NAMRU-4

An Introduction to NAMRU-4

HISTORY and ACCOMPLISHMENTS

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NAVAL MEDICAL RESEARCH UNIT No. 4
GREAT LAKES, ILLINOIS

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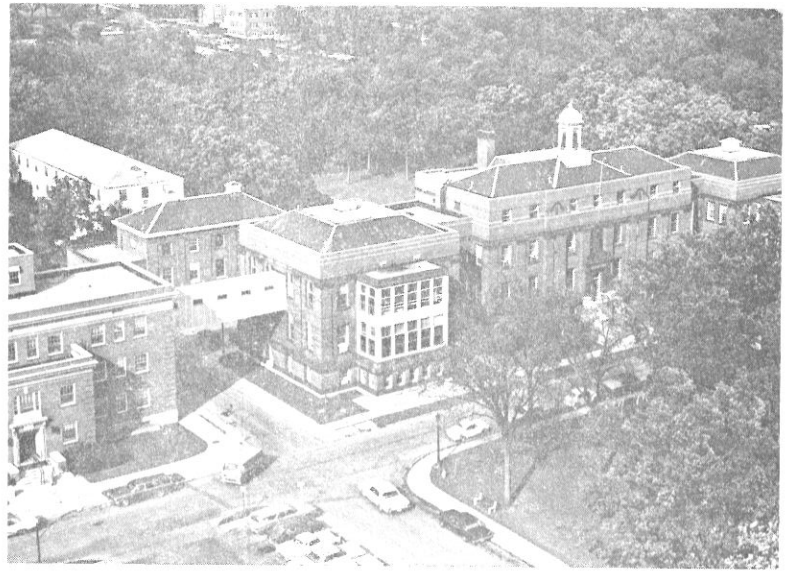
Building 2909, Great Lakes (above) was the site of NAMRU-4 from 1948 to 1961. Below is the present site, Building 1-H in the Naval Hospital compound. No photograph of the Dublin, Georgia, facilities are available.



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Origin

There are thirteen medical research activities within the framework of the Medical Department of the U. S. Navy. Of these, the Naval Medical Research Unit No. 4 is located within the Naval Hospital compound at Great Lakes, Illinois. The research interests of NAMRU-4 are now diversified, but its origin can be attributed to the seriousness of a single disease, acute rheumatic fever. During the Second World War, more than 25,000 new cases of rheumatic fever occurred in the Navy. By 1944, this disease ranked second as a cause of man-days lost due to sickness or non-combat injury, exceeded only by simple fractures. A new Naval Hospital was constructed at Dublin, Georgia to handle these patients. It was commissioned 22 January, 1945. The climate at Dublin was ideal for convalescence from the ravages of rheumatic fever. The attack against this disease was bolstered with the addition of the McIntire Research Unit for Rheumatic Fever. This Unit was commissioned 31 May, 1946. Present was Vice Admiral Ross T. McIntire, MC, USN, the Surgeon General of the Navy. Vice Admiral McIntire was also the personal physician and friend of the President of the United States, Franklin D. Roosevelt.

The original McIntire Research Unit staff consisted of four physicians, four laboratory technicians, four laboratory helpers, and was headed by Lieutenant Commander John R. Seal, MC, USN. The facilities included bacteriology, immunology, chemistry, and pathology laboratories, X-ray and electrocardiology sections, two wards, and a field station located at Great Lakes. The patients arriving at Dublin were mostly 17 to 25-year-old men from two Naval Training Centers; however, patients from Veterans hospitals were also admitted.

From Dublin to Great Lakes

A little more than two years after World War II, and 18 months after the commissioning of the McIntire Research Unit, the Dublin Naval Hospital, with its 18 buildings and 912 beds, was turned over to the Veterans Administration. Since there was a need for the Navy to continue its research on rheumatic fever, there was no reason to decommission the Unit. On 4 June, 1948, by order of John N. Sullivan, Secretary of the Navy, the McIntire Research Unit was officially re-established at Great Lakes as the Naval Medical Research Unit No. 4, with Commander John R. Seal as the Officer-in-Charge.

Confronted with transporting materials and personnel from Georgia to Illinois, Dr. Seal faced the problem of obtaining suitable facilities to house the laboratories and offices. He applied for and was refused a modern structure, Building 2711, now the Navy Examining Center in Forrestal Village. Eventually, an abandoned "H" type building, No. 2909, situated in the Farnsworth area of Camp Green Bay, was decided upon as the site for NAMRU-4. The surrounding yard was overgrown with tall and unsightly weeds that blocked the doorways. The building was filled with cobwebs and dust. Many of the windows were broken, and cracks in the floor admitted creeping vines that reached to the ceiling and clung to the walls. From this forbidding beginning arose polished laboratories with brightly painted woodwork and the flowered lawns that were to characterize the premises for the next 13 years.

Approximately one year was required to complete the move from Dublin to Great Lakes. On 7 June, 1949 the Unit was dedicated by the Surgeon General and placed under the Commanding Officer, Administrative Command, Great Lakes. The mission of the Unit was expanded to include study of the etiology, prevention, and control of acute respiratory disease as they affected Naval Recruits.

Thirteen Years in Building 2909

The next thirteen years saw a steady growth in the staff, expansion of departments, and improvement in laboratory facilities. The Unit included bacteriology, immunology, virology, chemistry, and biometrics departments, and a department of pathology which was later discontinued. A field laboratory was located in the recruit camp itself, and at one time two field laboratories were in use. The staff was increased to seven officers, 42 enlisted men and 23 civilians.

In 1950 NAMRU-4 hosted a meeting of the Commission of Acute Respiratory Disease of the Armed Foreces Epidemiological Board, an advisory group of distinguished persons in medical research.

The impact of the Korean conflict was keenly felt at NAMRU-4. The heavy turnover of Naval reservists and the increased number of recruits magnified the need for investigative work on acute respiratory disease and rheumatic fever.

Commander Seal relinquished the reins of NAMRU-4 on 14 July, 1954 after more than eight years as Officer-in-Charge. Dr. Seal demonstrated that penicillin prevents streptococcal epidemics and rheumatic fever. In recognition of this finding, he was presented the Edward Rhodes Stitt Award by the Association of Military Surgeons. Captain H. K. Sessions, MC, USN, relieved Commander Seal and remained as Officer-in-Charge until his retirement 15 months

later. Under Captain Sessions, ties with the University of Wisconsin were strengthened, and the use of tissue culture systems in virological research were advanced.

