles, and the patient begins to move around, at first very cautiously, then freely. Not infrequently however the rigidity of the neck with opisthotonos persists well into convalescence and disappears very slowly. There seems to be a considerable element of fear that prolongs the spasms in these cases. In the last moribund stage of the disease there is complete relaxation of the neck as elsewhere.

Rigidity and bowing of the spine go hand in hand with the rigidity of the neck.

Tenderness on pressure at the angle of the jaws is an early sign of some diagnostic importance.

Kernig's sign, like the neck sign, is a very early and constant symptom and is of very considerable relative diagnostic significance though present in other forms of meningitis. It is of little value in children under two years. The test is made by flexing the thigh on the abdomen, then attempting to flex the leg on the thigh. In most normal individuals the legs can be fully extended though in some this can be but partially accomplished. In such instances however there is a sudden sharp spasm of the hamstring muscles accompanied by acute pain referred

usually to the back of the leg and thigh, sometimes to the lumbar region. Thus, in meningitis cases during the active stage it is often impossible to extend the leg more than at right angles. I have tested this sign several thousand times in meningitis cases and have found it positive in 95%. As the disease declines, the sign becomes less pronounced. In the last moribund stages there is relaxation here as elsewhere in the body.

Vasomotor Phenomena.---Tache cérébrale is an erythema that appears quickly on slight irritation of the skin, well obtained by gently scratching the skin. This sign is only of minor relative diagnostic importance. Other vasomotor phenomena, such as spontaneous flushing and perspiring of different parts of the body, are commonly seen, especially in cases with marked hydrocephalus. Vomiting occurs in most cases at the onset. The characteristic feature is the fact that it appears causeless, that nausea and other evidence of gastro-intestinal disorder are usually absent. As hydrocephalus increases, vomiting becomes projective and almost uncontrollable. Bowels are often very constipated. Pupils are most often dilated, sometimes irregular, responding sluggishly or failing to respond to light.

Severe Pressure Phenomena: Pulse.---The pulse rate in meningitis is very irregular and is apparently independent of the amount of intracranial tension, temperature, or general condition. At times it is very slow, fifty or under. Most often it is rapid, averaging over one hundred. It is astonishing how comfortable and in what seemingly good condition patients having a tachycardia up to 160 will appear. Irregularity and intermitting of the pulse are early signs of considerable diagnostic value.

Irregularity in Respiration.---Respiration is most markedly affected by increasing intracranial tension. Many observers have studied this important change. Biot in 1878 described a type of respiration which has since been called Biot's breathing and by older authorities cerebral breathing. He considered the breathing to be characteristic of meningitis as against other cerebral conditions with respiratory disturbance. According to Biot, the "meningitis rhythm" lacks the rhythmical alterations of periods of apnea and periods of gradually increasing and decreasing respiratory movement which are the essential feature of the Cheyne-Stokes' type. The respiratory pauses occur at irregular intervals and the individual respiration showed variability as to both size and rate.

Connor and Stillman studied 43 cases of meningitis, making graphic tracings of the respiratory movements. Thirty-two of the cases were tuberculous meningitis, and respiratory irregularities were observed in all at some time during the illness, usually during the greater part of it. Of the remaining eleven cases, six were of

the epidemic type, four being secondary streptococcus meningitis and one acute syphilitic basilar meningitis. Two of the cases, both epidemic meningitis, failed to show the respiratory irregularities. One was a very mild case recovering in a few days and the other was a child who was very restless and had constant twitchings making it impossible to get satisfactory tracings. According to these authorities, respiratory irregularities appear early in meningitis. They divide them into the (1) Cheyne-Stokes' type; (2) Biot's meningitic type; (3) and undulatory type.

Cheyne-Stokes' type was observed in 53% of the meningitis cases. Biot's breathing also occurred in 27% of these cases.

Biot's breathing is characterized by: (1) Periods of apnea of varying length and occurring at irregular intervals; (2) constant irregularity in the rhythm and in the force of the individual respirations; (3) the frequent occurrence of deep, sighing respiration.

Biot's breathing was encountered twice as frequently in adults as in children, while the Cheyne-Stokes' type was present almost twice as often in children as in adults.

Connor and Stillman particularly call attention to the occurrence of deep sighing, saying that in their experience it is rare in conditions other than meningitis. It was observed in a great many cases and was of considerable diagnostic significance.

The undulatory type differs from the other two types of breathing in that the apnea does not constitute a feature. This form of respiratory disturbance was seen at some time in the course of almost every case.

