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Properties and Origin of Heparin: In 1935, heparin was identified by the author as a mucopolysaccharide resembling the chondroitin sulfuric acid of cartilage. The strongest heparin samples were found to contain about 26 per cent of a uronic acid and about 23 per cent of glucosamine, these components together making up about 90 per cent of the organic skeleton of heparin. The observation was made that heparin contains ester sulfuric acid, not only one group to each disaccharide unit, as in chondroitin sulfuric acid, but three groups making up not less than 45 per cent of the weight of the free acid.

The uronic acid in heparin is claimed to be glucuronic acid. Opinions still differ concerning whether heparin contains an acetyl group or not. All the other known polysaccharides containing an amino sugar are acetylated at the amino group. In heparin also there is no free $NH_2$ group. Acetic acid, however, cannot be obtained from heparin by applying the ordinary methods of analysis, except for a small quantity, from 10 to 15 per cent of the calculated amount, which could possibly be derived from impurities in the heparin preparations. Heparin is very difficult to purify, and the accompanying polysaccharides split off acetic acid easily. It is, in fact, doubtful whether any homogeneous pure samples of heparin have ever been prepared.

There are many details about the chemistry of heparin which are still uncertain. It will also be necessary to find out whether heparin is a definite chemical compound or whether it is a mixture of di- and trisulfuric acid esters of one and the same polysaccharide having a composition similar to that of Karl Meyer's hyaluronic acid. All kinds of polysaccharides acquire anticoagulant properties if thoroughly esterified with sulfuric acid.

The Mechanism of Action of Heparin. Heparin has a high molecular weight and carries an exceptionally strong electric charge, apparently the strongest of all the organic compounds of the animal body. The strongest preparations, which contain 13.6 per cent of sulfur in the sodium salt, consist of no less than 45 per cent of sulfuric acid, really a peculiar product of synthesis in the living organism. The strongest compounds of a similar nature hitherto known, the nucleic acids, contain only 25 per cent of phosphoric acid. The high content of ester sulfuric acid is the most outstanding feature in the structure of heparin. Heparin presents no known reactive prosthetic groups other than that of sulfuric acid which is a good one. All chemical findings therefore point in the direction that the anticoagulant activity is exerted through the electric charges of the high molecular polysaccharide. The same is the case with the physiological findings.

Heparin has a multiple effect, acting not only on the components of the coagulation system, on the thrombin, the prothrombin, and the thrombokinase, but also on many other systems. It neutralizes the serum complement interfering in the Wassermann reaction. It reduces the isoagglutinin titer of the serum, and it acts on different enzymes, preventing their action. In larger concentration (1 mg. per ml.) it also acts on the plasma proteins, strongly influencing the sedimentation rate of the red blood corpuscles. This multiplicity in action can most easily be explained as a physico-chemical action of the acidic

polysaccharide on the different proteins concerned. It is also known that the interaction between heparin and thrombin is reversible and very loose, it being reversed by adding an excess of thrombokinase.

It is a most interesting fact that the very few previously known synthetic organic chemicals which acted directly as anticoagulants, such as Liquoid Roche and some diazo dyes, were all sulfonic esters of high molecular compounds. All kinds of polysaccharides acquire anticoagulant properties if thoroughly esterified with sulfuric acid. Nature, in synthesizing heparin, has applied the same principle, and has done it in an excellent way, the product being not only highly active but also nontoxic. Even the polysaccharide polysulfuric esters so far prepared by various authors have more or less toxic properties.

The most convincing proof for the action mechanism of heparin was obtained through the finding of Chargaff and Olson that protamine instantaneously abolishes the heparin effect in vitro and in vivo. Its electric charge neutralizes the negative electric charge of heparin.

Protamine sulfate, from 50 to 100 mg., can be injected intravenously in man in 1 percent sterile solution. The coagulation time of the blood is thereby instantaneously brought down to normal.

It has recently been found by Seegers that the prothrombin cannot be absorbed on magnesium hydroxide if heparin is present. Evidently the physicochemical state of the prothrombin is altered.

A physico-chemical mechanism of action seems, therefore, to be the most probable.

There are facts, however, not so easy to explain. Thus Jaques found dog heparin to have a two and one-half times stronger anticoagulant effect than the same amount of ox heparin, whereas pig and sheep heparins are much weaker. They all have the same content of ester sulfuric acid. His findings have later been fully confirmed.

In spite of a strong ionic dissociation, heparin exerts an extremely low osmotic pressure in aqueous solution. This is the same phenomenon which E. Hammarsten studied in another strongly acidic compound of high-molecular weight, the thymonucleic acid of cell nuclei. Both these substances, heparin and the thymonucleic acid, in aqueous solution show only a fraction of the osmotic pressure which the degree of ionization would lead one to expect. The salts of heparin exert less than a tenth of the calculated osmotic pressure. The phenomenon involves an interesting protective mechanism which nature has developed to avoid high osmotic pressure and the resulting displacement of fluid when compounds with a high electric charge are deposited in cells. Otherwise, no nucleic acid could be stored

in cell nuclei, nor any heparin in the heparin-producing cells. The nuclei and the cells would be disrupted by the water entering from the outside in order to establish osmotic equilibrium on both sides of the nuclear and cellular membrane respectively. The sodium or potassium ions bound to the high molecular negative complexes of heparin and the nucleic acids respectively do not exert any osmotic pressure although they occur as ions.

This lack of osmotic pressure makes heparin very useful in blood analysis, because it does not cause shrinkage of the red blood corpuscles. It is the only anticoagulant to be used in hematocrit determinations. A concentrated 5-percent solution of heparin can also, without any drawbacks, be injected undiluted into the blood.

Heparin and the Erhlich Mast Cells. Heparin produces an extraordinarily strong degree of metachromasia, a purple violet staining with certain blue basic dyes. At a time when the sulfur content of heparin was denied by several authors, it was possible to demonstrate that it gave an exceedingly strong violet metachromatic reaction with toluidine blue, a reaction which a Belgian histologist, Lison, had shown in 1935 to be given only by high molecular esters of sulfuric acid. The metachromasia of cartilage is due to the chondroitin sulfuric acid. Heparin gives a 100 times stronger metachromasia than does this acid. By means of this reaction, the author and associates were able to demonstrate in 1937, together with Holmgren and Wilander, that heparin is produced by the mast cells of Ehrlich.

The mast cells, because of their position around capillaries and the small blood vessels without a muscular coat, are able to void their granular contents into the peripheral tissue juices, or almost directly into the blood stream; it is considered that this indicates that these cells together with the heparin may have a physiological function to fulfill. The mast cells evidently form a hormonal system, with the cells widely distributed around the capillaries in the body. Neoplastic and inflammatory tissues rich in capillaries are also rich in mast cells. Recently, Holmgren has shown that there is a steady and very considerable decrease of mast cells during the course of life. This reduction in number of the mast cells corresponds to the reduction of the capillaries with increasing age.

