1953

Survey of meningitis in children and recommended treatment

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A SURVEY OF MENINGITIS IN CHILDREN AND RECOMMENDED TREATMENT

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Submitted in Partial Fulfillment for the Degree of
Doctor of Medicine

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February 27, 1953

Omaha, Nebraska

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A SURVEY OF MENINGITIS IN CHILDREN AND RECOMMENDED TREATMENT

Introduction

An introduction to meningitis was given to the author while on pediatric service. The patient was a four year old girl, who had up to that time been in the hospital for approximately two hundred and ten days with a diagnosis of tuberculous meningitis. Even though the patient had been hospitalized for such a great length of time and was constantly being treated, she still suffered remissions and exacerbations. This situation posed several questions: Is the duration of the disease in this child unusual as compared to a comparable case? What is the best treatment for a case such as this? If one form of therapy fails, are there other therapeutic measures which may be used? What is the prognosis in this type of meningitis? How do other meningeal infections compare to this in incidence, hospital time, and therapy?

To answer these questions, it was thought best to review a series of cases from hospitals in this area. Therefore, the charts of all meningitis cases on file up to December, 1952 at Childrens Memorial Hospital and those from April, 1947 to December, 1952 at University Hospital were reviewed. The charts furnished information as to incidence, symptoms, hospital stay, diagnosis, and treatment but since both hospitals are staffed by about the same doctors, therapy was varied but little. To achieve an alternate therapeutic regime, a short review of the literature was made

and the findings were encouraging since there were at least two therapeutic courses for almost each type of meningitis.

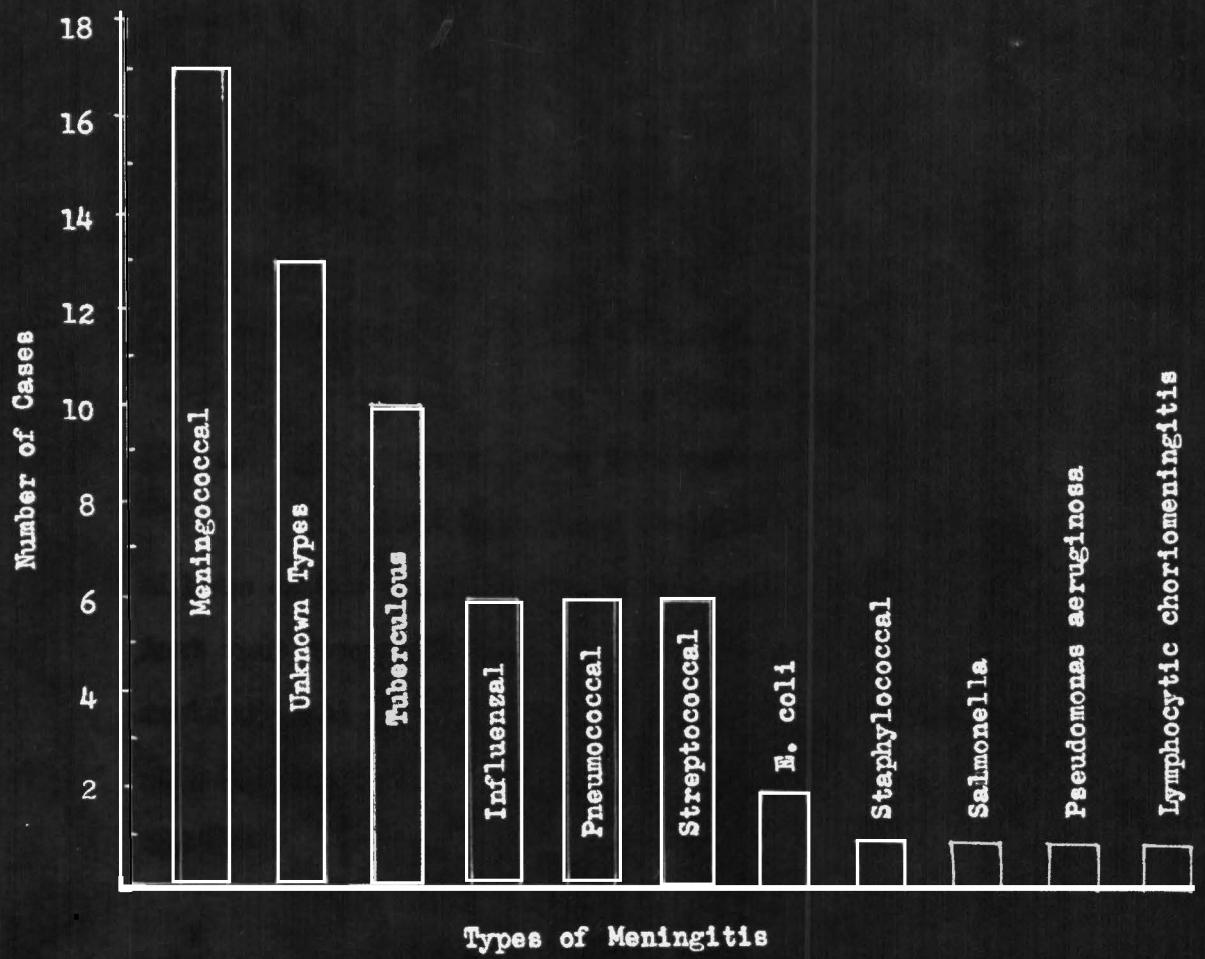
It is hoped that the following report will give the reader a better view of meningitis as it is today and will enable him to give a better prognosis to the patient through better diagnosis and treatment.

Incidence

In this survey, sixty-four cases were reviewed and after a break down of all the cases into types it was seen that 26.5 per cent were meningococcal; 20.3 per cent were unknown types; 15.6 per cent were tuberculous; influenzal, pneumococcal, and streptococcal each made up 9.0 per cent of the total and the rest were 3.0 per cent or under. Graph number 1 compares the number for each type.

No recent literature could be found that compared the incidence of the various types of meningitis but an article written last year discussing the incidence of meningococcal meningitis was reviewed[1] and since meningococcal meningitis is the major type in this series, it is believed that a correlation can be made between the two.