In discussing the diagnostic value of respiratory irregularities in meningitis, they state that irregularities occurred in 95% of cases of meningitis studies. Of the three types of arrhythmia, Biot's is unquestionably the most nearly pathognomonic of meningitis. In making tracings of several hundred patients, both adults and children, suffering from different diseases, they met it in only one case not meningitis. Most of the respiratory irregularities observed occurred when the patients were in a state of stupor or coma, but there were a number of exceptions to this rule.

The incidence of Biot's type in the tuberculous cases was distinctly less than in the non-tuberculous cases, there being five instances of it among the 32 tuberculous cases, 4 or 30% among the 13 adults and 5, or 17% among the thirty infants and children.

In a very large experience with epidemic, tuberculous and other forms of meningitis, I have always considered respiratory irregularity an important diagnostic and prognostic symptom. It has usually been absent in cases without appreciable hydrocephalus, i.e., in cases with little fluid. I have found it to be one of the most significant signs of hydrocephalus, indicating lumbar

puncture for relief of pressure. The most common irregularity occurring early in the disease has corresponded to the undulatory type described by Connor. Biot's type, usually called cerebral breathing, is of very considerable prognostic importance. I have seen it frequently in all types of meningitis but never in any other disease. It occurred late in the disease and was usually indicative of a hopeless outlook. Of several hundred cases that I studied I have record of only one case of epidemic meningitis that recovered after this type of breathing developed.

Bulging of the fontanel in young children occurs with hydrocephalus and is the most important physical sign of this condition. The fontanel is full, sometimes extremely tense. Crying causes the fullness to become more pronounced. Regular pulsation may be present. External heavy pressure over the bulging occasions considerable pain; if continued it produces stupor, convulsions, respiratory pressure symptoms, and death. Macewen's sign is of the same significance as the bulging fontanel."

TREATMENT

For the reasons stated under the mortality study the majority of the figures showing the effectiveness of serum therapy in meningitis, are worthless and for that reason only the treatment used by the New York City Department of Health is considered to be controlled satisfactory enough to demonstrate the effectiveness of the serum therapy.

Dr. William Park in January 1931 made the following statements, "During the past twenty years, fashions have changed from time to time in the method of administering the serum. In the earlier days, the serum was given intraspinally once in 24 hours for four doses and for a longer time if the fluid did not become sterile. A rather moderately sized dose of serum, about 20c.c. was advised at that time. Since then certain workers have advocated a more intensive method of treatment. They have administered the serum intraspinally every twelve, eight, six or even four hours. It has also been recommended that the serum be given intravenously or intramuscularly or both in all cases in addition to the intraspinal administration. This intensive method of treatment was greatly in vogue during and shortly after the war, but a study of the mortality in certain institutions where this method was carried out, has been very unconvincing as to its value. Indeed, the mortality of cases thus treated has been generally much higher than those treated more conservatively."

Josephine B. Neal in an article published in February 1931 she states, "Antimeningococcus serum has been accepted in the treatment of meningitis for about 23 years, and for more than 20 years its use has been very general. It seems a little strange that in spite of this long period there should still be so much difference of opinion in regard to its proper administration with respect to route, frequency and amount. There are several reasons why this is so. One reason is no doubt the fact that at times serum of poor quality has been used, and in an attempt to save life it has been given in large and frequent doses when a more conservative treatment had been ineffective. When this more intensive treatment also failed, the physician knew little more than before in regard to the relative merits of the two methods. Another reason, is no doubt, that the type of the disease has differed quite markedly in different outbreaks. In certain outbreaks the septicemic form of the disease has been very common. In perhaps the majority of cases, this form is relatively rare. A third reason probably lies in the fact already stated, that each case of meningitis must be studied and treated more or less on its own merits. One can therefore gain a comprehensive view of the disease only after quite extensive experience. It is a great mistake to draw conclusions

from the observation of only a few cases.

Our opinion in regard to the treatment of meningitis is based on an experience of 20 years with more than 1,000 cases. During this time we have compared our results with those obtained in institutions where more radical methods of therapy were employed. Our method is usually as follows: whenever lumbar puncture yields a cloudy or hazy fluid, antimeningococcic serum warmed to body temperature is immediately administered by gravity. Further serum treatment will depend on the cultural examination of the fluid, but all cases of purulent meningitis are treated as being of the meningococcus type until they are proved to be caused by some other organism. Intraspinal administrations of serum are continued about every 24 hours until at least two successive specimens of the fluid show no organisms by smear or culture.