A most interesting increase in the mast cell content of the tissues was observed in the victims of Hiroshima. A general bleeding tendency was observed in the survivors as a consequence of the irradiation. Histologists stated that there was a general increase of the mast cells in the tissues of the victims. A similar condition with hyperheparinemia has recently been produced by Garrott Allen in Chicago through roentgen-ray irradiation of dogs. There is also a disease with multiple petechial hemorrhages in the skin, urticaria pigmentosa, in which the pathologists long ago stated that there are abnormal local accumulations of mast cells in the skin. (Ann. Int. Med., Sept. '47 - J. E. Jorpes)

Multiple Myeloma: This study (based on 35 proved cases, in 18 of which autopsies were made) places emphasis on the clinical and anatomic features that characterize multiple myeloma. The authors conceive of multiple myeloma as a malignant disease of the skeleton primarily, which apparently originates in the myeloid formative tissue proper. Anatomically, practically every bone may become involved ultimately in a given case. The skeletal progress of the disease may be steady and rapid, sometimes from the beginning, and sometimes after a static period. In some cases, also, before the disease becomes spread over the skeleton it may flourish in one bone (as a so-called solitary myeloma) for months or even years. Though at autopsy the skeleton may be found riddled through with foci of myeloma, it is only infrequently that gross foci are found in the viscera and other extraskeletal tissue. Nevertheless, even in the absence of gross infiltrations, microscopic examination sometimes reveals varying numbers of myeloma cells within the spleen, the liver or lymph nodes, and occasionally in other organs as well. Also, in some cases, myeloma cells may invade the blood stream. Ordinarily, under these circumstances, relatively few myeloma cells are found in the blood smears, but in an occasional case they may be so numerous as to create a leukemic blood picture (so-called plasma cell leukemia).

Although there are these points of resemblance to other neoplasms of hematic origin, it should be emphasized that multiple myeloma presents a characteristic clinicoanatomic picture, centered around the skeletal manifestations of the disease and their sequelae, and that with rare exceptions this picture is readily distinguishable from that presented by any of the other neoplasms of hemopoietic derivation. In this connection the authors stress the diagnostic significance of hypercalcemia, hyperglobulinemia (and its associated hematologic manifestations) and Bence Jones proteinuria, the not infrequent presence of atypical amyloidosis in association with myeloma, and the well known renal changes which are of almost pathognomonic distinctiveness. The latter result commonly in fairly heavy albuminuria and often in renal insufficiency of a peculiar type. In regard to amyloidosis it was indicated that multiple myeloma is so often the basis for atypical amyloid deposits that the possibility of myeloma should be investigated in every case of idiopathic amyloidosis, even though the bones present no evidence of tumor either roentgenographically or on gross inspection at autopsy.

The tumor tissue in multiple myeloma tends characteristically to be composed of large aggregates of more or less compacted cells without any discernible intercellular material and without conspicuous supporting stroma. It has been recognized and must be emphasized that the cytologic picture is not the same in all specimens of multiple myeloma. Roughly, however, the tumors can be fitted into two general cytologic groups. In one, the tumor cells are quite uniform and predominantly small and have a superficial resemblance to plasma cells. It is to the myeloma showing this cytologic appearance that the name "plasma cell myeloma" or "plasmacytoma" is commonly applied. In the other group of myelomas the cytologic picture tends to be dominated by cells larger than those resembling plasma cells, but may be a rather variegated one. The

dominant cell shows fairly abundant cytoplasm and has a large, round, oval or even reniform, pale stippled nucleus. In any particular tumor site examined, one may also find some of the smaller cells resembling plasma cells, or on the other hand, find cells which are much larger than the dominant cells and frequently show nuclear atypism. Specifically, such atypical cells may present large and hyperchromatic nuclei, giant nuclei of bizarre shape, or two or more nuclei.

The authors are inclined to doubt whether there is any essential difference, except that of maturity, between the large and the small tumor cells. They consider that multiple myeloma is distinctive as a single and basically uniform disease complex and that it should not be subclassified, on the basis of cell type, into plasma cell, myeloid, erythroid, and lymphoid myeloma. The authors are inclined to hold with Wallgren and others that this neoplasm consists of distinctive tumor cells which are probably of myeloid formative or hematic origin (though not clearly resembling any normal marrow cells or their immediate precursors) and are best designated as myeloma cells.

Correlation of the cytologic aspects of the myelomas in the authors' material with the pertinent biochemical data strongly suggests that it is the large cell myelomas particularly which are characterized by hyperglobulinemia and, rather often, by Bence Jones proteinuria.

On the clinical side, in this series of cases of multiple myeloma, it was found that the great majority of the patients were between 40 and 60 years of age, though some were in their 30's, and one was only 13 when the first manifestations of the disease appeared. The data indicate that multiple myeloma may be slightly more prevalent in males than in females but do not support the often repeated statement that the condition is at least twice as frequent in males. In regard to the roentgenographic findings, the authors have found that the picture conventionally held to distinguish multiple myeloma - that of many bones, including the calvarium, riddled by clearcut punched-out osteolytic defects - represents the exception rather than the rule and applies only to certain cases in which the disease is far advanced. Indeed, very often one observes merely some vaguely defined rarefactions in a number of the bones or a single exuberant tumor focus in some one bone (commonly a femur or a humerus, but sometimes a vertebral body, a rib or a clavicle, an innominate bone, a bone of the calvarium or some other bone) without obvious involvement of the skeleton generally. Sometimes (when myelomatous infiltration of the marrow is diffuse) skeletal changes may not be apparent at all roentgenographically, or the replacement of the marrow by tumor may be reflected merely by some osteoporosis. As for the calvarium, this not infrequently fails to show numerous punched-out rarefactions, even when roentgenograms show clearcut and widespread involvement of the rest of the skeleton. In such equivocal or initially obscure cases one must utilize fully all the available diagnostic cues to arrive at a combination of significant findings constituting probable or conclusive evidence of the presence of multiple myeloma. Marrow obtained by sternal puncture is often of great value in establishing the diagnosis.

Multiple myeloma has too variable a clinical course to permit of any dogmatic statement in regard to prognosis. It is true that the average length of survival after the onset of symptoms is not likely to be more than about two years. However, there are occasional patients with multiple myeloma, particularly those in whom the disease was apparently localized at the onset, whose course may be protracted over a number of years, sometimes as long as ten years or more.

Problems in therapy are concerned mainly with palliation, particularly the relief of distressing bone pain, general supportive measures and the handling of such complications as fractures and compression of the spinal cord. In regard to general supportive measures, the use of repeated transfusions to combat anemia when this is present and the avoidance of prolonged bed care should be emphasized. The consensus of radiotherapists seems to be that roentgen therapy, if judiciously employed, frequently, though not invariably, has value in palliation but that it has relatively little influence otherwise on the course of the disease except possibly when one is dealing with what appears to be a solitary myeloma.

Experience with radioactive phosphorus ($P^{32}$) in the treatment of multiple myeloma is still limited but is sufficient to indicate what may be expected at best and what its limitations are. In some patients, but by no means all, radiophosphorus therapy has resulted in appreciable subjective clinical improvement, evidenced chiefly by relief of pain permitting restoration of more normal activity. Apparently, no concomitant significant change in the roentgenographic appearance of the skeletal lesions has been observed. Reinhard and associates concluded from their survey that radioactive phosphorus has not proved to be a really valuable therapeutic agent for the treatment of multiple myeloma and that the lesion does not respond as favorably to this agent as it does to roentgen radiation. Indeed, it was felt that radiophosphorus therapy had shortened the life expectancy of 3 patients by producing severe leukopenia and thrombocytopenia.

The administration of "stilbamidine" (4,4-diamidinostilbene) and "pentamidine" (4,4'-[pentamethylenedioxy] dibenzamidine) in conjunction with a diet low in animal protein has recently been advocated by Snapper for the treatment of patients with multiple myeloma, especially those with widespread but not large osteolytic lesions and with normally functioning kidneys. In such patients (15 had been so treated) he claimed to have observed a favorable influence on excruciating bone pain, but stated that the lesions persist and that treatment at best only checks the disease temporarily and does not cure it. Snapper pointed to the appearance of granules within the cytoplasm of the myeloma cells as an indication of the specific action of "stilbamidine" on these cells. The drug, however, has certain toxic effects, including injury of the trigeminal nerve in some cases, which is manifested in the development, following a delay, of facial anesthesia, and it seems that before employing the drugs in question for their palliative effect, one would be well advised to try roentgen therapy first in order to achieve the same result.