During the tenure of Captain Matthew J. Hantover, MC, USN, who relieved Captain Sessions in late 1955, the MEND Symposium (Medical Education for National Defense) was held. On 14, 15 and 16 February, 1956 some of the most distinguished names in medicine and microbiology assembled at Great Lakes. The original work on the discovery of the adenovirus group, then called "APC-RI viruses", was reported by groups from the National Institutes of Health and from the Walter Reed Army Institute of Research, working independently. Papers were also presented during a special program by speakers from NAMRU-4. It was at this session that Drs. Pelon and Mogabgab of NAMRU-4 announced the isolation of a virus called "2060", which later became recognized as the first of the Rhinovirus family of common cold viruses. The MEND Symposium was also significant for bringing Dr. Gene H. Stollerman to NAMRU-4 for the first time. Dr. Stollerman later accepted an appointment as a consultant to the Unit, a post he still holds after more than 15 years.

In January 1957, Commander B. F. Gundelfinger, MC, USN, became Officer-in-Charge. The Asian influenza epidemic was rapidly spreading, increasing in severity and endangering Naval recruits. This along with the Russian "Sputnik", sparked a new vigor in NAMRU-4 efforts. Captain L. F. Miller, MC, USN, became Officer-in-Charge in 1958 and a new era of controlled epidemioligical studies was launched.

Building 1-H

1961

A new 800 bed hospital was dedicated on 8 September, 1960 in the hospital compound near the Southwest boundary of the Great Lakes Naval Base. The new 12-story structure brought the sprawling complex of 31 miles of wards under one roof. Building 1-H, the old hospital, was emptied. On 14 June, 1961 the staff of NAMRU-4, under Captain L. F. Miller, MC, USN, moved from Building 2909 to Buildings 1-H and 43-H. The Unit now came under the command of the Commanding Officer, U. S. Naval Hospital, Great Lakes.

Since occupying Building 1-H, the Unit has become firmly rooted in its lakewide setting in the shadow of the new Naval Hospital. It slowly became apparent from the recognition received, that the earliest years of work on rheumatic fever and acute respiratory disease were now paying dividends. Visitors, alone or in groups, are now to be seen touring the laboratories. It is common to receive investigators from research facilities abroad for consultation with staff members or to observe the research operations of NAMRU-4. For the first time, NAMRU-4 investigators are now in demand as speakers at national and international meetings.

These are valid signs that NAMRU-4 is recognized and can stand securely on its merits. The research activities at NAMRU-4 are also recognized locally. Honors have been bestowed on NAMRU-4 employees on three separate occasions. Two staff members received Federal Employee of the Year awards (First Prize) and two members have been nominated for this award from among 60,000 Federal Civil Service workers in the Chicago area. In addition, three employees have been selected by the Bureau of Medicine and Surgery as their representative to the National Federal Employee of the Year awards.

A pneumonia crisis occurring in recruits during the early 1960's resulted in the dedication of a Mycoplasma Research Division on 19 September, 1962. This expansion advanced the capability of the Unit in the study of respiratory disease. The Research Unit now consisted of six scientific divisions: Biochemistry, Biometrics, Bacteriology, Immunology, Virology and Mycoplasma, and the Administrative Department which includes such support facilities as the Library, Special Operating Services and a Publications Division.

The Field Laboratory was moved 12 October, 1964 from its location in the Recruit Dispensary, Building 1109, into a new dispensary, Building 1017. From this laboratory, epidemiologists gathered their clinical material, and did their foraging into the recruit barracks.

In June 1964, Captain Robert O. Peckinpaugh became Officer-in-Charge, relieving Commander Charles H. Miller, who was Officer-in-Charge for a very short time between the departure of Captain L. F. Miller and the arrival of Captain Peckinpaugh. The following years saw a series of remodeling projects to make the various laboratories more suitable for research work. Also emphasis was placed on updating equipment. Such efforts resulted in a modern, well equipped research complex.

Control and management of NAMRU-4 was assigned to the Bureau of Medicine and Surgery on 1 January, 1965 with area coordination given to the Commandant of the Ninth Naval District.

The year 1966 marked the twentieth anniversary of NAMRU-4. In tribute to its two decades of existence, a scientific meeting was held on the 10th and 11th of June. The occasion was highlighted by the return of friends and alumni, some of whom had not visited the Unit in many years. Another event in 1966 was the opening of a Division of Nursing Research, headed by Dr. Lorraine Wallenborn. The mission of this Division was to improve the teaching within the Navy's Hospital Corps School. Offices were opened on the second floor of Building 1-H on 1 December, and work was carried on until January, 1969 when the entire Division was transferred to the Naval Medical Research Institute in Bethesda, Maryland.

A Separate Command and Southward Expansion

Throughout its life, NAMRU-4 existed under other Commands. On 13 April, 1968, however, Captain Robert O. Peckinpaugh, MC, USN, Officer-in-Charge, became the Units's first Commanding Officer.

The population pressure at Great Lakes was relieved when a new recruit training center was completed in Orlando, Florida in 1968. The Bureau of Medicine and Surgery felt that acute respiratory disease and pneumonia at this new installation should be placed under immediate study. On 4 September, 1968 the NAMRU-4 Component Research Laboratory was established at the Naval Hospital, Orlando, Florida.

The fourth in a series of meetings on meningitis, and the second to be held at NAMRU-4, was conducted on 23, 24, and 25 July, 1969. The purpose of the meeting, chaired by Captain James R. Kingston, MC, USN, was to bring together investigators of the Department of Defense and the Center for Disease Control, and contractors and advisors, who were active participants in research on meningitis and meningococcal infections. The resulting presentations and discussions have been compiled into a 267-page monograph.

In June 1971, another milestone was marked by the celebration of the Twenty-fifth Anniversary of the founding of the Unit. This occasion was highlighted, as had been done five years earlier, by scientific meetings on the 3rd and 4th of June, and the return of many friends and alumni.

On 27 April, Captain Charles H. Miller, MC, USN, became the second Commanding Officer of NAMRU-4 when he relieved Captain Peckinpaugh upon his retirement from the Navy.

MAJOR DISEASES AFFECTING NAVAL RECRUITS

The Naval Medical Research Unit No. 4 has been charged with providing essential information regarding communicable disease and medical problems of military significance. The procurement of such data is necessary if one is to uncover the etiology of a disease and the mode of transmission. Once these are known, plans can be developed and incorporated to control and prevent the infection. With this in mind, a brief description of the major diseases affecting Naval recruits, and the Navy as a whole follows.

Rheumatic Fever

Between the First and Second World Wars, rheumatic fever was of minor importance to the military, and its incidence and severity was low in the civilian population. This disease, however, emerged during World War II as an important cause of man-days lost. The Navy experience with the disease was two to three times greater than that of the Army, the number of cases admitted to the sick list being more than 25,000 between 1940 and 1946. A report from Dublin revealed that in 1945 and 1946 there were 1,917 patients included in a single study. The time lost by these patients ranged from 1 month to more than 18 months with an average of 5.2 months, or 234 days, per patient.