Since the advent and widespread use of antibiotics, it would be a natural supposition that the incidence of meningitis is less today than five years ago but this is not the case. As can be seen from Graph number 3, it is increasing, as determined by this survey. It must be explained that only the years 1949, 1950, and 1951 are accurate in showing the incidence in this survey because



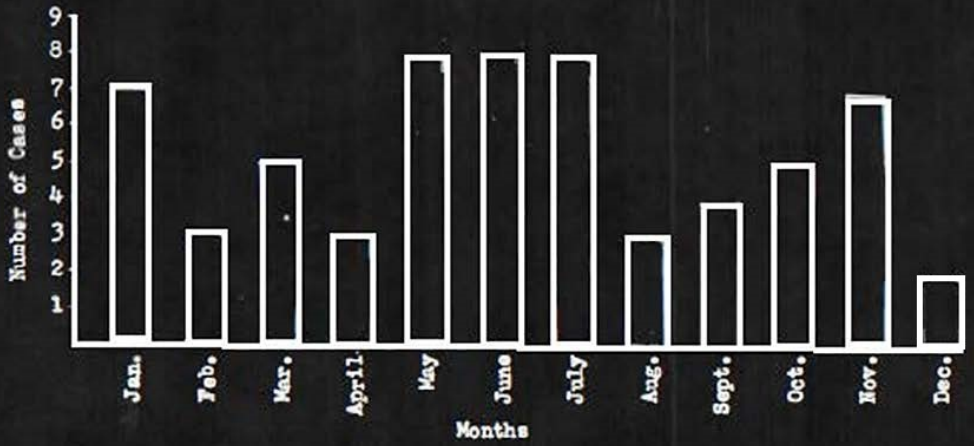
Graph No. 1: The above graph is a break-down into types of the 64 cases reviewed in this survey. The graph also shows the number of cases of each type of meningitis.

only one case in the last month of 1947 was reviewed, Childrens Memorial Hospital did not open until around September, 1948 therefore, the cases reviewed in this year were not complete and all of the cases for 1952 had not been filed at the time this survey was made so the cases for this year are not complete. Nevertheless, a definite increase in meningitis can be seen from the years 1949, 1950, and 1951.

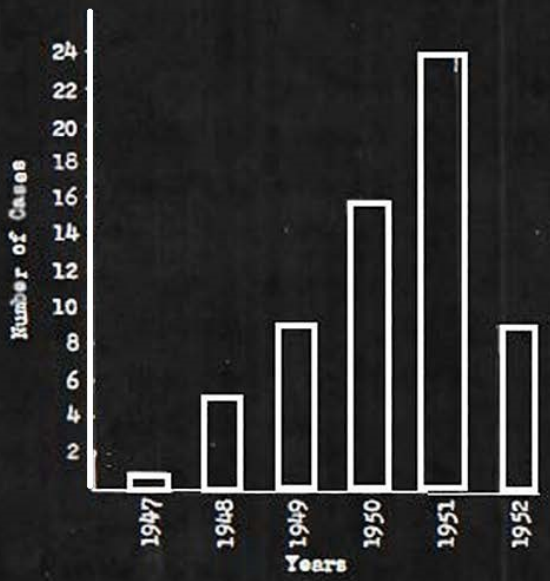
It has been reported that the incidence and mortality of meningococcal meningitis has been slowly rising after a five year decline from the 1943-44 epidemic.[1] In this series there has not been an increase in the number of cases of meningococcal meningitis each year but there has been an increase in the number of all meningitis cases.

It has long been recognized that meningitis spreads most rapidly, as do other diseases, at times and places of population congestion, where contact rates are high. This may be one explanation for the increase since, of the four epidemic crests in the United States, two came during war periods (1918 and 1942-43) and two came during periods of relatively high industrial activity during peace time (1929 and 1935-36).[1] The reported case rate for infants is four or more times higher than for school children and adults and since the birth rate has increased there is an unusually heavy inflow of susceptible persons into the population therefore an increase may also be explained in this way.

It is believed by Hedrich[1] that the present rise in the



Graph No. 2: The above graph illustrates the monthly incidence of all cases of meningitis reviewed taken as a whole.



Graph No. 3: The above graph depicts the number of cases of meningitis which occurred each year of this survey.

number of cases of meningitis will lead into an epidemic. One reason being that in the past when an epidemic wave started upward it tended to continue to an appreciable epidemic peak. Another reason being that inter-epidemic intervals have averaged about 8 years and it has been approximately 10 years since the peak in 1943.

With the facts that the incidence of meningitis are on the increase and the possibility that there may be an epidemic in the offing, we must not only be able to diagnose early and treat adequately but also know the seasonal cycle for each type of meningitis. In this series, taking all cases as a whole, the greatest number of cases occur in May, June and July then there is a sharp decline in August and a gradual rise through November. This may be seen from Graph number 2. The sharp fall in December can not be accounted for but with the high number of cases in both November and January it seems that the cases reported for December are in error.

The seasonal cycle will not be the same in all parts of the country since, as Hedrich reported, "meningococcal infections show a seasonal cycle in which, from the low in about September to the high point in early Spring, cases are multiplied on the average by four." In this series, meningococcal meningitis was most prevalent in late spring and early summer. Tuberculous meningitis had its highest incidence in late winter and spring while influenzal meningitis occurred mainly in late summer and fall, streptococcal meningitis occurring mainly in late fall and winter and pneumococcal

meningitis in late spring and late fall.

With the spread of meningeal infection throughout all seasons we must constantly be watchful for the first sign or symptom of meningeal irritation at all times rather than at any particular season.

Preceding Illness

It is believed by some that most cases of meningitis are preceded by some illness. For example, it is stated that there are three clinical stages of meningococcal meningitis, these being: nasopharyngeal infection, which is normally asymptomatic and extremely difficult to detect; invasion of the blood stream (septicemia); and meningitis.[1] In the present series, less than 50 per cent of the meningitis cases, taken as a whole, were preceded by an illness, as far as the recorded history is concerned. To account for the fact that there were so few reported ill before the meningitis showed itself clinically, it might be suspected that the preceding illness was so slight that either the patient did not report it to the doctor or the parents considered the illness so slight that they did not report it to the doctor during the history taking.

As can be seen from Chart number 1 the most common preceding illness for this series is the common upper respiratory infection. This includes all phases from a rhinitis to a pharyngitis and slight cough. The next most common illness occurring before the signs of meningitis appeared is pneumonia.

It will be noticed that the last illness listed is quite

Types of Meningitis		Preceding Illness: Upper Respiratory Infection	Pneumonia	Otitis Media	Rhinitis	Tonsillitis	Otitis Externus	Acute Parotitis	Myelomeningocele
Staphylococcal	(1)								
Unknown Types	(13)	5	1			1	1	1	
Salmonella	(1)	1							
P. aeruginosa	(1)								1
Pneumococcal	(6)	3							
Streptococcal	(6)	1		1					
Meningococcal	(17)	2			1				
Influenzal	(6)	2							
E. coli	(2)								
Tuberculous	(10)	3	1						
Lymphocytic Choriomeningitis	(1)								
Total	(64)	17	2	1	1	1	1	1	1

Chart No. 1: The above chart shows the incidence of a preceding illness in the various types of meningitis of this survey and the chart also shows the main types of illnesses.

debilitating and therefore predispose the patient to other ills. The upper respiratory infections probably cause their damage by seeding the system with organisms through
to the meninges.