Aside from treatment of fractures, especially those of long bones, surgical intervention has a place in the relief of transverse myelitis resulting from

extradural compression; this may be accomplished by laminectomy. Jacox and Kahn and Batts have shown that this procedure, if followed by roentgen therapy, may permit complete recovery of function and even survival thereafter for a number of years. They emphasized that laminectomy should always be done before roentgen therapy is given, in order to prevent further damage being done to the cord by swelling subsequent to irradiation. Also, the question of ablation of a limb for myeloma sometimes arises, but only in connection with the comparatively rare, ostensibly solitary myeloma of a long bone. In cases of this type, as noted, one can never be certain that tumor is not present in other bones in spite of their negative roentgenographic appearance. It is pertinent, however, to cite the remarkable case reported by Stewart and Taylor: The patient was alive and well eight years after forequarter amputation for a huge myeloma which had largely destroyed the upper third of the shaft of a humerus and was freely invading the muscles of the upper arm. (Arch. Path., Sept. '47 - L. Lichtenstein and H. L. Jaffe)

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Effects of DDT Mosquito Larviciding on Wildlife: The U. S. Public Health Service has investigated the effects from the routine use of DDT as a mosquito larvicide on wildlife at the Carter Memorial Laboratory. The purpose of the studies was to determine the dosage and the manner or physical state in which DDT could be routinely used as an anopheline larvicide without being significantly harmful to other organisms of economic or recreational value. Several types of dusters were used for DDT dust applications and air-pressure hand sprayers for the emulsions and solutions.

Effect on Fish: Applications of tight emulsions and solutions at the rate of 0.4 pound DDT per acre, or more, were detrimental to fish in shallow water. Single applications of dusts and solutions at the rate of 0.1, 0.05, or 0.025 pound DDT per acre caused no observed fish mortality. Routine treatments, however, at 0.1 pound per acre caused fish mortality between the third and tenth treatments, and the fish population was significantly reduced by a series of from 11 to 18 treatments in the ponds studied. It was indicated that routine treatments should not exceed 0.05 pound DDT per acre for small or shallow bodies of water. Routine application at this rate caused mortality to fish in shallow ponds in which the entire area was treated. It is believed that mortality will not be significant in larger, deeper waters in which only the margins are treated. In areas routinely treated with 0.025 pound DDT per acre no fish mortality was observed.

Effects on Surface Organisms Important as Fish Food. Several different formulae, methods of application, and concentrations of DDT were used in connection with experiments on more than 20 ponds. The methods used for determining the effects of routine treatment included quantitative sampling of the surface forms and counts of dead organisms on the water surface 24 and 48 hours after treatment.

Gross observations indicated that little apparent damage to surface organisms resulted from application of DDT as a dust. The seasonal trend of the

population of surface organisms was somewhat affected by routine treatments with dust at the rate of 0.1 pound of DDT per acre, but the changes were not as great as those caused by treatments with solutions of DDT in fuel oil.

DDT-fuel-oil solutions applied at concentrations as low as 0.025 pound of DDT per acre killed the large surface insects such as diving beetles (Dytisidae), whirligig beetles (Gyrinidae), water scavenger beetles (Hydrophilidae), and water boatmen (Corixidae). However, mortality resulting from applications of 0.05 or 0.025 pound per acre were proportionately much less than when applications of 0.1 pound per acre were used. Single treatments produce few significant changes. A comparison of the populations of surface organisms in the treated and check ponds indicated that seasonal effects of routine DDT treatments were quite marked. There was an increase in the number of hermaphrodite worms (Oligochaeta), nematodes (Nematoda), and copepods (Copepoda), and a decrease in midges (Chironomidae), true bugs (Hemiptera), beetles (Coleoptera), and May flies (Ephemerida). The number of insects as a group decreased in the treated ponds with the largest decrease occurring among the midges.

It would appear that the available supply of fish food is somewhat reduced by applications of DDT-fuel-oil solutions. The forms that increase in numbers are much smaller than those that are reduced in number by DDT and in general they are not as readily taken by fish. Reductions have not been sufficient to effect breeding stock, and since treatment is carried out in localized areas, the resulting restriction of food supply is probably not sufficient to limit seriously the over-all fish population.

Effects on the Plankton. Plankton is the chief food source for several species of adult fish and for most young fish. In order to determine the effect of DDT dispersal on plankton, ponds were selected on the basis of total population, physical and ecological similarity, and availability of control areas. DDT was applied as a dust, or as a solution in fuel oil. The concentrations ranged from 0.2 pound to 0.05 pound per acre of water surface. Weekly treatments were made over periods of from 6 to 18 weeks. Samples of plankton were taken prior to and 48 hours after treatment.

The studies indicated that the detrimental influence of DDT (as used for the control of malaria vectors) is so slight, in comparison with the larger variations due to climatic and other ecological factors, as to be relatively unimportant in upsetting the biological balance.

No specific groups of plankton were drastically killed by DDT treatments during the course of the experiments. A few groups showed a slight reduction in number in the treated ponds over the control, but in no instance were they reduced to any marked degree.

It appears that the use of DDT as a mosquito larvicide will be restricted more by its potential dangers to the fish and the higher forms of life directly than by any harmful effects on the plankton.

Effects on Birds. Airplane applications of DDT were made at weekly intervals over a period of 17 weeks on areas of the Savannah River Refuge, South Carolina. A 20-percent solution of DDT in a highly methylated naphthalene was applied at the rate of 0.1 pound per acre per treatment. No significant difference was noted in the numbers of pairs of breeding birds on the sprayed and unsprayed islands and dykes.

From 15 March to 7 August the numbers of singing males heard from week to week increased in both sprayed and unsprayed areas at the beginning of the nesting season, mildly fluctuated during the season, then dropped off at the end of the season. It was indicated that DDT had no harmful effects by the absence of a sudden drop or a general decline in the population of the sprayed area. Apparently DDT had no measurable effect on the population from week to week as the fluctuations of birds on both sprayed and unsprayed areas were similar.

Effects on Mammals. There was no effect detected on the population of the cotton rat or house mouse in the sprayed area. Calculated on a weekly basis, the fluctuations in the numbers of cottontail rabbits, cotton rats, and raccoons on sprayed and unsprayed areas from 13 May to 30 August roughly paralleled one another, indicating that DDT had no effect on the mammals of the sprayed area. (Pub. Health Reps., 11 April '47, Part I - C. M. Tarzwell; 29 Aug. '47, Part II - A. B. Erickson; Part III - E. L. Bishop)

NOTE - CNO letter Op-55R-6-JLH:jk, Serial 47P55R, 18 November 1946, "Large Scale Dispersal of Insecticides, Justification for" sets forth certain limitations in the use of DDT by the Naval Service and outlines the information required from all continental stations before requests for approval of its use can be considered. It limits the rate of application to a maximum of 0.3 pound DDT per acre. It is well known that malaria mosquito control by larviciding can be carried out effectively with dosages of from 0.025 to 0.1 pound per acre under optimum conditions. However, water areas, covered with a canopy of dense vegetation, debris, or biological films that retard the spreading of the oil may require heavier dosages. As a rule, somewhat higher dosages (from 0.2 to 0.3 pounds per acre) are required to control culicine larvae effectively. In all cases the minimum amount necessary for control should be used.