Since acute rheumatic fever appears to involve only connective tissue, patients exhibit a variety of symptoms. The major ones include fever, joint pain, various manifestations of heart disorders, abdominal pain, and chorea. There is a loss of weight and appetite, with weakness and fatigue. Skin disorders and subcutaneous nodules occur in the young. There is a constant fear of residual heart damage which decreases life expectancy. Follow-up studies on a large number of cases indicate that the majority of patients with severe cardiac involvement succumb within ten years. For these reasons, the cause, the methods of prevention, and the treatment of this disease warranted intense investigation.

Streptococcal Infections

While the cause of rheumatic fever remained unknown, it became increasingly apparent during World War II that cases of rheumatic fever followed outbreaks of respiratory disease due to the group A streptococci. The observation was also made that scarlet fever, a manifestation of streptococcal infections, preceded rheumatic fever. The group A streptococci, therefore, came under close scrutiny by NAMRU-4 investigators during the early 1950's. As many as 35 patients from each 1,000 recruits were admitted each week with respiratory disease. Bacteriological studies demonstrated that a group A streptococcus was often present, with as many as 50 percent

of these patients harboring the organism.

The clinical spectrum points to the seriousness of these infections. At the onset, there is often a high fever and sore throat. A tonsillar or pharyngeal exudate is often present and a skin rash may develop. The streptococcus multiplies in the lymphoid tissue of the tonsils and pharynx, and substances released by the organism are deleterious to local tissues, producing systemic disturbances and subsequent illness. Extension of the infection from the throat results in sinusitis, otitis media, mastoiditis, cervical adenitis, and impetigo. Blood stream invasion may occur with lesions appearing in areas such as joints and bones. It is now known that subsequent to streptococcal infections, rheumatic fever, glomerulonephritis, and mesenteric adenitis can develop. These complications arise from the initial respiratory infection, and usually occur one to three weeks after the infection subsides. It has been calculated, from studies of epidemics, that three percent of patients with untreated streptococcal infections develop rheumatic fever as a sequela. The task was to determine the factors responsible for these epidemics, and to develop methods for bringing the streptococcus under control.

Influenza

Influenza is a disease that can strike down scores of recruits and disable ships at sea. The name influenza (influence) is of Italian origin; they believed that the disease was "influenced" by the stars or the cold. Three types of influenza virus exhist: A, B, and C. These designations coincide with their rank of disease-causing ability. Influenza occurs in epidemic and pandemic forms, and has been responsible for much illness and many man-days lost in the Navy. During the Asian influenza pandemic in 1957, acute febrile respiratory disease reached the highest peak ever observed by NAMRU-4 with 122 out of 1,000 men admitted to the hospital in the first week of October. Serological testing of non-immunized patients revealed influenza A infection in 54 percent in early September, 67 percent in the last week of September, and 100 percent in the first week of October. No other infectious agent has ever achieved this level of attack at Great Lakes. In contrast with the A virus, influenza B occurs in the epidemic form with infections occurring in 40 percent of those hospitalized The influenza C virus is associated with mild illness and has not been extensively studied.

Infection with influenza may be asymptomatic, producing only a slight fever, or causing the prostrating disease that occurs during epidemics. There are chills, fever, headache, and muscular aches. The fever usually ranges between 101° to 106°F. In both pandemic and epidemic disease, the illness is severe, but brief, lasting seven to ten days. The most dangerous complication of influenza is a fatal infection of the lung either by the virus itself, by

a secondary bacterial pathogen, or by both. There is no specific treatment for influenza. NAMRU-4 has the responsibility of detecting the presence of influenza in the population, finding ways of controlling the epidemics, and developing a method of treatment.

Acute Respiratory Disease

The designation "acute respiratory disease", or ARD, was used originally to classify respiratory illnesses of unknown causes not diagnosed as influenza or streptococcal infection. The number of recruits contracting ARD has been startling, and placed a heavy burden on Naval Medical treatment facilities. During the early 1950's, 25 to 600 recruits were admitted weekly to the hospital. The illness occurred disproportionatly much more often as a disease of recruits than of other populations within the Navy. For example, in 1961, during peak incidence, 13 recruits were admitted for each admission from the Service Schools or the Administrative Command at Great Lakes.

The clinical signs of ARD are somewhat more severe and lasting than those of the common cold. The onset may be gradual or sudden, with fever, sore throat, malaise, and cough. The fever usually ranges from 100° to 104°F lasting from two to 12 days. In approximately 50 percent of the cases, there is a patchy exudate in the pharynx, and in many patients, a mild bilateral conjunctivitis occurs.

The demonstration of a new group of viruses in 1953 by Rowe and associates and by Hilleman and Werner, led to a vast amount of research that demonstrated that these viruses, called "adenopharyngeal-conjunctival agents" were the major cause of ARD in military recruits. They are now officially known as the adenovirus group, with type 4 adenovirus being the most prevalent among Naval recruits.

Primary Atypical Pnuemonia

The type of pneumonia in which a bacterial agent cannot be demonstrated has been referred to as "primary atypical pneumonia." During World War II, this syndrome was encountered at many of the military bases in England and the United States. In 1942, Scott Field, Illinois recorded 735 cases, and in 1944, it was reported that Jefferson Barracks, Missouri suffered 1,862 cases. At Great Lakes, non-bacterial pneumonia was rampant during the war. Following the Asian influenza pandemic in 1957, the incidence was again accelerated and in October, 1961, 24 cases/1,000 population/month represented the peak incidence with a total number of 2,500 patients admitted that year. The average length of stay of patients with pulmonary infiltrates was 30 days.

Meningococcal Infections

The organism known as the meningococcus (Neisseria meningitidis) causes fatalities in Naval recruits from year to year. Sulfonamides had been effective in treating this agent until 1963 when sulfa-resistant strains were found at San Diego. A Navy-wide program was organized in 1965 for investigating this infection, with NAMRU-4 being involved.

The graveness of meningococcal septicemia and meningitis can be appreciated from the 70 percent fatality rate reported for untreated cases. Meningococcal septicemia and epidemic cerebrospinal meningitis occur predominately in the very young and in military recruits. In Naval recruits, the carrier rates which fluctuate from month to month have ranged from a low of seven percent in San Diego to a high of 87 percent at Orlando. Despite the dissemination of the organism in the population, the incidence of disease is surprisingly low. Based on a 10.5 percent sample of 69,713 recruits at Great Lakes, it has been estimated that only five clinically diagnosed cases occurred in 39,187 carriers. A total of 159 cases were seen at Great Lakes during a 20-year period (1950-1970) with 13 fatalities (eight percent).