The question might arise that it would be impossible to do a spinal tap on all patients who come in with an upper respiratory infection therefore how can it be determined if the infection will go into meningitis? Lepper[2] states that the first invariable rule should be to examine every patient with an infection for signs of meningitis. "If the neck is stiff on flexion or the Kernig's sign is positive, a lumbar puncture should be performed. rigidity is absent and Kernig's sign negative, it is unlikely that meningitis is present, except in infants. In this particular group the physician should be alert to obtain spinal fluid if the fontanelles are bulging or there is a low weak cry."

Therefore, it can be well understood, from both the literature and this series that the preceding illness is a red flag which can be passed by with just a shot of penicillin or qualified by an examination for meningeal irritation and even when there is no sign of meningeal irritation at the first examination, meningitis is not ruled out.

Major Symptoms First Seen

It was stated above that in a report by Lepper[2] it is advised that every person who has an infection be checked for neck stiffness and the Kernig sign to determine if meningitis is present.

If both are absent, meningitis is unlikely. This series does not bear out his statement since only 15.6 per cent of all cases had neck stiffness when first seen. The number of cases with positive Kernig's signs is not known but from the number with back stiffness and leg stiffness it is estimated that the Kernig sign would be positive in about 7.8 per cent of the cases.

In referring to Chart number 2, the five findings first seen in this series were vomiting, fever, headache, lethargy, and irritability. Of these vomiting, not necessarily projectile in nature, and an elevation of temperature each have an incidence of 64.0 per cent of all the cases. This does not help clarify the diagnosis of meningitis in itself since most children with upper respiratory infections serious enough to see the doctor will have a fever and a significant number will have vomiting but these symptoms combined with lethargy and irritability could point to the diagnosis of influenzal or streptococcal meningitis or combined with irritability and a rash the disease could be meningococcal meningitis or combined with irritability, anorexia, and convulsions the diagnosis could be tuberculous meningitis. The point being made here is that the diagnosis of meningitis, or for that matter any other disease entity, should not be made only on the basis of two tests and if these tests are negative to minimize the possibility of meningitis to the point of neglect. As can be seen from Chart number 2, there are many possible combinations of symptoms which may fit into the diagnosis of meningitis and this is the fact that

Major Symptoms First Seen

Types of Meningitis		Vomiting	Temperature	Headache	Lethargic	Irritable	Anorexic	Convulsion	Nuchal Rigidity	Listless	Nausea	Neck Pain	Restless	Back Stiffness	Rash	Comatose	Twitching	Abdominal Pain	Partial Paralysis	Diarrhea	Dyspneic	Malaise	Backache	Disassociated	Sore Throat	Cough	Nasal Voice	Leg Stiffness	Petechia	Eye Pain
Staphylococcal	(1)								1	1								1								1				
Unknown Types	(13)	10	7	6	3	3		3	1	4	2	2		1		1	1	1		1		1		1	1	1		1		1
Salmonella	(1)		1	1	1	1	1																							
P. aeruginosa	(1)																	1												
Pneumococcal	(6)	3	4	2	2	1			1		1	1	1									1	1							
Streptococcal	(6)	2	4		4	2	2	2	2					1			1								1					
Meningococcal	(17)	13	13	7	2	5	3	2	3	3	2			1	4	2		2		1								1		
Influenzal	(6)	2	5	1	4	3	2	1	1				1	1		1					1			1						
E. coli	(2)						2			1										1	1									
Tuberculous	(10)	11	6	5	6	4	4	4		1			2				2	1	2	1	1	1		1			1			
Lymphocytic Choriomeningitis	(1)	1	1	1					1																					
Total	(64)	42	41	23	22	19	14	12	10	10	5	5	4	4	4	4	4	4	4	3	3	3	2	2	2	2	2	1	1	1

Chart No. 2: The above chart gives the major symptoms of the patient when first seen for each type of meningitis. The number in parenthesis after each type of meningitis is the number of cases of that particular type of meningitis reviewed in this survey.

should be remembered rather than trying to remember all of the possible symptoms or using only one or two tests for either proving or disproving the diagnosis.

Positive Physical Findings

After the patient has become sick and develops symptoms alarming enough to have the attention of a physician, certain physical findings will be present which may or may not be characteristic of the disease. As the disease progresses the physical findings will be more and more characteristic and diagnosis is more readily made. If one would attempt to make a diagnosis based on the first symptoms seen and the positive physical findings at that time it would not seem feasible if the patient were examined very shortly after the initial symptoms were seen because physical findings suggestive of meningitis usually are not present early. In this series the time between the appearance of initial symptoms and the time when a physical examination was done ranged from a few hours to two or three weeks. This fact may explain the inability to correlate the initial symptoms with positive physical findings.

Under the last topic, Lepper's advise was refuted when he suggested to not consider meningitis if there was neither neck stiffness or a positive Kernig since the impression was given that these were early findings and in this series it was shown that neither appeared early, but as can be seen from Chart number 3, 59 per cent of all cases reviewed had neck rigidity on physical examination and this is second to the most prominent physical finding in this

Major Positive Physical Findings

Types of Meningitis		Increased Temp.	Neck Rigidity	Pharynx Inflamed	Tonsils Inflamed	Lymphadenopathy	Dehydrated	Positive Kernig	Back Stiffness	Nasal Discharge	Postnasal Drip	Otitis Media	Hamstring Spasm	Hyperactive Reflexes	Dec. Light Reflex	Positive Brudzinski	Neck Pain	Inc. Lung Sounds	Heart Murmurs	Opisthotonus	Roving Gaze	Comatose	Absent Knee Jerk	Positive Babinski	Dec. Knee Jerk	Bulging Fontanelle	Flaccid Paralysis	Spasm of Extremities	Squint	Positive Hoffman	Ankle Clonus
Staphylococcal	(1)		1				1																								
Unknown Types	(13)	13	9	7	6	5	1		3	3	2	4	4	1	2	1	2	2	1	1			1		1	1	1				
Salmonella	(1)	1					1																								
P. aeruginosa	(1)																														
Pneumococcal	(6)	4	4	2		1	3	4	1	1		2				2	1	2		1	1	2		1	1						
Streptococcal	(6)	6	4	4		1	2		2	1		1	2	2	1		1			1	1	1					1	1			
Meningococcal	(17)	16	10	10	4	4	5	8	3	6	7	2	3	3	2	4	4	1	3	1			2	1			2				
Influenzal	(6)	6	3	3	3	2	1	1	1	1	1	1	1	1		1		1													
E. coli	(2)																								2	1					
Tuberculous	(10)	4	6	5	4	5	4		4	2	3	2	1	3	5	1		2	1	1	3	2	1	2	1		1		1	1	1
Lymphocytic Choriomeningitis	(1)	1	1	1	1			1	1																				1		
Total	(64)	51	38	32	18	18	17	15	15	14	13	12	11	10	10	9	8	8	5	5	5	5	4	4	3	3	3	3	3	1	1