Circular 11 of the Fish and Wildlife Service, U. S. Department of the Interior, 1946, gives the following recommendations for minimizing danger to wildlife:

Use DDT for the control of an insect pest only after weighing the value of such control against the harm that will be done to beneficial forms of life. Wherever more than a small area is involved, consult county agricultural agents, State or Federal entomologists, wildlife and fishery biologists, and United States Public Health Service officials.

Use one-fifth pound or less of DDT per acre in an oil solution to avoid damage to fishes, crabs, or crayfishes; use less than 2 pounds per acre to avoid damage to birds, amphibians, and mammals in forest areas. Because of its greater effectiveness, use smaller quantities of DDT in emulsions.

Use DDT only where it is needed. Wherever it is applied by airplane, provide careful plane-to-ground control to insure even coverage and to prevent local overdosage.

In forest-pest control, wherever feasible, leave strips untreated at the first application to serve as undistributed sanctuaries for wildlife, treating these strips at a later time or in succeeding seasons if necessary. In the control of early-appearing insect pests, apply DDT, if possible, just before the emergence of leaves and the main spring migration of birds; for late-appearing pests, delay applications, whenever practicable, past the nesting period of birds. Adjust crop applications and mosquito-control applications so far as possible to avoid the nesting period.

Because of the sensitivity of fishes and crabs to DDT, avoid as far as possible direct application to streams, lakes, and coastal bays.

Wherever DDT is used, make careful pre- and post-application observations on mammals, birds, fishes, and other wildlife (Preventive Medicine Div., BuMed)

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Tobacco and Gingivitis: The significance of tobacco in the development of ulceromembranous gingivitis and in the formation of calculus was investigated in a statistical study by J. J. Pindborg and reported in the Journal of Dental Research for June 1947. One thousand four hundred and thirty-three Marines between the ages of 16 and 28 were subjected to dental examinations and at the same time were questioned about their daily consumption of tobacco in the form of cigarettes, cigars, and pipe tobacco. From the results of the dental examinations, the condition of the gingivae were classified into the following three groups: (1) normal, (2) chronic simple marginal gingivitis, and (3) ulceromembranous gingivitis. Also, according to their answers on the smoking of tobacco, the Marines were divided into the following three groups: (1) no consumption of tobacco, (2) consumption of tobacco less than 10 Gm. per day, and (3) consumption of tobacco 10 Gm. or more per day. All these data were tabulated and analyzed with the following conclusions drawn:

Seemingly, the incidence of chronic simple marginal gingivitis is not affected by tobacco smoking, whereas the incidence of ulceromembranous gingivitis is markedly different in nonsmokers and smokers. Although 1.5 per cent of the nonsmokers had ulceromembranous gingivitis, 10.7 per cent of the Marines smoking more than 10 Gm. of tobacco a day had this disease. Moreover, the number of Marines with normal gingivae declines from 33 per cent in nonsmokers to 22.5 per cent in the heavy smokers.

Further, with a greater amount of tobacco smoked, there seems to be an increased possibility of developing calculus. Although 39.7 per cent of the nonsmokers are without calculus, only 17.5 per cent of the persons smoking more than 10 Gm. of tobacco a day are calculus-free.

On the basis of the results, nothing was inferred concerning the manner of action of the tobacco. It was assumed, however, that since tobacco-smoking may play a role in the development of ulceromembranous gingivitis, smoking should be forbidden during treatment for this condition. (Nav. Dental School, Bethesda, Md.)

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The Use of Tetraethylammonium Chloride in the Treatment of Experimental Acute Arterial Insufficiency: In the treatment of acute arterial injuries of the major vessels, attention is immediately directed toward two objectives: (1) controlling hemorrhage and (2) overcoming the resultant acute arterial insufficiency to the tissues normally supplied by the artery and its branches.

The circulation is normally re-established by means of collateral circulation, in which pre-existing channels undergo dilatation. This restoration of blood flow may or may not be adequate, depending upon the vessel involved and the level of interruption. The arterial insufficiency may be manifest by coolness, trophic changes, decreased functional tolerance, ulceration, and gangrene. Therapy, in most instances, must be directed toward augmentation of the secondary, or collateral, circulation.

Numerous authors have pointed out that inadequacy of the collateral circulation, notwithstanding injury to these vessels, is frequently due to an element of vasospasm, which acts to diminish the caliber of these vessels. This active vasomotor tone is the direct result of an outflow of vasopressor impulses from an intact sympathetic nervous system. The normal tone maintained in health is further increased by reflex spasm resulting from the proximate arterial injury. It has been demonstrated clinically and experimentally that interruption of this sympathetic outflow by various methods results in an increased blood flow through collateral channels, as evidenced by a rise in skin and deep temperatures, decreased venous filling time, increased oscillometric readings, and the prevention of tissue death.

Leriche and Stricker and Orban in a series of experiments proved conclusively the value of sympathectomy in the prevention of massive gangrene and death following extensive arterial resections in animals. They found that following resection of the terminal aorta and its branches in the dog, more than four fifths of their animals died in from 24 hours to 4 days with paralyzed, cold, cyanotic, and edematous hind limbs. If, however, bilateral lumbar sympathectomy was performed just prior to the arterial resection, the animals showed little ill effects. Within 24 hours they could stand and walk, with warm hind limbs and little evidence of circulatory insufficiency. At the end of a week, they were as active as normal animals.

The following series of experiments was undertaken to determine the efficacy of chemical sympathetic blockage in experimental acute arterial injuries. No attempt has been made to compare results of treatment with the tetraethylammonium ion with other methods of sympathetic interruption.

Because the result of aortic ligation alone varies as it concerns survival of the animal or gangrene of the posterior extremities, and because several authors have reported varying percentages of deaths following excision of the trifurcation of the aorta, in this series a more extensive resection was carried out. The operation was extended to include the deep circumflex iliac vessels which constitute one of the major collateral channels following aortic ligation. If these vessels had their origin above the inferior mesenteric artery, they were ligated and divided at that point. In this manner, the arterial supply to the extremities was reduced to a critical level.

A group of 30 adult mongrel dogs, weighing from 9 to 15 kilograms, was selected. Identical operative procedures were carried out on all animals in the group under surgical anesthesia obtained by the intravenous administration of sodium pentobarbital.

In the experimental group, administration of tetraethylammonium chloride was begun immediately after excision of the arteries. It was given intramuscularly as a sterile 10-percent solution in the proportion of 25 mg. per kilogram body weight every 8 hours for 3 days.

All the animals were allowed food, water as desired, and offered exercise at least once daily, as tolerated.

In the control group of 10 dogs, 9 of the animals died within from 24 hours to 7 days. The majority of deaths were within a 4-day period. Autopsy revealed in each instance that death was not due to hemorrhage from the ligated arteries or to peritoneal infection. Prior to their death, these animals exhibited the same findings as reported by Leriche: hindlimb paralysis, coldness, cyanosis, and varying degrees of swelling.

In the group of 20 animals treated with tetraethylammonium chloride, 14 of the animals survived. These animals regained excellent functional activity within from 2 to 6 days. Of the remaining 6 dogs which died, 3 deaths were the result of infection of a posterior extremity. One of the remaining animals died within 12 hours of operation, and the other from an undetermined cause on the tenth postoperative day.

Arteriograms were performed immediately following ligation and excision of the aorta in control animals. In such instances there was little filling of the collateral channels by the contrast media. In the animals which survived, following tetraethylammonium chloride therapy, a graded increase in filling of the vessels could be roentgenologically demonstrated.