In meningococcemia, there is usually a sudden onset with fever, chills, malaise, myalgia, and apathy. Frequently, the initial complaints are recurrent fever, rash, arthralgia, acute polyarthritis, nausea and vomiting, with the rash being the most striking feature. In the severe form, acute, fulminating meningococcemia, there may be massive purpura with adrenal involvement together with encephalitis. In this condition, the illness is often fatal.

Patients with meningitis usually present signs and symptoms of irritation of the meninges such as pain in the neck and back, muscular spasms, and stiff neck. As the infection progresses, restlessness, irritability, delirium, and convulsions occur. The permanent impairment resulting from meningococcal infections and their complications include deafness, ocular palsies, blindness, mental changes, and hydrocephalus. To prevent these infections, either through immunization or antibiotic prophylaxis, has become a high priority objective of NAMRU-4.

ACCOMPLISHMENTS

Perusal of the reprint file of papers published over the past twenty-five years has revealed many enlightening features of various infectious agents and their affect on Naval recruits. In pursuing information in any area of the medical sciences, one strives for positive results. The attainment of negative results, however, should not be disregared as they produce knowledge of what not to do, thus saving time, money, and effort. The patients may be saved as well. With this in mind, let us look at the positive and negative accomplishments of NAMRU-4.

Rheumatic Fever and Streptococcal Infections

Rheumatic fever and streptococcal infections were given much emphasis in the late 1940's and early 1950's. A major problem of importance to the clinician was that of determining whether the rheumatic process was active or quiescent. If an error was made, a patient might be unnecessarily confined to bed for long periods of time. Two simple laboratory tests, the Weltman serum coagulation reaction and the Cutler sedimentation test, were analyzed for their sensitivity in detecting the active or inactive state of rheumatic fever. A high order of agreement was found between these tests and abatement of the rheumatic process.

The drug known as Benadryl was widely accepted in the mid-1940's as a therapeutic agent for the control of a number of allergic phenomena. At that time, rheumatic fever was believed to be an allergic response to the group A streptococcus. The clinicians of NAMRU-4, therefore, considered Benadryl as a candidate for possible favorable influence on the course of this disease. Testing this drug on rheumatic fever patients demonstrated that it had no effect on the disease.

In the mid-1940's, the tonsils of patients with low-grade activity were removed and then the patients were treated with penicillin. Whether or not this procedure had an adverse effect on the patients was unknown. The results of a study at the Dublin Naval Hospital to answer this question disclosed that such a procedure could be used with safety in patients.

The incidence and circumstance of any disease must be understood in order to attack it effectively. The records of 1,917 consecutive patients admitted to the Dublin hospital were analyzed for demographic, epidemiologic, clinical, and laboratory factors which were deemed relevant. An important finding of this survey was that of the men contracting rheumatic fever in the Navy, 13 times as many had experienced the disease prior to enlistment. It

was believed then that this disease could be curtailed in the Navy by excluding those applicants for enlistment who had experienced rheumatic fever.

It became known that group A streptococci were capable of producing substances which could destroy red blood cells. Two substances were identified: streptolysin "O" and streptolysin "S". Antibodies to the "O" lysin were noted to significantly increase in sera of patients suffering from streptococcal infection and were observed to attain abnormally high levels in rheumatic fever. The demonstration of such increasing titers was diagnostic and the testing for the "O" lysin became a universal tool for the study of streptococcal infections. NAMRU-4 workers made significant contributions by developing technics for the production and titration of streptolysin "O" and its antibody. These technics were utilized for the commercial production of streptolysin "O" antigen which permitted tests to be run in any hospital laboratory. Studies on streptolysin "S" disclosed that it was non-antigenic and, therefore, probably unimportant as a laboratory tool.

Penicillin treatment of streptococcal infections was pursued with vigor beginning in 1951. If the organism could be erradicated by daily administration of oral penicillin, then hospital admissions for both respiratory infections and acute rheumatic fever would be prevented. A series of studies was initiated in 1951 and followed for 15 years. The first problem concerned mainly that of dosage, and experiments had to await the occurrence of recognized streptococcal epidemics. In the earliest experiments, it was observed that small oral doses of penicillin indeed prevented the acquisition of streptococci by recruits, but did not eradicate the carrier status. Stepping up the dosage to 500,000 units of penicillin by giving two daily doses of 250,000 units each had a dramatic effect on an epidemic at Bainbridge, Maryland. The streptococcus was eradicated and rheumatic fever was aborted; in a sharp outbreak of streptococcal infections at Great Lakes, however, this penicillin regimen did not suppress the epidemic and rheumatic fever cases occurred. The kind of penicillin preparation and route of administration was therefore changed to 600,000 units of benzathine penicillin administered in a single intramuscular dose. This treatment provided protection for three to four weeks and eradicated the group A streptococcus from carriers. After more study, the 600,000 unit dose was found inadequate and a 1,200,000 unit dose was determined as being adequate if given in the second week of training. Over the past 14 years, streptococcal infections and rheumatic fever have been virtually eliminated in Naval recruits by the use of penicillin. This accomplishment is considered by many as a major step in medicine. In conjunction with penicillin prophylaxis, both erythromycin and chlortetracycline (aureomycin) were tested for the prevention of streptococcal infections in recruits. The results indicated that both were effective.

In seeking to control the spread of streptococcal infections, it was necessary to pinpoint where such spread occurs. A 1950 study of two companies of recruits indicated that spreading of the infection occurred in the sleeping quarters.

Influenza

Studies of influenza epidemics proved rewarding and informative. Little knowledge existed on the clinical importance of influenza type C. In 1952 and 1954, during epidemics of respiratory disease, a total of 45 strains of influenza C virus were isolated and identified. These viruses occurred simultaneously in the same epidemic. It was determined that the C virus was associated with mild illnesses and that they did not shift antigenically over the two-year period. The experience of NAMRU-4 with this virus was unique and quelled the fears of epidemiologists who had only slight knowledge of its characteristics.

In 1954, the first variation of influenza B virus since the 1940 Lee strain was isolated from a recruit by NAMRU-4 virologists. It was determined from the prototype strain GL-1750-54B, that a major shift in the antigenic composition had occurred. The virus was therefore incorporated in a standard vaccine used throughout the United States in both the military and the civilian population; and it was to be incorporated in all the polyvalent vaccines for the next ten years.

Influenza viruses for diagnostic antigens were prepared by harvesting infected allantoic fluid from chick embryos. Unfortunately, pooled fluid underwent deterioration during refrigerator storage prior to its use. By modifying the technic for precipitating and purifying the virus, NAMRU-4 scientists were able to concentrate and stabilize the virus for five years or longer.