Chart No. 3: The above chart gives the major positive physical findings for each type of meningitis. The number in parenthesis after each type of meningitis is the number of cases of that particular type of meningitis

series. Nevertheless, it is again reiterated that this finding occurs later in the course of the disease and may be absent on the first examination. A positive Kernig was found on only 23.4 per cent of all patients at the physical so this is even a less reliable test for ruling meningitis in or out.

It will be noticed from the chart that an increased temperature is first in incidence, occurring in 80.0 per cent of all cases reviewed and an inflamed pharynx is the third most prominent physical finding, occurring in 50 per cent of the cases.

Several of the physical findings and symptoms can be correlated so that a better understanding of the over-all picture may be had. For example, the infection itself will produce an increase in temperature but when there is vomiting for any length of time dehydration will develop and this will cause a higher temperature. Also with a nasal discharge there will also probably be a postnasal drip which may be the cause of the pharyngeal inflammation and the pharynx may have been the site from which the organisms entered the blood stream.

From this correlation it can be seen that therapy depends a great deal on what is found in the history and physical examination but the laboratory findings too are important not only to arrive at a diagnosis but also as an aid in determining the type of therapy and the duration of therapy.

Chart number 4, except for the segmented leukocytes in blood, gives only abnormal laboratory findings for each type of

Abnormal Laboratory Findings						Types of Meningitis: Staphylococcal	Unknown Types	Salmonella	P. aeruginosa	Pneumococcal	Streptococcal	Meningococcal	Influenzal	E. coli	Tuberculous	Lymphocytic Choriomeningitis
Blood					RBC below 4.5/cu. mm.		4			3	2	9	5	1	2	
					Hemoglobin below 14 gm.		3	1		3	3	12	7	1	13	
					WBC above 10,000.		11		1	5	5	14	5	2	12	1
					Predominant WBC - Segs.		7	1	1	4	4	13	2	1	11	1
					Predominant WBC - Lymph.		1			1	1	3	2		1	
Spinal Fluid					Urinalysis		2	1		1		9	4	1	2	
	Color				Clear	1	1					3	1	1	9	
					Cloudy		9			6	4	8	4	1	4	
					Xanthochromic		2								1	
					Bloody		2				1					
					Character - Clotted						1	1		1	1	
	Principal Cell				RBC Over 1,000/cu. mm.		2									
		WBC			Type - Polys.		9			3	5	14	5	1	3	
					Type - Monos.	1	1	1		2		1	1		10	1
			Number		0 to 100	1	1	1			1	3	1		4	
					100 to 1000		5			1			1		7	1
					1000 to 10,000		4			2	3	8	5		1	
					Over 10,000		3			3	2	6		1		
					Pressure above 200 mm. water								2		2	
					Sugar below 50 mg.%		4			5	5	8	5	1	11	
					Protein above 40 mg.%		6	1		4	3	13	4	1	9	
					Chlorides below 720 mg.%		1						4		7	1
					Positive smear		3	1		4	2	8	5			
					Positive culture		1	1		6	4	8	5	1	1	

Chart No. 4: The above chart is a break down of the abnormal laboratory tests for the various types of meningitis in this survey.

meningitis and from these many interesting things may be observed. It may be noticed that 40.6 per cent of all cases had a low red cell count and that 67.1 per cent had a low hemoglobin. This may well be a nutritional anemia which probably developed from the onset of the illness due to the infection and anorexia. Next, of all cases, 87.5 per cent had an increased white cell count in the blood and the majority of these had predominence in the number of segmented forms while a small number had a normal differential. Those cases with an increase in lymphocytes consisted of only a small percentage of all cases.

An abnormal urinalysis was found in 31.2 per cent of the cases with the largest number occurring in meningococcal meningitis. The abnormalities consisted mainly of albumin and acetone which could probably be explained on the basis of dehydration and starvation but occasionally white cells and red cells would be found in the urine in significant numbers which denoted some renal irritation possibly due to the septicemia.

It is usually considered true that when a person shows signs of meningeal irritation and the spinal fluid is clear with few cells, the illness is caused by a virus. In this series, 56.2 percent of the cases had cloudy spinal fluid but, and this is the important fact, 25 per cent had clear fluid and 18.7 per cent showed a hundred white cells or less in the spinal fluid which would be consistent with a viral disease such as poliomyelitis. There were two cases with bloody fluid, which may have been due to faulty

technique in drawing the fluid, and there were three cases with xanthochromic fluid.

Four cases had fluid which clotted. The formation of a clot or web on standing denotes increase in fibrinogen which is usually accompanied by other proteins. This occurs in some infectious diseases, especially tuberculous meningitis according to the literature but in this series, out of 10 cases of tuberculous meningitis only one had spinal fluid which clotted. There were three other cases, streptococcal, meningococcal, and E. coli, which showed a clotted fluid.

The majority of cases, 62.5 per cent, had spinal fluid in which polymorphonuclear leukocytes were the most predominent cell. In 28.1 per cent of the cases mononuclear leukocytes were the predominent cell and of these 55.5 per cent occurred in tuberculous meningitis. Since an increase in monocytes as well as a low cell count occurs in most virus infections, to make a diagnosis in a questionable case from these laboratory findings alone would offer the possibility of a gross error as can be seen from Chart number 4.

As was noted above, 18.7 per cent of all cases showed 100 cells or below in the spinal fluid, 23.4 per cent had 1000 white cells or under, 35.9 per cent had 10,000 white cells or under, and 23.4 per cent had over 10,000 white cells in the spinal fluid.

It is believed that the number of cases with a spinal

fluid pressure above 200 mm. of water shown on chart number 4 is not an all inclusive count and therefore will not be considered but is included on the chart for the sake of completeness.