The results obtained from chemical blockage of autonomic ganglia are thought to be due to a removal of vasomotor constriction of collateral vessels, thus permitting their dilatation. In these experiments the immediate time interval following arterial resection, referred to by Leriche as "the critical period," appears to be the optimum time for removal of vasomotor constrictor impulses. Once an increased collateral circulation is established, it is able

to maintain itself, and it probably undergoes graded increases over later intervals, as evidenced by the increased tolerance daily for exercise.

In view of these experimental results, it is suggested that tetraethylammonium chloride may become a valuable adjunct in the clinical treatment of acute arterial injuries involving major vessels. (Surgery, Nov. '47 - F. W. Cooper et al.)

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Naturally Occurring Histoplasmosis in Rodents: During the course of an intensive study of histoplasmosis in a rural county in Virginia where four human cases and three canine cases of histoplasmosis have been reported (see Vol. 9, No. 10, the 9 May 1947 issue of this News Letter), a search was made for an animal reservoir of histoplasmosis. From November 1945 through August 1947, 1,620 animals, mostly small rodents, were collected.

Histoplasma capsulatum was isolated from 1 house mouse (Mus musculus), as previously reported, and from 10 rats (Rattus norvegicus). The mouse was trapped at a farmhouse where one of the dogs with histoplasmosis had lived. The rats were trapped at 3 farms where there was no previously known history of histoplasmosis. The mouse was caught in November and the 10 rats in June, July, August, and September. The strains of H. capsulatum isolated were similar and they were entirely typical of strains isolated from human cases.

This is the first reported instance in which H. capsulatum has been isolated in culture from naturally infected wild mice and rats; it was previously isolated from man and dogs only. This extension of the host range of histoplasmosis may be an important step in explaining its worldwide distribution and its sporadic appearance in a fatal form in man. (Pub. Health Reps., 14 Nov. '47 - C. W. Emmons)

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Vitamin K for the Relief of Chilblains: Chilblains consist of a reaction to cold in susceptible persons. The predisposing factors in such people are assumed to be defective peripheral circulation, with increased permeability of the vessel walls and diminished coagulability of the blood. Because the same abnormalities are present in persons with avitaminosis K and are corrected by the administration of the vitamin, it seemed logical to treat chilblains with vitamin K.

Stewart and Rourke showed that hypoprothrombinemia results from lack of vitamin K and that the prothrombin level in such cases could be restored to normal by the vitamin. Scarborough and Macfarlane pointed out that hypoprothrombinemia gave rise to a delayed coagulation time, and concluded that a capillary defect might also be present in that condition. A somewhat similar condition occurs in the allergic manifestation known as urticaria. Black studied the

prothrombin level in a number of cases of chronic urticaria and found it diminished in 65 per cent. He also found that the condition could be relieved by vitamin K therapy, the most marked improvement, in fact, occurring in those cases with lowered prothrombin level.

On these considerations is based the treatment in a small series of cases. Unfortunately, it was not possible to estimate the prothrombin times in these cases, and the results are based on clinical observations alone. The prolonged spell of severe weather last winter afforded a unique opportunity for assessing the efficacy of the treatment. A commercial preparation of acetomenaphthone, synthetic vitamin K, was used throughout.

Eight patients with chilblains, ranging from the mildest manifestation to severe and ulcerated forms, were treated. In 4 there was complete alleviation of symptoms and signs, the response in one being exceptionally good. In the other 4 there was an improvement. Because two of these patients defaulted before treatment was completed, the final result was not known. In the remaining two there was improvement, especially of the actual chilblains, although the perniotic condition of the digits remained; and in one there was a recrudescence of symptoms in spite of continued treatment.

In this small series of cases the administration of vitamin K would definitely seem to have exerted a favorable influence on chilblains. The dosage appears to vary from individual to individual, and is not related to the severity of the condition. On an average, a dose of 20 mg. twice daily was found most generally useful. Again, in some cases a short course of treatment was sufficient to give protection for a long period, whereas in others it was necessary to continue the dosage to prevent recurrence of the lesions.

As regards the mode of administration, it was considered that intramuscular injections were superior to the oral route. They were, however, accompanied by considerable pain and had to be abandoned since the patients objected to this for the possible cure of their relatively minor ailment.

In 1941, Howell suggested that prothrombin and fibrinogen might be constantly formed and consumed in the blood, the result being the formation of fibrin, which in some way might provide nourishment or protection for the cells of the capillary walls. It was on this assumption that the work on urticaria was done.

It is suggested that in chilblains there might be a similar impairment of this mechanism, with resultant damage to the capillary walls, the cause in this case being cold rather than allergic stimulus. The individual susceptibility might be explained by a mild hypovitaminosis-K in certain individuals. Kark and Lozner showed that this hypovitaminosis could, in fact, occur in adults owing to causes other than liver disease. In any case it would seem worth while giving vitamin K a further trial in chilblains. (Brit. M. J., 1 Nov. '47 - D. P. Wheatley)

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Streptomycin in the Treatment of Meningitis: Meningitis due to Mycobacterium tuberculosis or to Gram-negative bacilli is not of particularly frequent occurrence but nevertheless is of great importance because of a high mortality and a failure to respond to the various types of therapy, including sulfonamides and penicillin, which have given favorable results in the coccal infections.

Meningitis Due to Hemophilus Influenzae. This condition, which is of the most frequent occurrence of those cases caused by Gram-negative bacilli, occurs largely in infants and small children, particularly during the first two years of life. Strains of H. influenzae are of two main varieties: one a smooth, encapsulated and presumably virulent form, and the other a rough nonencapsulated and avirulent form. The rough or so-called "respiratory" strains are occasionally implicated as the cause of meningitis, but they are found usually as normal saprophytic inhabitants of the upper respiratory tract of man. The smooth, encapsulated variety, on the other hand, is found mostly in cases of meningitis. In addition to its presence in meningitis, it may be found in the respiratory tract usually in conjunction with acute respiratory infections. During respiratory infections the rough form may undergo transformation to the smooth variety. There are six known serological types among the smooth strains of H. influenzae. The type b strains account for over 90 per cent of cases of influenzal meningitis.

The predominance of the disease during the first two years of life may be related to the low bactericidal action of infants' blood against H. influenzae, type b. The history common to these patients is that of an upper respiratory infection followed by the onset of meningitis. It is assumed that in most cases the organisms reach the meninges by the blood stream following invasion through the respiratory tract. Although H. influenzae meningitis is usually a "primary" disease of the meninges, cases of infection may certainly occur by extension from foci of infection in the nasal accessory sinuses and ears or may follow fractures involving these areas.

The use of combined sulfonamide and type specific rabbit antiserum in the treatment of meningitis due to H. influenzae, type b, has resulted in a marked lowering of the over-all mortality rate, from nearly 100 per cent to as low as 7 per cent. The latter figure, however, is based on the results obtained in one series of 28 cases, and other authors have reported higher mortality rates up to 50 per cent with this therapeutic regime. Among the drawbacks to serum therapy in this disease are: (1) type b antiserum, the only type available, is ineffective if the causative organism is not of this type; (2) the incidence of serum reactions is high, occurring in 12 of one group of 27 patients, with two instances of severe anaphylactic reaction in that small series; and (3) the cost is high, and the antiserum is not generally available.