The isolation and propagation of influenza viruses was an awkward, expensive, and laborious procedure. Virologists of NAMRU-4 were the first to succeed with an alternate technic using human tissue cultures. After considerable experimentation with various types of human cells, the lung and kidney proved the most successful for sustaining influenza A and B. A monkey kidney tissue culture system, developed as a substitute for human kidney tissue cultures, is now used world-wide for the isolation of influenza viruses.

Much of the work with influenza has been directed toward preventing the disease through immunization. During the Asian influenza pandemic of 1957, a monovalent vaccine, prepared from this virus strain, was tested by giving a small intracutaneous dose (0.1 ml) and a subcutaneous dose of 1.0 ml. The smaller intracutaneous dose gave 25 percent relative reduction in illness as opposed to 8 percent for the larger dose.

During this same pandemic, both influenza and adenovirus vaccines were tested singly and in combination. The influenza vaccine contained 200 chick cell agglutinating units per dose, and the adenovirus was a polyvalent preparation containing virus types 3, 4 and 7. When both vaccines were administered, there was a 68 percent reduction in febrile respiratory disease. When influenza vaccine was given alone, the reduction was 60 percent; and when adenovirus vaccine was given alone, the reduction was only 28 percent.

The biometricians of NAMRU-4 became noted for the development of a new equation for resolving the effectiveness of vaccines. This formula, called "IVE" (intrinsic vaccine efficacy) took into account the relative reduction of illness in the vaccines in relation to the control patients who become infected with the agent being tested.

$$IVE = \frac{\text{Clinical relative reductions}(\%)}{\text{Control patients infected}} \times 100$$

The IVE equation, now used by many investigators, is a novel and useful method for evaluating vaccines under development.

A monovalent Asian influenza vaccine, in combination with adenovirus vaccine, was tested in 12,510 recruits during the Asian influenza pandemic. The effect of febrile respiratory disease was calculated by the IVE. The results disclosed that the influenza vaccine, when given by itself, protected 100 percent; the adenovirus vaccine protected 68 percent and the combined vaccines protected 73 percent.

A new influenza virus vaccine prepared from the hemagglutinating fraction of the influenza virus was tried in recruits for acceptability and antigenicity. The new vaccine was shown to produce one-sixth as many febrile or systemic reactions, and one-half the number of local reactions as the standard vaccine. The antibody response to the hemagglutinin vaccine was rapid and titers were slightly higher than with the standard vaccine. Another preparation containing the hemagglutination antigen with mineral oil and arlacel A showed a superior antibody response. These studies were responsible for the development of an improved influenza vaccine for use in military and civilian populations. The problem arose as to which of these vaccine preparations should be used. An acceptability study performed on 38 different preparations of influenza vaccines showed that the hemagglutinating fractions, prepared by zonal centrifugation and given intramuscularly in 0.5 ml doses, produced the least local reactions.

A study to determine the effect of route of influenza immunization and dose was conducted in 1970-71. Immunization was

given intracutaneously, subcutaneously and by nasal spray. The intracutaneous route was shown to give a greater seroconversion rate using a smaller antigen dose than either the other two routes. The intranasal route was the least effective on stimulating either nasal antibody or serum antibody as compared to the intracutaneous or subcutaneous routes.

A cold-adapted attenuated live influenza virus vaccine has been evaluated for antigenicity and acceptability in recruits during the summer of 1971. There were no adverse reactions and doses of 7.5 log EID_{50} of influenza A produced an 80 percent seroresponse. The same dosage of influenza B stimulated a 50 percent seroresponse. These vaccines were used in a protection study during January, 1972.

There exists a great need for antiviral compounds for treating or preventing influenza and other viral infections. A synthetic organic amine compound (amantadine hydrochloride) was reported to offer protection against influenza A_2 infections. Tested by NAMRU-4, this compound passed acceptability tests, inhibited seroconversions from natural infections by influenza A_2, but not influenza B; and did not affect antibody responses from immunizing with influenza vaccines. These accomplishments have supported the belief that amantadine may well prevent type A influenza infections during an outbreak of this disease, and encouraged further work on this compound.

Acute Respiratory Diseases

A six-year study was conducted in the late 1940's to determine whether or not ultraviolet radiation of recruit barracks might reduce the incidence of ARD and streptococcal infections. The reduction in the incidence was consistent, usually ranging from 20 to 30 percent. The airborne bacteria were reduced markedly during certain time periods, ranging up to 90 percent reduction. The carrier rate of group A streptococci, however, was not affected, and heavy contamination of the air sometimes occurred in the barrack subjected to UV radiation. The concept of installing UV lights in all recruit barracks, as well as further studies, was abandoned.

In the early 1950's antihistaminic drugs were considered beneficial to patients suffering from upper respiratory illnesses, such as the common cold. Studies were undertaken in Naval personnel at Great Lakes to substantiate or dispel this belief. The following conclusions were drawn from trials with these drugs; 1) placebos were as effective as the drug in officers and senior petty officers; 2) the drugs had no effect in Navy male recruits, and 3) no beneficial effect was obtained in Navy Wave recruits.

Another attempt to control respiratory illnesses in the

barracks by use of triethylene glycol gas was made. Gas generators were installed in the test barracks, and if successful, would be installed in all the barracks. The gas reduced airborne bacteria by 65 percent, but the recovery of streptococci was not affected, even when the floors were oiled in the gas-treated barracks. Triethylene glycol gas did not prevent epidemics of influenza, streptococcal infections, or other ARD's.

In the hope of controlling ARD with antibiotics, the use of erythromycin was investigated in recruits with ARD of unknown etiology. The drug had no effect on the disease and it was recommended that it not be used.

The causative agent of most of the respiratory diseases was unknown, though believed to be of viral origin. In the early and mid 1950's, a program was initiated in the search for new viral agents. The effort resulted in the appearance of a new cytopathogenic agent in tissue culture. This new agent was recovered from a recruit with a mild common cold-like illness and was designated virus "2060". The "2060" virus proved to be the first of a series "2060" virus strains, and later the forerunner of the rhinovirus group of agents now known to cause the common cold.

The isolation and characterization of a new group of viruses resulted in NAMRU-4 conducting extensive studies on the adenoviruses. In 1954 and 1955, serologic rises to these agents were demonstrated in 40 percent of the recruits. Types 3, 4, 5, and 7 were identified. These observations indicated that further work was necessary, and after 17 years is still continuing.