The dose of serum is usually 20c.c. if as much or more fluid has been obtained. If the amount of fluid withdrawn is great and the serum runs in easily by gravity, without untoward symptoms on the part of the patient, 30 to 40c.c. may sometimes be administered. On the other hand, in certain instances when only a small quantity of fluid is obtained we may inject more than the amount of fluid withdrawn provided the serum runs in easily and no unfavorable symptoms result. It is desirable to drain the subarachnoid space as completely as possible before injecting serum, but if the fluid is under greatly increased pressure, care should be taken to withdraw slowly. Using this precaution, 50 to 60 c.c. or more of fluid may be safely withdrawn. If headache develops during the removal of the fluid, it usually quickly disappears when the serum is injected. Almost the only condition under which we inject serum oftener than once in 24 hours is when the fluid is under so greatly increased pressure that a puncture at more frequent intervals seems indicated to relieve it. This rarely occurs.

Some physicians have recommended graduated doses of serum for young children, depending rather arbitrarily on the age. We have not found this necessary. We depend rather on the amount of fluid withdrawn and the ease with which the serum runs in by gravity in determining the size of the dose, but it is necessary to exercise more than ordinary care in removing fluid and injecting serum in young babies.

It is rarely safe to give fewer than 4 doses of serum. A case of average severity will require perhaps from 6 to 8 doses, and cases are occasionally seen where 20 or more are necessary before the fluid becomes sterile. As stated, the serum treatment is continued until 2 successive fluids are free from organisms. This is by far the most important indication for stopping treatment. Another indication, of less value, is the return to normal of the spinal fluid sugar. The cell count of the spinal fluid is, by itself, of comparatively little value. When two sterile

spinal fluids have been obtained it is usually safe to stop the serum treatment, temporarily at least. It is often necessary to do several lumbar punctures during convalescence for the relief of pressure, and these fluids should be carefully examined and cultured, as the return of organisms would indicate additional serum treatment. I have emphasized the laboratory tests as a guide to the administration of the serum, as it is rare indeed that the clinical picture is not accurately reflected or even predicted by the changes in the spinal fluid. If, however, the symptoms do not improve after the fluid becomes sterile, and the serum has been temporarily discontinued, it is well to resume the injections, as they may be due to a localized meningitis with adhesions which may be favorably influenced by the continued use of the serum.

If signs of blocking develop, recourse should be had to ventricular or cisternal punctures and the administration of serum by these routes. In babies where the fontanelle is still open, ventricular puncture is to be preferred to cisternal as it is less dangerous and more certain of success, since the block is quite as likely to be above the cistern as below it. We have occasionally encountered cases where little or no fluid has been obtained by lumbar puncture and yet serum has run in easily by gravity, and there have not been signs of increased pressure. Several such cases have made satisfactory recoveries without resorting to ventricular or cisternal punctures.

We are, perhaps, more conservative than many in doing ventricular or cisternal punctures. I have never seen any immediate harm follow a ventricular puncture. On the other hand, comparatively few babies where this treatment has been necessary have recovered. I do not believe that we know at present what may be the after effects of repeated trauma to the brain tissue. As regards cisternal punctures I do know that death has occasionally followed promptly, due to hemorrhage. It seems unfortunate that these fatalities are not reported, as we not infrequently read accounts of large series of cases without accident written by physicians using this technic in patients with syphilis of the central nervous system. The dangers are much greater, I believe, when there is an active inflammatory process with layers of adhesions in the neighborhood of the cistern, as is likely to be the case in meningitis. Cisternal punctures should be attempted only by those who have had adequate practice on the cadaver.

In regard to the intravenous or intramuscular injection of serum, we believe that this is indicated only in cases of meningococcus septicemia without meningitis, or in those cases of meningitis which show a prolonged invasion of the blood stream by the organisms as indicated by repeated positive blood cultures or a rash that shows a tendency to persist or recur. While it is probable that in practically

all cases of meningitis there is an invasion of the blood stream early in the disease, we think that in the very great majority of cases this invasion is transitory and that injections of serum other than intraspinally are unnecessary. In some instances this has been proved by blood culture and in many more it has been very definitely established by the rapid fading of the rash and the clinical improvement of the patient. The intravenous administration of serum is not without danger, as a severe or fatal reaction occasionally follows. Several such instances have been brought to our attention. Certainly patients tolerate serum much better by the intraspinal than by the intravenous route.

In cases that run a chronic course and in the occasional case that does not tolerate serum, we have used an autogenous vaccine, often with apparently good results. We have given the vaccine both subcutaneously and intraspinally. We are not prepared to claim too much for it as in some cases no benefit has followed its use. My colleague, Dr. Applebaum, has recently reported a case in which an autogenous vaccine was administered both intraspinally and subcutaneously after sensitivity to serum developed. The patient recovered.