Penicillin has usually been considered ineffective against H. influenzae and it was first used as an aid in the isolation of that organism. It has, therefore, not been given an adequate therapeutic trial in cases of meningitis due to this organism. A number of strains of H. influenzae isolated from cases of human

infection have been tested for sensitivity to penicillin and the majority of smooth strains were found to be completely inhibited by 1.5 units per ml. or less. Rough strains, however, usually required from 2.5 to 5.0 units of penicillin per ml. for complete inhibition and some were not inhibited by 5.0 units per ml. Penicillin X is somewhat more effective than penicillin G. Zinnemann treated 15 patients with H. influenzae meningitis with combined sulfonamide and penicillin therapy and 8 recovered. Antiserum was used in only one of these patients, who died. The course of the illness in these patients was protracted and relapses were frequent after the therapy was stopped. Others have reported cures from the use of sulfonamides and penicillin in a few cases. Inasmuch as certain conditions may arise in the treatment of meningitis due to H. influenzae which necessitate a change of therapy, the possible usefulness of penicillin should be borne in mind.

Streptomycin is effective against H. influenzae in vitro and in experimental infections. The sensitivity of most strains ranges from 1 to 5 micrograms per ml., concentrations that are easily obtained with therapeutic doses in man.

A number of authors have reported on the effectiveness of streptomycin in cases of meningitis due to H. influenzae. Among the 100 cases cited in the report of the National Research Council there were 17 deaths. These cases cannot be considered as adequately reflecting the value of streptomycin since other agents were also used in a large proportion of them and the streptomycin was often used only after the other therapies had failed.

On the basis of published reports, the chief hazards of streptomycin treatment in H. influenzae meningitis are: (1) the development or appearance of streptomycin-resistant strains of H. influenzae during treatment and (2) the occurrence of complicating secondary infections due to streptomycin-insensitive organisms.

Streptomycin-resistant strains of H. influenzae have been noted to appear during therapy in five of the patients with meningitis that have been reported upon to date.

The occurrence of secondary complicating infections during streptomycin therapy of influenzal meningitis by organisms relatively insensitive to streptomycin was described by Weinstein. Three of his 9 patients developed complicating staphylococcal infections while receiving streptomycin. One of them died of staphylococcal pneumonia despite penicillin therapy; the second had meningitis, and the third otitis media; both of the latter recovered after penicillin was given.

At the Boston City Hospital, 16 infants and children with meningitis due to H. influenzae have been treated with streptomycin and all but one of them have recovered.

The ages ranged from 4 months to 5 years, and 10 of the patients were less than one year old. Blood cultures were done before streptomycin was started

in 10 patients and were positive in seven. It was the practice to discontinue other medications when streptomycin was begun, though in the severely ill patients this was not always done. In 15 patients there was a satisfactory response to streptomycin with prompt disappearance of the organisms from the cerebrospinal fluid. The clinical response of these patients was fairly rapid, improvement usually occurring in from 24 to 72 hours of therapy. This improvement was manifested by a return to a normal state of consciousness, cessation of convulsions and irritability, and return of the ability to feed properly. The subsidence of the fever was somewhat slower than the other clinical and laboratory evidence of improvement; the temperature did not usually reach normal for a period of from 4 to 7 days.

The patient who did not respond to streptomycin was a 6-month old infant who had had convulsive seizures for several days before entering the hospital. Streptomycin was begun on the seventh day of illness and cultures of the cerebrospinal fluid were negative thereafter. There was no clinical improvement, however, and death occurred on the third day of therapy. The cause of death was not determined.

Neurological sequelae were noted only in a nine-month old infant whose treatment was begun on the sixth day of the disease, and following recovery the patient was deaf and blind.

The appearance of resistant strains of H. influenzae was not demonstrated in this series. It is not possible, however, to rule out the presence of such resistant organisms in some localized areas of infection in the fatal case even though the cerebrospinal fluid cultures were negative before death.

Complicating infections, notably acute pharyngitis and otitis, occurred during or after the course of streptomycin therapy in 4 patients and possibly in a fifth. It was not always possible to identify the causative organisms in these infections. The institution of sulfadiazine, however, was followed by subsidence of fever and symptoms in each instance.

The occurrence of secondary fever after an initial response to therapy suggests one of at least four possibilities: (1) a relapse of the original infection, (2) focal purulent complications such as a brain abscess, (3) a secondary complicating infection by another organism, or (4) drug fever. Obviously, the proper interpretation of the secondary fever is very important. In the present series, secondary fever, apparently related to the streptomycin, appeared in five patients and possibly in three others. In these cases the secondary fever subsided promptly after the streptomycin was stopped.

The course of the cases of streptomycin fever is of interest. The initial fall in temperature occurred between the fourth and seventh day of therapy and was accompanied by clinical and laboratory evidence of improvement. A secondary rise in temperature occurred shortly thereafter and continued as long as the streptomycin was given. The clinical and laboratory evidence of improvement continued in these cases in spite of this fever. In most of the patients both the

intramuscular and the intrathecal injections were stopped at about the same time. In one case, however, there were two febrile episodes, the first subsiding when the intrathecal injections were stopped, and the second only after the intramuscular injections were discontinued.

Meningitis Due to Other Gram-Negative Bacilli. Infections of the central nervous system by Gram-negative bacilli other than H. influenzae are infrequent. The coliform organisms are the ones most often implicated. The incidence of meningitis due to coliform bacteria is highest in infants under three months, suggesting a low degree of resistance to such infections in this age group. The other Gram-negative bacilli which are less often encountered as the cause of meningitis may occur in any age group, and comprise a wide variety of organisms including Alkaligenes fecalis, Aerobacter aerogenes, Klebsiella pneumoniae, Pasteurella tularensis, Proteus morgani and Proteus vulgaris, Pseudomonas aeruginosa, the salmonella group, Serratia marcescens, and others. Meningitis caused by these organisms usually occurs by direct extension from an adjacent focus of infection in the paranasal sinuses, ear, mastoid, a brain abscess or a meningocele. It may follow skull fractures or contaminated lumbar puncture or spinal anesthesia procedures. It may also arise by hematogenous spread from a distant focus of infection; cases of coliform meningitis in infants seem to arise largely in this manner.

The use of sulfonamides has resulted in some lessening of the mortality in this type of meningitis but such infections are still quite serious and penicillin apparently has little to offer. The outcome in some of these cases may also depend on successful surgical drainage of purulent foci of suppuration.

Several authors have reported on the use of streptomycin in meningitis due to this group of Gram-negative bacilli. Although the over-all mortality in their cases is high (45 per cent), it is probable that in many of these patients as in those of influenzal meningitis, treatment with streptomycin was begun late and only after therapy with other agents had failed.

Streptomycin has been shown to be active in vitro against most of these Gram-negative bacilli, and it is effective in experimental infections of animals with some of them. The early institution of intramuscular and intrathecal streptomycin when combined with surgery wherever indicated should, therefore, go far towards lowering the mortality rates in meningitis due to these organisms Inasmuch as systemic infections with Brucella and Salmonella, including typhoid fever, have not responded favorably to streptomycin, its effects in meningitis due to these organisms cannot be predicted. Streptomycin should, nevertheless, receive a trial in these infections.

At the Boston City Hospital eight patients with meningitis due to Gram-negative bacilli, other than H. influenzae, have been treated with streptomycin, and 6 of them have recovered. There were 3 patients with meningitis due to Pseudomonas aeruginosa (Bacillus pyocyaneus), and one patient each with

meningitis due to Proteus morgani, Aerobacter aerogenes, Escherichia coli communis, Hemophilus parainfluenzae, and a "pleuropneumonia-like" organism.