Adenovirus infections were diagnosed by: 1) isolation of the virus; 2) by demonstrating complement fixing antibody titer rises, and 3) by demonstrating a rise in neutralizing antibody titer. These methods required equipment and technics not available to all laboratories. The indirect hemagglutination test was therefore developed. This reaction proved to be as sensitive and reliable as the other more cumbersome technics and is still used today in various laboratories.

Studies on differentiation and characterization of the adenovirus group demonstrated that the various types could be differentiated by thermal inactivation characteristics. Evidence was thus obtained to show the existence of definite groups of these agents.

HeLa cells were used to gain understanding of the virus particle and the complement fixing components of the adenovirus. It was demonstrated that the complement fixing antigen and the virus were produced independently.

While it was well known that the adenovirus was responsible for much of the ARD in recruits, close observations indicated other agents might also be active in the population. A study conducted by repeatedly sampling ten men, as they passed through training, indicated that other agents or factors were responsible for the chronic type of respiratory disease seen so frequently in the late 1950's.

The approach to controlling ARD through immunization with adenovirus vaccines has been under investigation for 15 years. In the first trial, conducted at Great Lakes, an inactivated trivalent adenovirus vaccine containing types 3, 4 and 7 adenoviruses was given to newly arrived recruits. The results disclosed that 55 percent of febrile ARD was prevented. Furthermore, the number of cases of non-bacterial pneumonia were also reduced.

A cultural and serological study of samples taken from men attending sick call at the recruit dispensaries revealed that ARD was often associated with two or three mixed infections, namely, adenoviruses, group A streptococci, and influenza viruses. Further studies disclosed that mixed infections occurred more often in hospitalized patients. These results emphasized the complexity of the etiology of the respiratory infections of recruits.

During epidemics of ARD, cases of rubella were frequently observed. The etiology of rubella was poorly understood and a search for an adenovirus resulted in the isolation of the virus from the blood and urine of recruits suffering from rubella. This was the first demonstration of adenovirus viremia and viruria in recruits.

In 1959 and 1960, a carefully planned clinical and laboratory study was performed using two recruit companies; one in the winter and the other in the summer. The results showed that the highest incidence of ARD occurred in the second week of training, and that adenovirus accounted for only a small portion of the milder illnesses. However, 50 percent of the febrile ARD seen at sick call were adenovirus-associated. Adenovirus infections were observed to be clinically more severe in the winter and it was also disclosed that a pre-existing non-adenovirus respiratory disease pre-disposed the recruit to an adenovirus infection.

A long series of studies on the effectiveness of dosage and administration of adenovirus vaccines produced a number of interesting results. A 0.5 ml dose of a polyvalent vaccine was as effective as a 1.0 ml dose in preventing ARD and pneumonia. Thus, should a vaccine be in short supply, small dosages could be used. Severe respiratory illnesses were reduced, while illness prevalence remained unchanged. Testing adjuvant adenovirus vaccines disclosed that one-fourth ml doses were as effective as

1.0 ml of aqueous vaccine, and that the pneumatic jet gun was as effective as needle and syringe.

A newly developed live adenovirus vaccine, type 4, given orally was reported to be of value in preventing ARD. In the first trial by NAMRU-4, the live vaccine was compared with a killed vaccine. These vaccines reduced febrile ARD by 43 percent, one being as effective as the other. Another study resulted in 50 percent reduction, and in 1966, a mass immunization of all recruits was undertaken with the live, oral vaccine. The effect was to sharply curtail a rising incidence of ARD with rates dropping from 30/1000/week to 3/1000/week within 14 days. Since this program was undertaken, the incidence of febrile ARD has not returned to the former high levels observed for so many years.

Another approach to the control of ARD was the concept of furnishing protection by use of gammaglobulin. It was demonstrated that febrile ARD was reduced by 20 percent in gammaglobulin recipients, but that milder respiratory illnesses were unaffected. Pooled hyperimmune gammaglobulin from recruits who had experienced ARD was no more effective than the standard gammaglobulin.

In the course of investigating ARD, the virological work has been extensive and the procedures were difficult, time-consuming, and expensive. An achievement that greatly improved the output and eased the labor, was the adaptation of tissue culture to microtiter plates. This innovation has been well received and is currently in world-wide use.

Studies by NAMRU-4 investigators working at the Naval and Marine Corps training centers at San Diego demonstrated how crowding and close contact influences the incidence of ARD. Illness rates were studied simultaneously in the Naval recruit camp and in the Marine Corps training camp situated side by side and separated by a fence. Among Navy recruits, the incidence of respiratory illnesses was three times greater than in the Marine Corps trainees. In the early weeks of training, the Navy recruits were divided into companies and were free to mix. Marines, on the other hand, were divided into platoons that were sent to battalions separated physically from one another. The latter system afforded less opportunity for new arrivals to intermingle with the older men on board.

The San Diego Naval Training Center was closed in 1963 to new arrivals because of an outbreak of meningococcal disease. After an interval of four weeks, training was resumed, but contact between men already aboard and men arriving was prevented. Crowding was also minimized. There was a great reduction in febrile ARD among the recruits entering under the new environmental conditions, with rates of 6/1000/week as opposed to the prior rates of

15/1000/week. The effect was particularly noticable for Mycoplasma pneumoniae infections which were 2.7 percent in the new, less crowded environment as opposed to 18.4 percent for the older, more crowded camp. These observations emphasized the need for manipulating the environment and system of handling men if ARD in Naval recruit training centers was to be controlled.

Primary Atypical Pneumonia and Mycoplasma Research

One of the earliest adenovirus strains isolated was from a patient with primary atypical pneumonia by investigators at Walter Reed. Further investigations in other laboratories suggested that adenoviruses were a major but not the only cause of these pneumonias; a close examination of data, however, from controlled studies by NAMRU-4 investigators, indicated other factors were involved.

For many years, a drug was sought for the effective treatment of primary atypical pneumonia disease which did not respond to penicillin. Studies performed at Parris Island indicated that dimethylchlortetracycline (declomycin) was helpful. A study of this drug at Great Lakes indicated that patients who received it improved, as demonstrated by earlier ambulation, quicker control of cough, more rapid clearance of lung infiltrates, and shorter hospital stay. The drug was particularly effective, strangely enough, in those patients presenting evidence of viral infection.

Much knowledge of the pneumonia cases at Great Lakes was derived from epidemiological studies. They showed that 80 percent of pneumonias in an epidemic occurred before the third week of training, and in the summer and autumn, with a lesser peak in the winter. When routine immunizations were given to all recruits it was found to accentuate the incidence of pneumonias, but penicillin prophylaxis did not produce such an effect. The incidence of this type of pneumonia was twice as great in those recruits who lived in the Northern half of the United States, and reduced in men who arrived from the South. Men who weighed less than normal were more apt to contract pneumonia than men weighing more than normal.