The general treatment and nursing of patients with meningitis are most important. They should be disturbed as little as possible and if they are restless, sedatives must be administered. Adequate nourishment should be given and the fluid intake must be sufficient. Care should be taken to prevent acidosis. Retention sometimes occurs, so that catheterization is necessary. Constipation is the rule and enemas or high colonic irrigations are better than purgatives."

"Meningitis is certainly a very serious disease and every effort should be made to produce a more effective serum. We have done some experimental work in producing an antibody. The results are encouraging but the preparation of the antibody is still in an experimental stage."

"The response of many patients to serum treatment is almost spectacular and the results are highly gratifying."

Augustus Wadsworth in an article of February 1931 states, "Perhaps the most striking instance of the comparative potency of the 6-strain serum which we are now distributing is to be found in the report on a series of cases treated at the Post-Graduate Hospital in New York City by Wright, DeSanctis, and Sheplar. These came from one district in New York City and were evidently severe. The first 10 were treated with different commercial and other serums. All died. The remaining 34 received this 6-strain serum, with only 4 deaths: 2 were moribund when

treated and 2 developed pneumonia. It is important to note that subsequent experience indicated that conditions relating to the character and severity of the cases had not changed, nor had the relative effectiveness of the serums which were substituted at intervals when the distribution of the 6-strain serum to the hospital was withheld. However, a much larger number of cases treated under as uniform conditions as possible is required to obtain significant comparative results."

"The clinical reports, the statistical comparisons of the mortalities in large series of cases, and the results of comparative testing in the laboratory all indicate the advance that has been made in the preparation of antimeningococcus serum."

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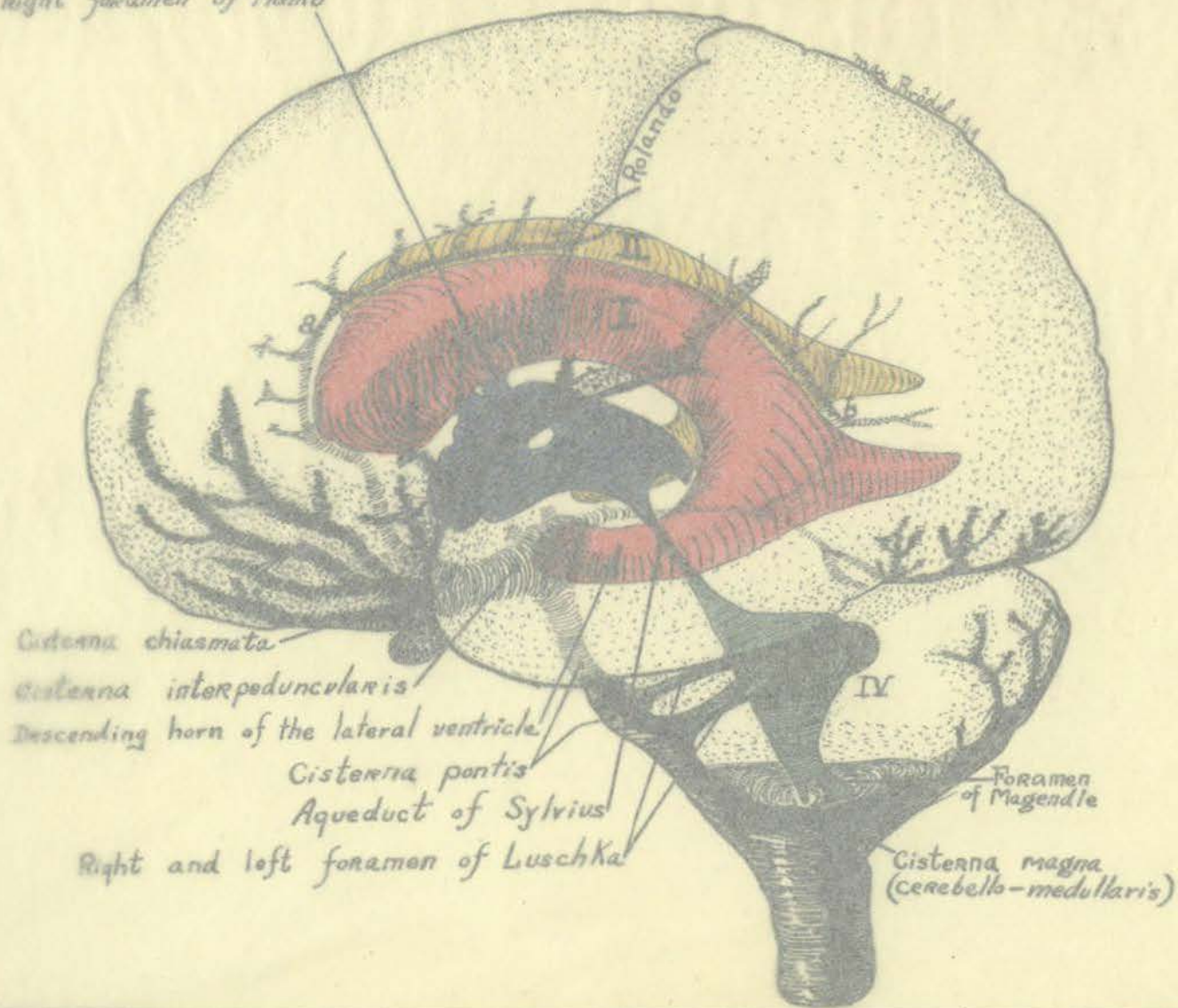
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left and right foramen of Monro