The pathogenesis in these cases is of interest. In 3 patients the meningitis was secondary to trauma to the head; in 3 others it was secondary to infection of a congenital meningocele; one case followed a diagnostic lumbar puncture and in another the meningitis was associated with a bacteremia.

Penicillin with or without sulfadiazine had been given to all of these patients without effect before the institution of streptomycin. Moreover, in one case the meningitis developed during penicillin treatment for diarrhea and in another it began during prophylactic administration of sulfadiazine and penicillin following a fracture of the skull. One or both of these agents was also given during the streptomycin administration in 5 of the patients.

There were two deaths in this group of 8 patients. One of these deaths was in a 12-day old infant and followed the development of streptomycin resistance by the infecting organism. The other occurred after only 12 hours of treatment in an infant who was moribund when the streptomycin was started.

There was evidence of clinical improvement shortly after streptomycin was begun in all of the patients who recovered. In three of them, however, organisms persisted in the cerebrospinal fluid for a varying number of days during streptomycin treatment. Secondary fever attributable to streptomycin occurred in four and possibly a fifth patient; in these cases, as in those due to H. influenzae, clinical and laboratory evidence of improvement continued during the secondary febrile episode. There were no complicating infections with other organisms in any of these cases. The only residual neurologic damage among those who recovered was a right facial palsy in one patient. As already noted, a resistant strain appeared during treatment in another patient who died. In another patient, the organism was recovered from the cerebrospinal fluid throughout the period of treatment; the organism retained its original sensitivity for 6 days and was resistant during the last four days. The organism then disappeared from the spinal fluid, and the patient recovered.

Tuberculous Meningitis. There are more cases of meningitis due to Mycobacterium tuberculosis than those caused by Gram-negative bacilli. Infants and children are affected more often than adults. Tuberculous meningitis probably arises in most cases by hematogenous spread from a focus of infection elsewhere in the body, although in some cases it occurs by direct extension from a tuberculous lesion of the brain. Prior to the use of streptomycin tuberculous meningitis was a uniformly fatal disease.

Streptomycin was early shown to be effective against M. tuberculosis in vitro, and in experimental infections in animals. The in vitro sensitivity of a large number of strains of M. tuberculosis isolated from cases of human infection was found to be less than 1 unit per ml.

Reports are now available in 32 cases of tuberculous meningitis that have been treated with streptomycin. At the time when they were reported, 13 of this

group of patients were still living. The incidence of permanent neurologic damage was high, however, and the survivors had been followed for only short periods after cessation of streptomycin therapy. The remarkable fact was that they were alive and that their disease was apparently arrested. Histopathological findings in fatal cases have also given evidence of the effectiveness of streptomycin in such cases.

Of considerable interest is the fact that parenteral therapy alone has proved inadequate in these cases. Two patients were noted to develop signs of meningitis during intramuscular streptomycin therapy for miliary tuberculosis, and the meningitis apparently responded only after streptomycin was also given intrathecally. The 4 survivors among the 7 patients treated by Hinshaw and his coworkers all received both intramuscular and intrathecal therapy but those who died had received the drug only intramuscularly. A prolonged period of combined parenteral and intrathecal streptomycin seems indicated in this condition.

The appearance of streptomycin-resistant strains of M. tuberculosis has not been reported as occurring specifically during therapy of tuberculous meningitis but resistant strains have appeared frequently in patients with pulmonary tuberculosis while on streptomycin therapy. There is no reason to believe that similar resistant strains will not also be noted during the streptomycin treatment of meningeal tuberculosis.

The largest single intrathecal dose of streptomycin, 200 mg., was given initially to a patient who exhibited transient irritability and some clonic movements of the lower extremities shortly after this injection; this was followed by a marked rise in temperature. Cerebrospinal fluid removed 24 hours after this injection showed a marked increase in the number of leukocytes, mostly polymorphonuclears, and there was also a moderate increase in protein. The cerebrospinal fluid findings gradually returned toward normal when the size of the intrathecal dose was decreased.

Three patients with tuberculous meningitis have been treated with streptomycin at the Boston City Hospital. In each instance the diagnosis was proved by guinea pig inoculation of cerebrospinal fluid obtained just prior to institution of therapy. Streptomycin was given intrathecally and intramuscularly to all three patients. There was one death in this group.

A trial of the simultaneous use of streptomycin with one of the sulfone drugs such as Promin, Diasone or Promizole, in the treatment of tuberculosis certainly seems indicated since such a combination appears to be more effective than the use of either alone in experimental infections in animals.

The findings in the present cases indicate that streptomycin is of considerable value in the treatment of meningitis due to Gram-negative bacilli. The drug should be given both intramuscularly and intrathecally. In adults an intramuscular dose of 1 Gm. every 6 hours and a single daily intrathecal injection of 50 mg. appears to be adequate for most cases. Somewhat larger doses, 1 Gm. every four hours intramuscularly and from 50 to 100 mg. intrathecally twice a day for

one or two days, may be given but are probably not necessary in most cases, Infants and small children may be given about 25 mg., or slightly more, per pound of body weight per day intramuscularly and from 10 to 50 mg. daily by the intrathecal route.

Most patients with meningitis due to Gram-negative bacilli seem to respond well to streptomycin alone if the treatment is started early in the course of the disease. If treatment is begun late, however, or if the patient is severely ill when the treatment is started, sulfadiazine should probably be given in addition. Likewise, in cases due to H. influenzae, type b, specific antiserum and sulfadiazine should also be given under similar circumstances. The possibility of inhibiting the development of streptomycin-resistant strains by the combined use of sulfadiazine and streptomycin has been suggested. Penicillin should also be used whenever an infection with a susceptible organism is present or suspected. The possible use of large doses of penicillin specifically for their effect on certain Gram-negative bacillus infections warrants further exploration.

In tuberculous meningitis, the early and persistent use of streptomycin may offer the only hope of arresting the disease. It is essential that cerebrospinal fluid be obtained for culture or guinea pig inoculation, or both before streptomycin is started since these procedures may later yield negative results and leave the diagnosis in doubt. The streptomycin should be given in these cases both intramuscularly and intrathecally over a period of 3 or possibly 4 months. The doses required in cases of tuberculous meningitis may be somewhat smaller than those used in infections with Gram-negative bacilli due to the greater sensitivity of the strains of M. tuberculosis. The intrathecal doses should be given daily for from 3 to 5 weeks and at gradually increasing intervals up to twice weekly thereafter.

Excessively large individual doses by intrathecal injection should be avoided in all cases. They are known to produce serious reactions in animals and in humans. It appears likely that the concentration of streptomycin in the solution injected as well as the total amount may be an important factor in these reactions as has been suggested in the case of penicillin.

The results in these cases and in similar cases reported by others seem to justify the following conclusions:

1. Streptomycin is the only agent now available which may arrest the progress of tuberculous meningitis.

2. Streptomycin is the most effective single agent in the treatment of meningitis due to Gram-negative bacilli, including H. influenzae. (Ann. Int. Med., Oct. '47 - T. F. Paine et al.)