It was found that spinal fluid sugar was below 50 per cent in 60.9 per cent of the cases and protein was above 40 mg. per cent in 64.0 per cent of the cases which is quite consistent with bacterial infections of the meninges. The chlorides were below 720 mg. per cent in only 20.3 per cent of the cases but this low figure is due to the fact that a spinal fluid chloride determination was not run on every case. It is believed that a chloride determination is a good diagnostic point in the differentiation of encephalitis, poliomyelitis, or neurosyphilis from acute tuberculous meningitis, which they may clinically resemble. These conditions, unlike meningitis, show normal chlorides.

The demonstration of specific organisms on smear or in culture is the means of establishing diagnosis. As can be seen from Chart number 4, the smear and culture are not positive in every case and sometimes the culture is positive when the smear is negative. It was noted in reviewing the charts that many times both the smear and culture were negative the first or second time a lumbar puncture was done but possibly the third time one or the other, or both, would be positive.

It is shown that from the correlation of the above discussion and from chart number 4, the laboratory studies are recognized as being very valuable adjuncts not only in diagnosing meningitis

as a whole but also as the means of diagnosing the various types of meningitis. It also must be recognized that all cases will not give a textbook picture, which is important to remember.

When First Treated After Initial Symptoms and Duration of Treatment and Illness

On first thought, it may be supposed that the earlier the patient is first treated after the initial symptoms, the shorter will be the illness but, as was determined from this survey, that is not the case. The fact that so many variables enter into each case makes a correlation such as this almost impossible.

To list a few of these variables, begin with the fact that some of the patients will be more undernourished and physically exhausted than others. Another fact is that a patient may have been treated early but treated improperly or inadequately. "A false start of treatment and the patient may be condemned to weeks of unnecessary injections. A false start and the disease may be suppressed enough to be masked but not eradicated".[2] Also, to be considered, the patient may have a coincident illness with the meningitis which will prolong treatment, illness, and hospital stay.

After noting the above facts, it was determined that the only correlation that could be made would have to be on the basis of an average of the number of days when the patient was first treated after the initial symptoms; the duration of the treatment; the duration of the illness; and the total number of days from the onset of the illness to the dismissal from the hospital. Chart

Types of Meningitis	Average Number of Days: When first treated after initial symptoms.	Duration of treatment.	Duration of illness.	Total days (from onset to dismissal)
Staphylococcal	5	36	25	72
Unknown Types	2.1	16	14.7	19.9
Salmonella	7	36	43	43
P. aeruginosa	0	18	18	18
Pneumococcal	3.6	18.3	16.5	35.3
Streptococcal	2.1	14	10.3	21.5
Meningococcal	3.2	14.2	8.8	17
Influenzal	21	36.5	24.5	46.8
E. coli	2	73.5	52	94
Tuberculous	11.7	148.1	152	175.7
Lymphocytic Choriomeningitis	2	22	14	24

Chart No. 5: The above chart shows the average number of days of involvement with each type of meningitis in this survey.

number 5 shows a comparision of these averages and it is believed that only in this way do the figures offer any possibility of being of value. The chart's main use would be to give any interested person the approximate time that the patient may be hospitalized figuring from the day of onset of the illness. It must be remembered, however, that even though these are average figures, the variations from them may be quite significant and that they be used accordingly.

Types of Treatment

As can be readily understood, the type of treatment used in each case reviewed would be so varied, as far as dosage and length of administration, it would be a study in itself to list each separately and it would also be confusing for the reader since many dosages vary but slightly. Therefore, under this heading, only the antibiotics and specific drugs used for a particular type of meningitis will be discussed. In another section in this paper, the recommended treatment for each type of meningitis will be presented.

The judicial use of all drugs in meningitis, as well as any other disease, is very important and this fact can not be overemphasized. To reiterate, "A false start of treatment and the patient may be condemned to weeks of unnecessary injections."[2] Not only the type of treatment is important but also the dosage should be regulated according to the illness and no set dosage should be given for all similar clinical entities. "The doses which are sufficient for such infections (respiratory) do not penetrate the

blood-brain barrier in sufficient quantities to cure meningitis. The meningeal infection then spreads insidiously and when it becomes obvious that it is out of control, it is too late."[2] This is a very important point since approximately one-third of the cases studied had received antibiotics from two to fourteen days before the patient was sent to the hospital with the possible diagnosis of meningitis.

Another point that should be stressed is the fact that certain antibiotics have been shown to be greatly limited in their therapeutic efficacy by emergence of resistance of the strain during the course of the treatment in a number of infections when only one agent is used at a time.[3] To prevent the emergence of resistant strains, two antibiotics should be used as determined by sensitivity tests and optimal doses must be used so that if the strain develops resistance to one type of therapy the other drug will be present in sufficient strength to eliminate the resistant strain. Here, someone may ask about the antagonism of antibiotics. It seems that this is only "an interesting laboratory phenomenon and proof of its therapeutic importance is lacking."[3]

By referring to Chart number 6 it can be seen that in most cases penicillin and sulfadiazine were used in a synergistic manner and in tuberculous meningitis penicillin and streptomycin were used together. In the one case of lymphocytic choriomeningitis, aureomycin was probably used against the virus and penicillin to combat any secondary infection. The treatment of this case may be contrast-

Specific Treatment

Types of Meningitis		Penicillin	Sulfadiazine	Streptomycin	Aureomycin	Chloromycetin	Dihydrostreptomycin	Terramycin	PASA	Promizole	Intrathecal Streptomycin	Desoxycorticosterone	Immune Globulin	Penicillin Intrathecal (IV)	Penicillin	Sulfasuxidine	Sulfathiazole	Veridase
Staphylococcal	(1)	1	1	1	1	1												
Unknown Types	(13)	12	10	5	8	3	1	1					1					
Salmonella	(1)	1	1	1	1	1												
P. aeruginosa	(1)																	
Pneumococcal	(6)	6	6		1	2	1	1						1	1			
Streptococcal	(6)	6	5	2	1	1		1										
Meningococcal	(17)	17	15	4	3	3	2									1		
Influenzal	(6)	5	5	3	1	3	3	1					1					
E. coli	(2)		1		1	1	2	2										
Tuberculous	(10)	10	5	9	3	3	6	2	7	6	5	1	1					1
Lymphocytic Choriomeningitis	(1)	1			1							1						
Totals	(64)	59	49	23	18	18	17	8	7	6	5	2	2	1	1	1	1	1

Chart No. 6: The above chart gives the main treatment for each type of meningitis. The supportive therapy is discussed under the main topic.

ed with the treatment shown for the case of staphylococcal meningitis and for that of the Salmonella infection. It appears from chart number 6 that a search was being made for the most effective drug through the trial and error method but in reality, in the staphylococcal infection, four of the drugs were given for a time before a report of sensitivity was made and then two drugs were used which were proven by the test to be most effective. In the Salmonella infection no sensitivity test was reported so no specific treatment was used, only a random sampling of several, giving the patient no help and the case ended with an autopsy.