Investigation on the Eaton Agent as a cause of primary atypical pneumonia was accelerated when it was demonstrated at the National Institutes of Health that this agent was a Mycoplasma. Mycoplasma pneumoniae was isolated from Naval recruits and antibodies detected in their sera. The strain, M-52, was placed in the American Type Culture Collection. The role of this organism was shown to be important, especially in the fall of the year when up to 50 percent of patients admitted with pneumonia were found to have this infection. The association of this infection

with the cold agglutinin response was firmly established at Great Lakes and the limitations of the diagnosis of M. pneumoniae infection by this method was delineated.

Much of the work on the mycoplasmas, all difficult to grow and manipulate in the laboratory, has been directed toward diagnostic methods. A selective medium and color test for the isolation and identification of mycoplasma was developed at NAMRU-4. Serological identification procedures were improved and new cultural media were advanced for detecting mycoplasma in patients. A major biological characteristic of M. pneumoniae, resistance to methylene blue, was uncovered at NAMRU-4, and is now cited as a criterium for differentiating this organism from other mycoplasma species.

In procuring throat cultures for the isolation of mycoplasma, data were obtained by NAMRU-4 showing that these organisms often occurred as a mixture of several species. This information served to demonstrate that the standard methods in use were inadequate, and that the problem was more complex than previously supposed.

Experimental work at NIH suggested that M. hominis was the causative agent of exudative pharyngitis and tonsilitis in man. This condition was the most common clinical finding in Naval recruits. A study performed at NAMRU-4, however, was first, of several studies, to demonstrate that this organism could not be found in the naturally occurring disease.

M. pneumoniae antibody titers were reported to be significantly elevated in a series of patients with Stevens-Johnson syndrome, but the organism was not isolated. One of the first isolations of this agent from a case of this disease was accomplished at NAMRU-4. Follow-up studies, however, did not support the hypothesis that the pneumoniae agent was an important factor in this disease as it occurs in recruits. Another complication of respiratory infections is the Guillian-Barre' syndrome, also believed to be associated with M. pneumoniae. The isolation of the agent was accomplished by NAMRU-4 personnel from one of four patients with this disease.

A need was seen for a handbook on the handling of mycoplasma in the laboratory. This need was filled by "A Laboratory Guide to the Mycoplasmas of Human Origin", compiled at NAMRU-4. This booklet has been widely accepted and is currently in use in medical schools and universities.

The demonstration of cold agglutinins in the sera of patients with primary atypical pneumonia has been a valuable help in the diagnosis of this disease. The performance of the test was laborious and the time taken to obtain the results made it impractical. A rapid screening test, utilizing a few drops of

citrated blood incubated in an ice cube tray in an ordinary refrigerator, was found to be a reliable method for demonstrating antibodies in patient sera.

A number of investigators contended that M. pneumoniae was actually the L-phase of a bacterium, especially a streptococcus. An analysis of serological data revealed that men who enter the Navy with evidence of previous exposure to M. pneumoniae have a greatly reduced incidence of streptococcal infections as they pass through training.

New technics of isolation developed at NAMRU-4 have included a new medium containing HEPES buffer supplemented with tissue culture ingredients. When used for direct isolation of the mycoplasma, it was found to increase isolations by a factor of three.

Meningococcal Infections

One notable and disturbing fact about meningococcal infections is that they are a major cause of death in Naval recruits year after year. To deal with this situation, emphasis was placed on the treatment and prevention of this disease. The meningococci mainly affect young children and military recruits, but have been shown to be present in a number of individuals referred to as carriers. These people do not exhibit clinical signs of the disease, but are capable of transmitting it to susceptible individuals. A medium was developed by researchers at the Center for Disease Control, Atlanta, Georgia, and a NAMRU-4 investigator, which was useful in increasing the detection of meningococcal carriers by 50 percent, and strains could be grouped serologically from primary cultures.

An effective way to deal with meningococcal infections would be to eliminate the carrier state. Sulfadiazine was considered the drug of choice for this type of infection until the Spring of 1963 when there was an outbreak of meningococcal meningitis at San Diego. The carrier rate rose to a high of 70 percent. The drug was useless in this epidemic.

NAMRU-4 workers immediately began testing other antibiotics. An extensive study was conducted on penicillin G, ampicillin, oxytetracycline, and erythromycin to determine their effect on reducing the carrier state of sulfadiazine-resistant meningococci. Oxytetracycline and erythromycin were more effective than oral penicillin G, but did not completely eradicate the carrier state. Ampicillin was superior to penicillin, but it also did not produce results comparable to those of the sulfonamides. Proper isolation, typing, and judicious antibiotic therapy was indicated.

An extensive NAMRU-4 epidemiological study of meningococci in

Naval personnel at Great Lakes in 1968 led to some interesting observations. An analysis of continuous bacteriological and serological sampling revealed that there was always a nearly constant infection rate among new recruits, and that 85 percent of all meningococcal carriers entering Great Lakes harbored sulfadiazine-sensitive organisms. Control companies not receiving sulfadiazine had about 5 percent more meningococcal carriers upon graduation than other companies treated at the onset of recruit training.

Group Y meningococci were found to be the most frequent serological group isolated from Naval recruits, whereas, group B strains were found most frequently among civilians and sea duty personnel.

It was also demonstrated that clinical disease occurs less often following infection with the group Y organism than with either the B or C groups. A serological response followed meningococcal infections. It was interesting to note that seasonal variation of disease contraction in recruit camps was similar to the incidence of clinical disease in civilians. Sulfadiazine-resistant strains were found more often in the military than in the civilian population.

In 1968, a method was developed at NAMRU-4 which improved the methods of identification of meningococcal strains. The procedure relied on characteristic fermentation patterns of meningococci in Mueller-Hinton broth.

Two antigens were prepared which possessed the sensitivity and specificity required of serological tests for determining seroresponses to meningococcal infections. These antigens could be used to detect antibody in sera of people with clinical meningitis or in the sera of nasopharyngeal carriers of meningococci. These antigens were particularly useful because of the simplicity of the diagnostic test.

Field trials of the effectiveness of antibiotics in eliminating the carrier state were found to be costly and difficult. A method had to be designed to predict the in vivo effectiveness of drugs in order to determine the best drug for field use. In 1968, NAMRU-4 investigators found that concentrations of antibiotics in sera and saliva samples of carriers could be ascertained by biological methods. It was determined that in order to be effective in the elimination of the carrier state that a particular drug must be present in saliva in a concentration approaching the in vitro minimal inhibitory concentration of the drug for the infecting organism.