Cisterna chiasmata

Cisterna interpeduncularis

Descending horn of the lateral ventricle

Cisterna pontis

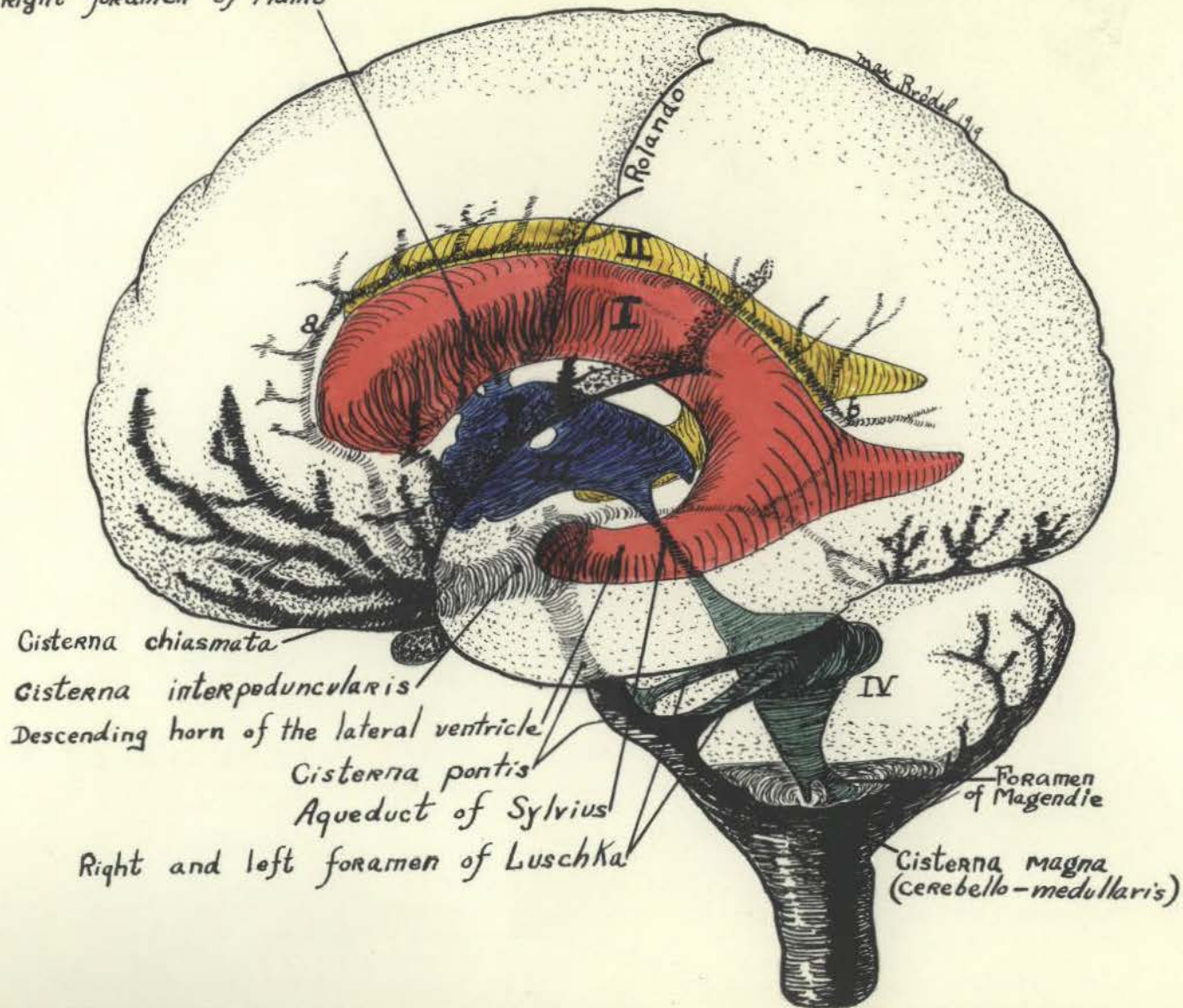
Aqueduct of Sylvius

Right and left foramen of Luschka

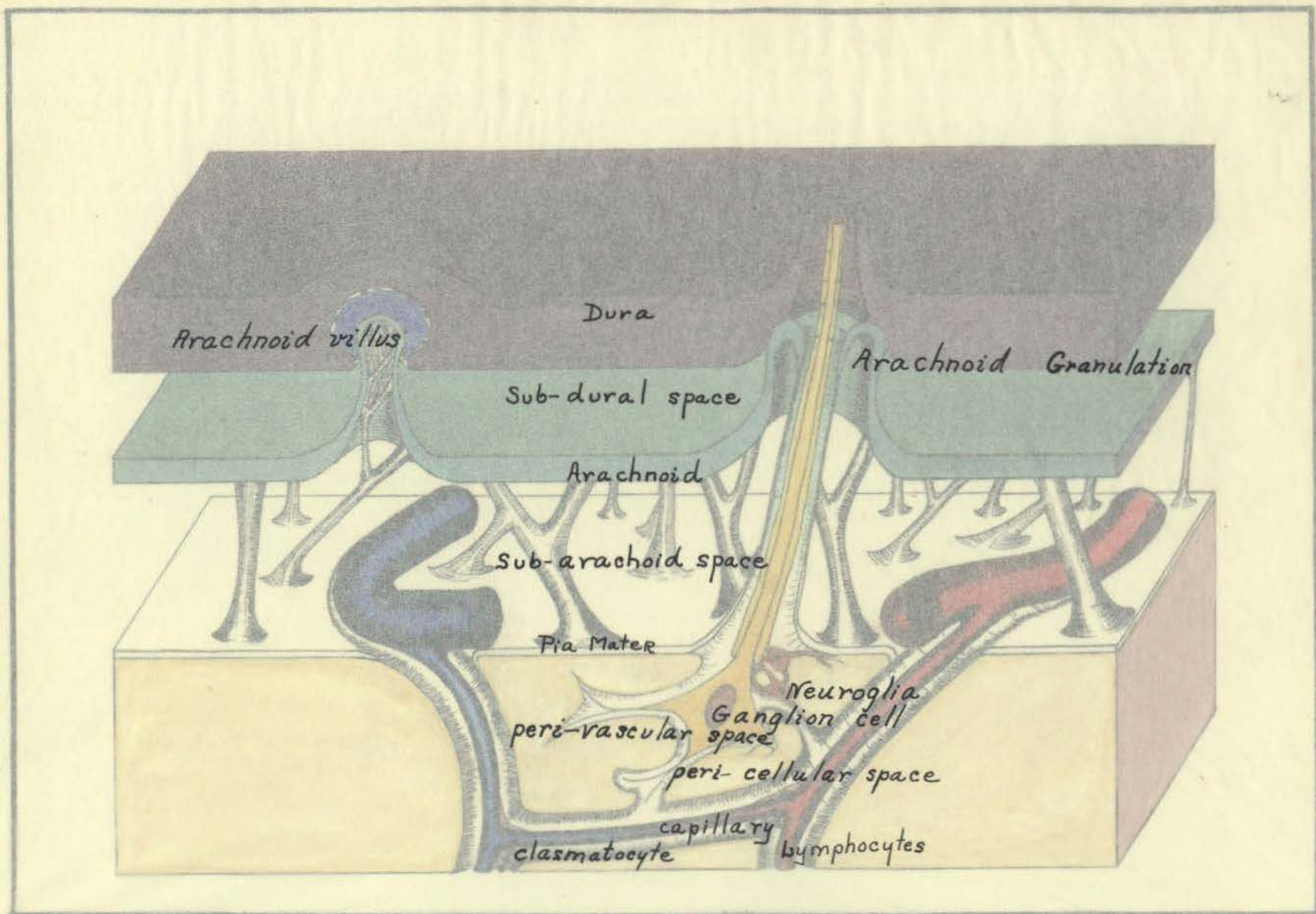
Foramen
of Magendie

Cisterna magna
(cerebello-medullaris)

Left and right foramen of Monro







Schematic Representation of the Central Nervous System,
With Reference to the Circulation of the Cerebrospinal Fluid.