The case of infection with P.aeruginosa shows no specific type of treatment being used. This was due to the fact that the patient expired before any specific therapy could be started.

Supportive therapy is not discussed in length or given on any chart or graph in this paper but, nevertheless, a wise choice can materially shorten the hospital course by improving the physical and nutritional states so that the physiological defenses are able to work along with the antibiotics. Of the drugs used in a supporting manner, aspirin heads the list, then vitamins and iron, with parenteral fluids next in frequency of use. This could be expected since, it will be recalled, fever, anemia, and dehydration had a high incidence in the physical and laboratory findings. Whole blood was used in a few cases to combat severe anemia. Fifty per cent intravenous sucrose, desoxycorticosterone, and adrenal cortical extract were used rarely but they are very valuable when used

properly.

Status of Patient on Dismissal

The title of this section, when the paper was first being formulated, was "The Incidence of Cure with the Treatment Used" but this was changed to the present title when the implications of such a title were realized. In meningitis, as in any other illness, the cure does not solely depend on the treatment but also depends on the early recognition of the specific disease state, proper differentiation into etiologic groups, if possible, and the determination of the sensitivity of the isolated organism to the antibiotics before treatment is started.

Therefore, in order to use Chart number 7 so that it has any real significance, Chart number 5 should be observed to see when the patient was first treated; Chart number 6 shows how the patient, or the majority of patients, was treated; and then by correlating these two findings Chart number 7 has a definite meaning.

It is a well known fact that even today with our present antibiotics, tuberculous meningitis has a high morbidity and mortality rate and this is also found true in the present series. It is seen from Chart number 7 that meningitis caused by both Salmonella and P. aeruginosa organisms have a hundred per cent mortality but it is believed that this fact is due to only a single case under each group and that if there were a larger number of cases this mortality rate would fall rapidly. Streptococcal meningitis seems to have a high mortality rate but again this is probably due to too

Status of Patient at Dismissal

Types of Meningitis		Improved	Nervousness	Muscle Weakness	Paralysis	Convulsions	Hydrocephalus	Central Nervous System Damage	Expired
Staphylococcal	(1)			1					
Unknown Types	(13)	12			1				
Salmonella	(1)								1
P. aeruginosa	(1)								1
Pneumococcal	(6)	5			1				
Streptococcal	(6)	4							2
Meningococcal	(17)	16		1					
Influenzal	(6)	6							
E. coli	(2)					2			
Tuberculous	(10)	3					2	5	
Lymphocytic Choriomeningitis	(1)	1							
Total	(64)	47		2	2		2	2	9

Chart No. 7: The above chart depicts the condition of the patient at the time the patient was dismissed from the hospital.

few cases but even if the percentages are not accurate, the figures show that out of 64 cases of meningitis, 9 deaths occurred or a little over 14 per cent died. "The reason that a significant number are still dying from the various meningitis infections could be due to: (1) Failure of early clinical diagnosis of meningeal irritation. (2) Inadequate laboratory facilities for accurate and rapid identification of the etiologic agents. (3) Lack of the necessary discrimination in selection and use of therapeutic agents."[3]

Recommended Treatment

The possible number of drugs that could logically be used for treating meningeal infections is large but just to treat does not mean a cure. To list a few of the items which may be used for therapy in meningitis there are streptomycin, the sulfonamides, penicillin, terramycin, aureomycin, chloromycetin, Polymyxin B, streptokinase, Promizole, and several new types such as Neopenil and Isoniazid. Depending on the therapy and acceptable means of administration they may be given orally, intramuscularly, intravenously, or intrathecally and the dosage may vary from a very minimal amount of tremendous doses.

When one considers the many types of therapy, the several means of administration, and the variations of dosage, the ability to choose the correct treatment seems like quite a task but our improved understanding of the principles governing the selection and dosage of agents for each etiologic variety is primarily the result of investigations along two lines "(1) The significance, mechanism,

and prevention of emergence of resistance of the infecting agent. (2) The character of the action of the antibacterial agents on sensitive bacteria and the manner in which this trait influences dosage and duration of treatment."[3]

The maintenance of desirable levels of penicillin is now easily accomplished by using procaine penicillin, which permits the slow absorption of the drug. An exception to this rule is meningitis caused by an organism for which penicillin is the most important single agent and then the concentration should be high and reached rapidly. Even when infection of the meninges is present, the transfer of enough penicillin to attain bactericidal concentrations in the spinal fluid can be accomplished only by reaching high blood concentrations by means of enormous doses, intramuscularly or intravenously. However adequate spinal fluid concentrations are not reached for 8 to 12 hours after these doses are started, therefore, there are clear indications for one intrathecal dose at the same time that the other injections are being made.[3]

It is believed by some that due to the development of new antibiotics and improved methods in using old ones, there is less need for intrathecal therapy, nevertheless, it was noted in the literature that intrathecal therapy is still being advised in certain cases.

Sulfonamides serve as important adjuncts to a number of antibiotics, especially sulfadiazine, and still hold first place in meningococcal infections. There is no rationale for attempting

to obtain concentrations in the blood higher than 10 or 15 mg. per 100 cc. when using this drug. It is also known that the drug diffuses well into the spinal fluid. The subcutaneous route is best for administering this drug.[3]

Aureomycin, chloromycetin, and terramycin have proved to be effective therapeutic agents against those organisms which are the most frequent causes of pyogenic meningitis, however, only chloromycetin has been found in desirable concentrations in the spinal fluid.[3]

In vitro Polymyxin B exerts the most rapid lethal action of all the agents against many organism in small concentrations but as yet clinical trials have not been sufficient to evaluate the drug completely.[3]

PAS (para-aminosalicylic acid) shows high promise as a suitable additive agent in therapy of meningitis. A high spinal fluid level is attained by subcutaneous administration and there is little recovered from the spinal fluid after oral administration but oral administration is preferred by several authors. It was also found that PAS increased the survival rate, especially in patients with miliary tuberculosis.[4]

Since the mortality rate from tuberculous meningitis is so high, much study, as well as much controversy, has centered around the treatment of this disease and out of it has come many therapeutic measures combined in many different ways because as yet there is no treatment of choice which gives the patient a good prognosis if

there is survival.