Using the minimal inhibitory concentration concept, studies were conducted on 49 antibiotic agents. Results indicated that Coumermycin A_1, did not eliminate meningococci from the nasopharynx of carriers, and in its present form was not recommended for use.

Rifampin, compared with controls, reduced the percentage of carriers in Naval recruits by 80 percent, and was well tolerated in four daily 600 mg doses. The levels of rifampin in serum samples exceeded the minimal inhibitory concentration needed to inhibit meningococci in vitro. Its efficacy in eliminating the meningococcal carrier state being established, it was believed safe and effective in carriers of sulfadiazine-resistant organisms under limited conditions.

Minocycline, given to carriers in a regimen consisting of an initial 200 mg dose, followed by 100 mg every 12 hours, reduced the carrier rate by 60 percent, with the drug being well tolerated. Minocycline was also tested among personnel in the Service School Command using larger doses for a shorter period of time. Personnel were given 200 mg of the drug twice daily for two days, and saliva samples were collected at four hours after the third dose. Twenty-three carriers were used as controls. There was a 68 percent reduction in carriers, but the side effects of the drug prevented continuation of the experiment.

Minocycline and rifampin were tested for their effectiveness in eliminating the group C meningococcal carrier status of recruits at Orlando, Florida in the Spring of 1970. Minocycline was about 60 percent effective and rifampin about 90 percent. Minocycline-resistant strains did not emerge, but a relatively small number of rifampin-resistant strains did appear. A secondary objective of creating a recruit center populated with carriers of relatively apathogenic meningococcal strains, such as Y and RAS-10 was not accomplished.

A group C meningococcal polysaccharide vaccine was developed by the Army. An opportunity for NAMRU-4 personnel to evaluate this vaccine was afforded at the Marine Corps Recruit Depot, San Diego in 1969, when clinical cases of group C infections began appearing. The vaccine was administered to 3,018 Marine recruits. Results indicated that the vaccine appeared group-specific, it stimulated the production of hemagglutinating antibody response, but did not stimulate production of complement fixing antibodies; it afforded however, good protection against clinical disease.

Vaccines to groups A and C meningococci were developed at NAMRU-4. They were tested in prison volunteers for antigenicity and acceptability. No toxic reactions were observed. More than 90 percent of the vaccinees developed significant rises in titer when determined by hemagglutination tests. Eighty percent of the men with no initial titer produced a bactericidal antibody response.

A counterimmunoelectrophoretic test has been developed at NAMRU-4 for detecting meningococcal group-specific antigens in

spinal fluid and serum. It was rapid, sensitive and specific. This method of identification of soluble meningococcal antigen in serum would provide laboratory assistance in the rapid diagnosis and prognosis of meningococcal disease. The test procedure has been extended to pneumococcal and H. influenzae antigens resulting in a rapid (30 minute) method of identifying the bacterial antigens associated with meningitidis in children and adults.

L-Phase Organisms

An L-phase of beta-hemolytic streptococci was induced at NAMRU-4 in 1956 by exposure to penicillin on a solid medium containing a high concentration of sodium chloride. The bacterial forms were isolated from 10 Naval recruits at Great Lakes. Beta-hemolytic streptococci of the original serological group and type were regained from the L-colonies of 9 out of 11 strains.

NAMRU-4 personnel are also conducting research into the L-phases of meningococcal organisms. A group B meningococcal L-phase was stabilized in 1966, and more recently groups A, Bo and RAS-10 L-phase organisms have been stabilized. L-phase meningococcal antigens are being developed as part of the vaccine program. A whole cell preparation subjected to sonic oscillation, is awaiting antigenicity and acceptability studies in prison volunteers. This preparation is antigenic in rabbits, and it is low in toxicity, non-pyrogenic, non-lethal, and protective in an active mouse protection test against homologous and heterologous bacterial challenge.

An interesting phenomenon was discovered while studying the fractions of the L-phase of a group B strain of meningococci. A soluble hemagglutinating fraction was extracted which directly hemagglutinated chicken red blood cells. This fraction used in a hemagglutination-inhibition test, showed the presence of an inhibitor in the sera of recruits and other personnel. The presence or absence of this inhibitor appears to have some relationship to the acquisition of meningococcal infections as a low titer resulted in the isolation of a meningococcus.

APPENDIX A

NAMRU-4 OFFICERS IN CHARGE

J. R. Seal, LCDR MC USN (McIntire Research Unit)	May 1946
J. R. Seal, CDR MC USN (NAMRU-4)	Jun 1948
K. H. Sessions, CAPT MC USN	Jul 1954
M. J. Hantover, CAPT MC USN	Oct 1955
B. F. Gundelfinger, CDR MC USN	Jan 1957
L. F. Miller, CAPT MC USN	Aug 1958
C. H. Miller, CDR MC USN	May 1964
R. O. Peckinpaugh, CAPT MC USN	Jun 1964

NAMRU-4 COMMANDING OFFICERS

R. O. Peckinpaugh, CAPT MC USN	Apr 1968
C. H. Miller, CAPT MC USN	May 1972

APPENDIX B

MISSION AND TASKS

Mission: To conduct basic research in the biomedical sciences, provide essential information in diseases and medical problems of military significance, recommend control measures for communicable diseases that are endemic or epidemic to specific areas world-wide; and, as required, provide training in research techniques.

Tasks: The following tasks are assigned to accomplish the mission:

a. Conduct research into the etiology and modes of transmission of acute communicable diseases of the respiratory tract and develop and test methods for the control and treatment of these diseases.

b. Provide such specialized diagnostic laboratory support to their medical activities as may be required to enable them to identify and control epidemic respiratory diseases.

c. Collect and evaluate data on the application of control measures for acute communicable respiratory diseases which will enable the Bureau of Medicine and Surgery to recommend the limited or general adoption of such measures throughout the Naval Service.

d. Conduct other studies on medical problems of recruits as may be opportune or as directed by the Bureau of Medicine and Surgery.

e. Train personnel of the Naval Medical Corps, Medical Service Corps and Hospital Corps in the techniques and procedures used in clinical, epidemiological, and laboratory research pertaining to acute respiratory diseases.

f. Provide or undertake such other appropriate functions as may be authorized or directed by higher authority.

APPENDIX C

NAMRU-4 Consultants and Affiliations

Consultants

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Affiliations

Armed Forces Epidemiological
Board
Commission on Acute
Respiratory Diseases
Commission on Immunization
Commission on Influenza
Commission on Streptococcal
and Staphylococcal Diseases

National Institute for Allergy
and Infectious Diseases
Division of Biological
Standards
Laboratory of Infectious
Diseases
Center for Disease Control
World Health Organization

APPENDIX D

NAMRU-4 PUBLICATIONS

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