Modified from *The Journal of Experimental Medicine*, vol. 46, 1927, p. 615 - L. S. Kober plate 24 ^{2nd} from *Archives of Neurology & Psychiatry*, vol. 14, 1925, p. 251, III, E. Aycock.

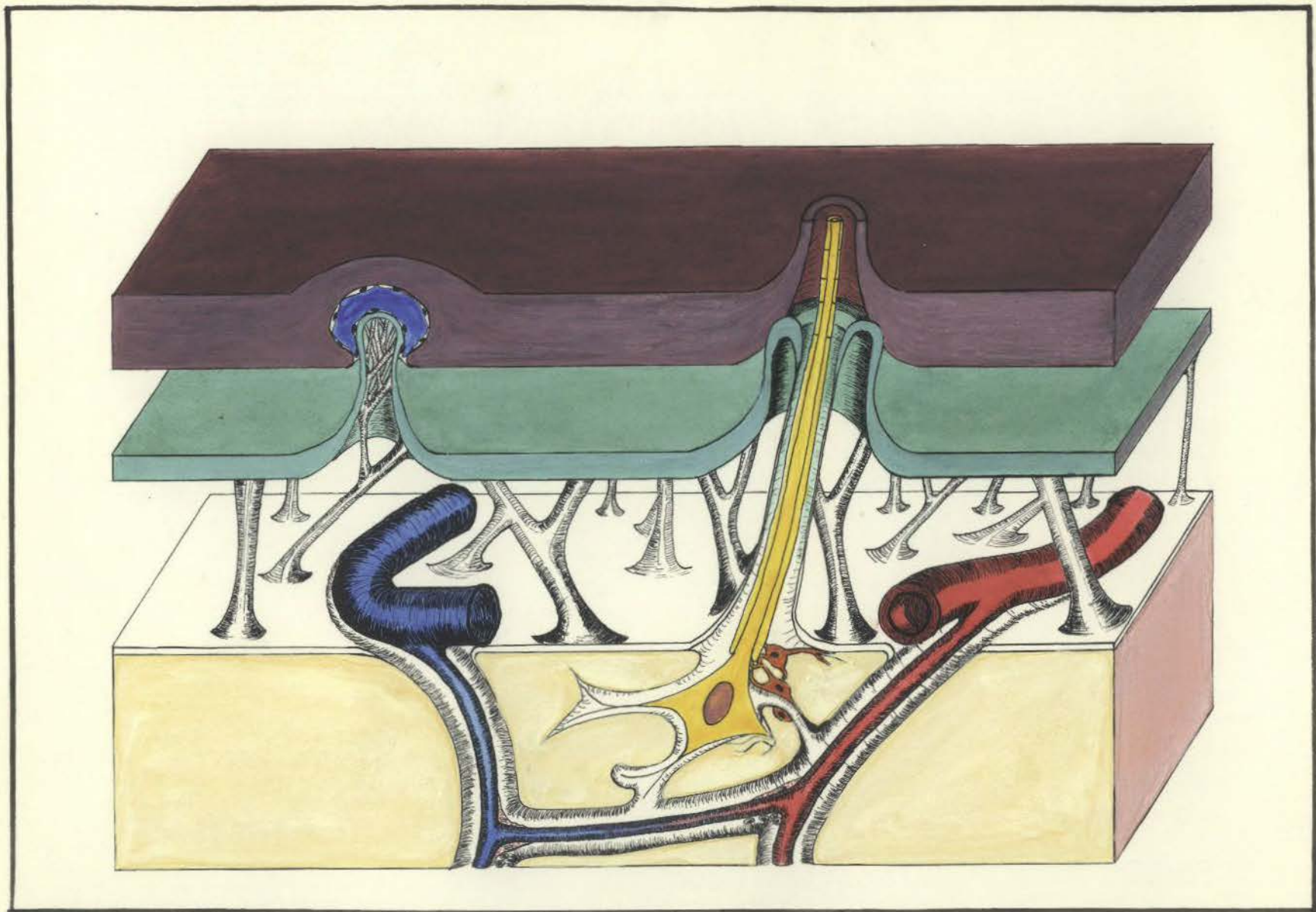
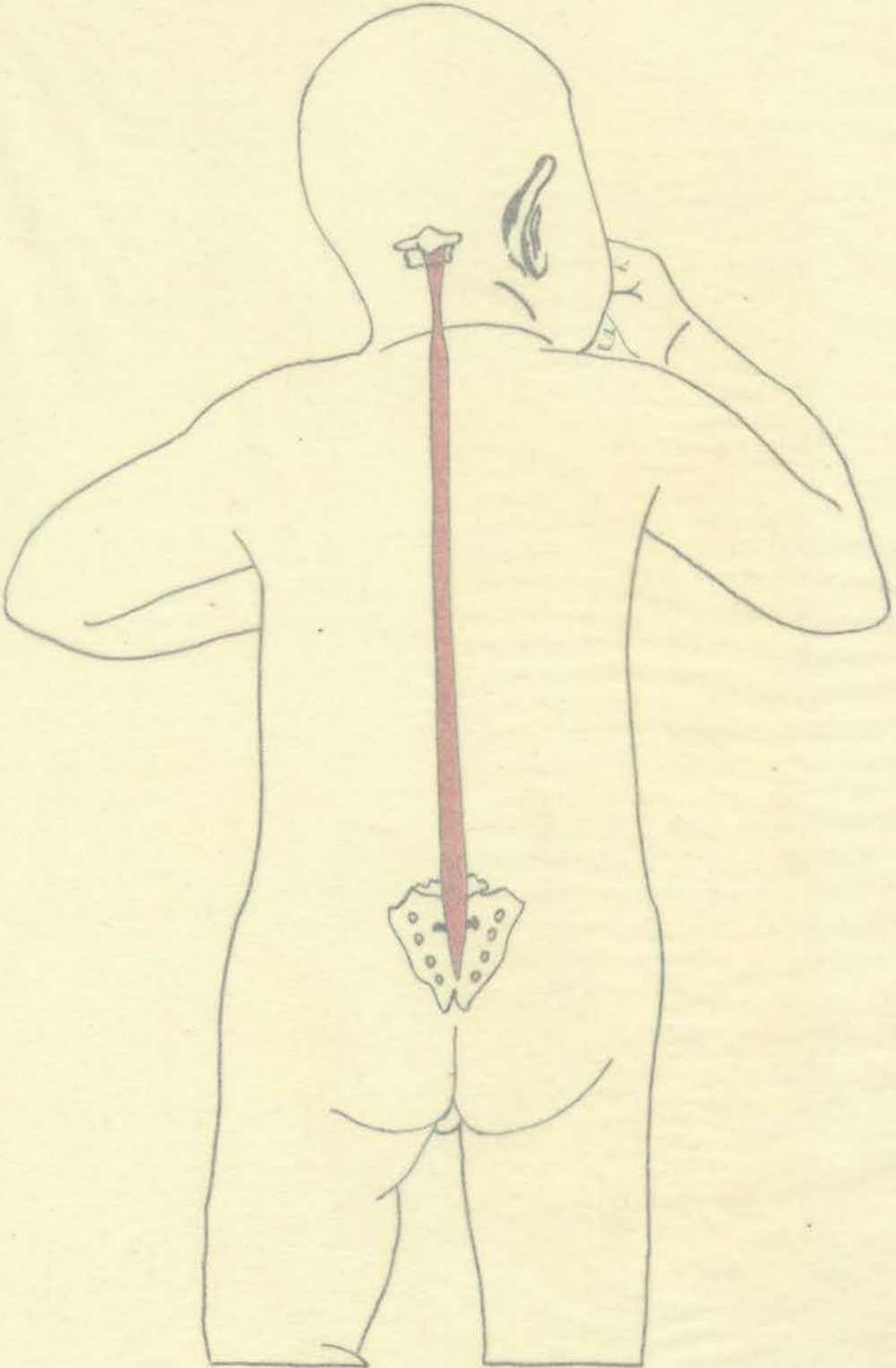


Diagramm zur Entwicklung des Keimbahnsystems bei der Bildung des Keimbahnsystems. Die Keimbahn ist in der Mitte dargestellt, die sich in zwei Richtungen ausbreitet. Die Keimbahn ist in der Mitte dargestellt, die sich in zwei Richtungen ausbreitet. Die Keimbahn ist in der Mitte dargestellt, die sich in zwei Richtungen ausbreitet.



The Extent of Spinal Cord of the Retic at the Fifth Thorax.
"Diagnosis and Treatment of Surgical Diseases of the Spinal Cord and its Membranes."
by Charles D. Elsborg (1918), p. 24, fig. 6.