There are many causes of failure in the treatment of tuberculous meningitis but from the pathological aspect the most important is the development of obstruction in the cerebrospinal circulation. Pathological studies show that it is caused by deposition of fibrin and tuberculous granulation tissue, mostly around the brain stem in the cisterna ambiens. Later the deposit organizes into fibrous tissue.[5]

In the investigation undertaken by one group streptokinase appeared to have no effect in reducing the number of blocks occurring during treatment.[5]

In another group, streptokinase was combined with streptomycin intrathecally and streptomycin was also given intramuscularly as the recommended treatment and over a ten month period, of 9 patients so treated, 4 died and 3 have chances of surviving with central nervous system disturbances.[6]

In still another group streptomycin was used intramuscularly for 180 days, streptomycin intrathecally for 40 injections and Promizole uninterrupted for 3 years. Sixteen out of twenty-one patients survived but a high percentage of survivors had some degree of neurological disability.[5]

The above studies show that there is still much to be desired in therapeutic measures and trials are constantly being made to reduce mortality and improve the prognosis in tuberculous meningitis as well as the other meningitides. At the present time

central nervous system complications seem to jeopardize a favorable prognosis.

A study was made to test the efficacy of intrathecal streptomycin since it has been found that streptomycin is irritating to the meninges and causes thickening of the leptomeninges. In this study it was found that streptomycin given intramuscularly appears in small quantities in the cerebrospinal fluid if the meninges are normal but in larger quantities if the meninges are infected. Still in one series of 5 patients treated with only intramuscular streptomycin all 5 died and in another case of 6 patients treated in the same manner all 6 died.[4]

Also, another study was made from a different point of view pertaining to central nervous system damage. Since it has been reported that there is a subdural fluid collection in 50 per cent of patients recovering from meningeal infections caused by a variety of pyogenic agents, one investigator adopted the policy of performing subdural punctures in patients with meningitis if there is: fever after 48 to 72 hours of treatment, positive cerebrospinal fluid culture after 48 hours of treatment, convulsions after apparent subsidence of infection, focal convulsions at anytime, vomiting after apparent subsidence of infection, any gross neurological abnormality during the immediate convalescent period, and an unsatisfactory course on the basis of clinical impression.[3]

Subdural fluid collections were found most often, in one series, in patients who had been treated with streptomycin intra-

muscularly but the antibiotic was not administered intrathecally.[3]

To fix any set rule for doing a subdural puncture may bring positive findings in some cases but it is known that some infants who show evidence of widespread damage early in the course of their infection show no subdural fluid, yet they remain defective children.

Evaluation of the subdural puncture can not be made at this early date but it was listed here as another method of treatment that may be contemplated when some of the above symptoms arise.

The following are the treatments of choice for the various types of meningitides as given by two investigators. The first in each group is the treatment of choice by this author based on this survey and the literature. Supportive therapy will not be given here since it will vary with the particular case and dosages will not be given since that is beyond the scope of this paper.

Treatment of Staphylococcal meningitis:

1. Penicillin, intramuscularly and intrathecally and aureomycin, orally.[3]
2. Penicillin, intramuscularly and intrathecally and bacitracin, intramuscularly and intrathecally or streptomycin, intramuscularly.[2]

Treatment of unknown types of meningitis:

1. If patient is under 10 years treat the same as for influenzal meningitis and if over 10 years treat the same as

Treatment of Salmonella infection of the meninges:

1. No specific treatment was given by either investigator but from this survey aureomycin, orally, penicillin, intramuscularly and sulfadiazine, orally were given.

Treatment of P. aeruginosa infection:

1. Polymyxin B, intramuscularly and intrathecally and streptomycin, intramuscularly and intrathecally.[3]
2. Polymyxin, intramuscularly and intrathecally.[2]

Treatment of pneumococcal meningitis:

1. Penicillin, intramuscularly and intrathecally and sulfadiazine, subcutaneously and chloromycetin, intramuscularly or intravenously.[3]
2. Penicillin, intramuscularly with or without streptomycin.[2]

Treatment of streptococcal meningitis:

1. Same as for pneumococcal meningitis.[3]
2. Same as for pneumococcal meningitis.[2]

Treatment of meningococcal meningitis:

1. Penicillin, intramuscularly and sulfadiazine, subcutaneously and if patient shows signs of Waterhouse-Friderichsen syndrome, treat with cortisone orally, intravenously and intramuscularly.[3]
2. Gantrisin or sulfadiazine intravenously and orally

or penicillin intramuscularly.[2]

Treatment of influenzal meningitis:

1. Chloromycetin, intravenously and intramuscularly and orally and sulfadiazine subcutaneously. A subdural tap should be done if indicated.[3]
2. Aureomycin, intravenously and orally or terramycin, intravenously and orally.[2]

Treatment of meningitis due to E. coli:

1. For mild infections: same treatment as for influenzal meningitis. For severe infections: add to the above streptomycin, intramuscularly and intrathecally.[3]
2. Same treatment as for influenzal meningitis.[2]

Treatment of tuberculous meningitis:

1. Streptomycin, intramuscularly for 6 months and intrathecally for 6 weeks and PAS, orally for 6 months and Promzole, intramuscularly for 6 months. In very severe cases use PPD or streptokinase and streptodornase intrathecally.[3]
2. Isoniazid, intramuscularly or orally. Streptomycin, intramuscularly and intrathecally.[2]

Treatment of lymphocytic choriomeningitis:

1. No specific treatment was given by either investigator but from this survey penicillin, intramuscularly and aureomycin, orally and desoxycorticoster-

one were used.

Postdismissal Follow-up

It was almost impossible to investigate the present status of all the cases reviewed in this survey but the outcome of well over half is known which is believed to be a representative group.

Those cases which expired are given on Chart number 7 and therefore are not included here on Chart number 8.

It was quite interesting to note the comment of the parent, even on those cases which were fully recovered at the time, about the child having a "change in personality" by being more nervous and restless.

The patients who seemed to be frequently ill were troubled with upper respiratory infections and pneumonia mainly.

The ataxia noted in the 3 cases which recovered from tuberculous meningitis could be caused by 8th nerve damage due to streptomycin but the case which recovered from pneumococcal meningitis had had no streptomycin therapy and therefore the ataxia could be due to arachnoiditis.

The high number of survivors of tuberculous meningitis which show neurological disturbances is not unusual but is alarming and as survivors increase the problem increases: mental retardation is the commonest type of disability and motor disturbance in one or more extremities is next most common.[4]

Of those cases which expired and on which an autopsy was done, the most common findings were bronchial pneumonia, increased intra-

Post-dismissal Follow-up

Types of Meningitis		Complete Recovery	Restless Nervous	Frequently Ill	Ataxia	Muscle Weakness	Partial Paralysis	Convulsions	Brain Damage	Not Contacted
Staphylococcal	(1)	1								
Unknown Types	(13)	1	1			2	1			8
Salmonella	(1)									
P. aeruginosa	(1)									
Pneumococcal	(6)	1		1	1	1		1		2
Streptococcal	(6)							1		3
Meningococcal	(17)	3		1						12
Influenzal	(6)	2						2		
E. coli	(2)							1	1	
Tuberculous	(10)			2	1	3		2	3	
Lymphocytic Choriomeningitis	(1)									

Chart No. 8: The above chart gives the complications which occurred after the patient was dismissed from the hospital, Patients which expired are not listed on the chart but the number at the side of each etiologic agent is the total number reviewed, therefore those which expired may be computed from this chart.

cranial pressure and pulmonary atelectasis.

Summary and Conclusions

It was shown by this survey that the majority of cases in this area were meningococcal meningitis with unknown types being second most common and tuberculous meningitis third in incidence.

Even though we have the antibiotics and other drugs which should help us to combat meningitis, there is an increase in the incidence for the year 1949, 1950, and 1951. The number for 1952 was not used since all were not recorded at the time this survey was made. The increase noted in the three years listed above is consistent with an increase over the country which may develop into an epidemic.

The seasonal cycle for meningitis in this series shows peak during the months of May, June and July with a drop in August and a gradual rise to another peak in November and January. The significant drop in December can not be accounted for.

When a preceding illness was noted it is interesting to note the large number who had an upper respiratory infection but it is just as interesting to note the number who presumably had no preceding illness. It is possible that the illness was so slight as to pass un-noticed.

The five symptoms first seen most often in this series were vomiting, fever, headache, lethargy, and irritability. The first three of these are not diagnostic of meningitis unless the vomiting is projectile in nature and in this series only three cases re-

ported projectile vomiting. Only 15.6 per cent of the cases had neck stiffness when first seen and only 7.8 per cent had a possible positive Kernig's sign.

The most frequently found physical sign at the time the patient was admitted to the hospital was neck rigidity (59.0 per cent) which is very suggestive of meningeal irritation. Pharyngitis was found in 50.0 per cent of the patients. A positive Kernig sign occurred in only 23.4 per cent of the cases.

The laboratory studies of the spinal fluid are very helpful in making a diagnosis since, usually, in meningitis many cells will be present and the fluid cloudy but this is not always the case since a significant number of the cases in this series had spinal fluid which was clear and which had a cell count of 100 or less. It was found that the type of cell present in the spinal fluid was usually a polymorphonuclear leukocyte except in tuberculous meningitis where a mononuclear leukocyte was found to be the most predominent cell.

Another finding in the spinal fluid in many cases but not all cases, was a decreased sugar and increased protein while the chloride determination was low in a few cases but this may be accounted for by the fact that it was not ordered on every patient.

Smear and culture of the spinal fluid should be done on every case since in some cases one was positive while the other was negative.

A hypochromic anemia was found in a significant number of

cases to warrant consideration during therapy.

The white cell in the blood was increased in number in the majority of the cases with most cases showing the segmented form more predominent.

No correlation could be made between the length of time a patient would be ill and when they were first treated since so many variables enter into the picture such as physical condition of the patient and preceding illness.

The type of treatment used in most types of meningitis reviewed centered around penicillin and sulfadiazine. The variations from this came in "Unknown types" where aureomycin was used considerably as well as penicillin and sulfadiazine, tuberculous meningitis where penicillin and streptomycin were used to a great extent, and lymphocytic chriomeningitis where penicillin and aureomycin were used. Supportive treatment was not included since it would vary so greatly with the case but fluids and blood should not be neglected.

The incidence of cure was quite high in all cases, with a significant number of cases shown, except in tuberculous meningitis where 50 per cent expired. Of those who survived but had some residual we find muscle weakness, paralysis, hydrocephalus, and central nervous system damage.

Since there is still a significant number of deaths in meningitis as a whole, the best methods of treatment are still to be determined but even at the present time there is a recommended

treatment for each type of meningitis. There are several elective types of therapy which can be deemed as necessary only by the physician acquainted with the case.

The postdismissal follow-up was not conclusive since a large number of patients could not be contacted but of those contacted it was interesting to note the large number who were reported to have had "a personality change" by being more nervous and restless. The number who had ataxia after having had tuberculous meningitis probably suffered an eighth nerve injury due to streptomycin.

Post-mortem findings in the combined cases consisted mainly of lung involvement and evidence of increased intracranial pressure.

To conclude, we are all looking for a treatment which will reduce the death rate but it is the author's belief that the answer does not entirely lie with the treatment. There are three very important steps that come before the treatment and they are the early diagnosis of meningitis, the etiology of the meningitis and to find out what antibiotics the organism is most sensitive to if one is isolated.

The only way which we can make an early diagnosis is to know what to look for and then look for it in every case and not just the most severe cases. We have three means of diagnosing: history and symptoms, physical findings, and the laboratory. The latter is for confirming positive cases and checking doubtful cases. The earlier a case is diagnosed and treated correctly the

more effective will be the treatment.

In order to give the correct treatment, the etiological agent must be determined as well as the antibiotic which will most inhibit or kill the organism. The smear and the culture are the important factors here. It must be remembered, though, one or the other may be negative, therefore both must be carried out in order to give the patient the full benefit of our facilities.

After the diagnosis, etiology, and antibiotic-organism sensitivity studies are established, the treatment is then initiated. From this survey and a review of the literature it is firmly believed that in all cases two antibiotics should be used, as determined from sensitivity tests, and the dosage should be safe but yet massive to prevent the development of a resistant strain and to insure early maximum therapeutic effect and the minimum sequelae. Also, with massive doses, more of the drug will diffuse into the spinal fluid but in certain cases where the organism is extremely sensitive to the drug and it is feasible to use the drug intrathecally, this method of administration should be used.

The supportive therapy should not be neglected because as the general physical status of the patient is improved the better will the body's defenses be to help in combating the disease.

Therefore, to decrease the mortality rate, first diagnose, then determine the etiology, and then treat using the correct drugs, as determined by sensitivity studies, the proper amount and the most advisable

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