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Study of Motion Sickness: In this last of a series of investigations done by means of the vertical accelerator at Wesleyan University, the design was to

discover how motion sickness rates are affected by wave frequency when the accelerations in the waves are held fixed. Using waves with a constant acceleration of 0.20 g, frequency was controlled by the duration of application of upward and downward accelerations. By this means wave frequencies of 13, 16, 22, and 32 cycles per min. were obtained, having amplitudes of 9 feet, 5 feet 4 in., 2 feet, 6 in., and 1 foot, 1 in. These frequencies are the same as those used in previous studies in this series, when time between accelerations, level of acceleration and other aspects of the waves were varied. Other significant variables were counterbalanced or controlled. In this study on 120 subjects it was shown that sickness varied with the energy per wave; the biggest wave produced the most sickness, the smallest wave the least. The sickness rates obtained were 37, 37, 10, and 7 per cent in going from the large slow wave to the small fast wave. The corresponding sickness indices (with vomiting counting twice as much as lesser sickness) were: 53, 47, 10, and 7. This decrease cannot be attributed to total energy expended on the subjects, since this was roughly constant. Nor can it be attributed to acceleration-level, which was also constant for all waves. It must, therefore, be attributed either to the time-character of the waves or to the energy per wave, since these were the variables. It does not seem possible to attribute it wholly to their time-character. Two previous studies showed maximum sickness for waves of 16 and 22 cycles per min., but this study placed the maximum at 13 cycles. Energy per wave must, therefore, be a significant factor in production of sickness. However, this study has not shown that wave duration has not played a part.

The interpretation of the results of the present study may best be considered with the results of the four previous studies of the influence of wave characteristics upon sickness rates. In this series of five investigations there has been control or variation of four aspects of the waves:

1. The rate of work done during the exposure period (wave energy X wave frequency).
2. The energy per wave.
3. The time per wave (cycling rate).
4. Acceleration level and wave form.

This series of investigations is incomplete from the scientific point of view so that no final conclusions yet seem justified. Nevertheless, some tentative conclusions should be drawn.

It seems most reasonable to regard the motion-sick state as an accumulative phenomenon. Presumably, certain centers within the nervous system are stimulated into activity by motion receptors. It may further be assumed that such central activity would, in the absence of continued stimulation, show a gradual decrement. Overt sickness, according to this view, is the consequence of a rate of stimulation (or increment) which exceeds the rate of decrement.

If these assumptions can be accepted, it could be considered that each wave (or half-wave) can make a certain contribution to the central activity which eventually results in sickness. Therefore, the sickness-producing capacity per wave

and the total number of waves required to produce sickness are both of interest.

Time per wave (cycling rate) was varied in the first, third, and present studies; it was held constant in the second and fourth studies. The first study, however, had the most direct bearing on the authors' interpretation of wave duration as a variable. In this study, acceleration level and energy per wave were held constant, but time per wave and rate of work varied. The results obtained showed that a certain intermediate wave duration and rate of work yielded maximum sickness. This leads to the question whether wave duration or rate of work was the significant factor. If the initial assumption that each wave produces an increment toward the sick state is accepted, it would be improper to attribute the results obtained to the work rates, since sickness did not increase (but decreased) with work rate. Wave duration is, then, the significant variable. There appears to be an optimum duration for the given set of conditions.

Acceleration level was held constant in the first, second, and present experiments; it was varied in the third and fourth. The first-named studies showed that sickness can vary enormously while acceleration is constant. The present study, in particular, shows that sickness varies under constant acceleration even when the rate of work is roughly constant. The third study duplicated the first in respect to wave durations, energy per wave, and work rates, but allowed acceleration to vary with wave duration. The results, in general, paralleled those of the first study except that the sickness rates obtained from slow waves with low accelerations were greater than from the first study's slow waves with high accelerations. It was therefore concluded that acceleration is a significant factor. This was further confirmed by the fourth study, in which acceleration was the only variable - rate of work, energy per wave, and total wave duration being held constant. Sickness rates were thereby shown to be affected by the nature of the acceleration in a wave.

Energy per wave was held constant in the first, third, and fourth studies; it was varied in the second and present study. The second study held constant acceleration and (roughly) wave duration, but energy per wave and rate of work were allowed to vary. Sickness decreased as the two latter decreased. The present study held constant acceleration and (roughly) rate of work, but energy per wave and wave duration were allowed to vary. It is obvious from the results obtained that energy per wave is a factor in sickness. Sickness was found to decrease with decreasing energy per wave although rate of energy was held roughly constant. Furthermore, this decrease cannot be attributed wholly to the other variable (wave duration), since the variation of sickness with wave duration does not follow the form previously found in the first and third studies.

Rate of work was varied in the first three experiments and was held constant in the last two. In the second experiment rate of work was varied with energy per wave and the sickness obtained varied in the same way. Taken alone, therefore, it does not allow attributing the sickness to one or the other. In the first and third studies rate of work varied as wave duration varied. Because intermediate work values yielded maximum sickness, the major features of the

results obtained are attributed to wave duration and to acceleration level rather than to rate of work, which, it is assumed, should bear a uni-directional relationship to sickness. The fourth experiment (in which rate of work was held constant) has no direct bearing on establishing the role of rate of work, except as further proof that it is not the only significant variable. But the present experiment has a most important bearing, since rate of work was held (roughly) constant, and yet sickness varied. Therefore, it is concluded that rate of work (considered independently of the character of the waves that contribute to it) has not been shown to be a significant variable.

In general conclusion, then, it would appear that the capacity of a wave to induce sickness depends on wave duration, acceleration level, wave form, and energy per wave. It is clear that the effect of any one of these variables depends upon its relation with the others. Enormous differences in the nauseating properties of waves were obtained. For instance, some waves were roughly 20 times as nauseating per unit of energy as other waves.

The elucidation of the receptor mechanics or of the central nervous system physiology which underlies these differences in wave effectiveness must wait upon further studies. It is hoped to investigate the relationship of wave characteristics to sickness for other wave forms (especially sinusoidal) using human subjects, and to extend the studies to dogs preparatory to physiological studies. It is especially desired to undertake eighth nerve action-potential studies in relation to wave characteristics. (J. Exper. Psychol., Oct. '47 - S. J. Alexander et al.)

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Reports on USN Research Projects:

A Method for Screening Antimalarial Compounds in the Mosquito Host. This particular study was undertaken to devise a method which would permit of more direct screening for certain drug qualities against a specific malarial parasite, or which would permit the screening of compounds for prophylactic effect against the human malarial parasite without the need for infecting undue numbers of human beings.

With a drug-diet method devised for the administration of anti-malarial compounds it has been found that quinine, quinacrine, plasmochin, and SN6911, administered in maximally tolerated doses to mosquitoes infected with Plasmodium gallinaceum, have no effect on sporozoite production or sporozoite viability. On the other hand, in infected mosquitoes treated with adequate concentrations of sodium sulfadiazine, oocysts fail to develop properly and sporozoites are produced only rarely, and those that are produced appear to be incapable of producing infection when inoculated into normal chicks.

From the known effects of sulfadiazine and the other drugs cited, on sporozoite-induced infections of P. gallinaceum, it would appear, therefore, that there is a definite relation between drug activity and effect in the sporozoite-infected

vertebrate host and drug activity and effect in the infected invertebrate host.

With this method it may become possible to evaluate compounds directly in the mosquito host for their prophylactic activity against the human malarial parasite. The method may offer another means for studies on parasite metabolism or for studies on the mechanisms of drug action. (Proj. X-539, Rep. No. 6, 22 Sept. '47, Nav. Med. Res. Inst., Bethesda, Maryland - L. A. Terzian)

Design of a Semiautomatic Night Vision Scotometer: The scotometer described in this study is an instrument designed to measure the size of the central scotoma of the dark-adapted eye. Radial measurements of separation of test light and fixation point are made along eight equally spaced meridians. Choice of meridian and test-light settings are accomplished mechanically. Test light, fixation point, and indicator dials are self-luminous.

Two subjects were tested on the scotometer. It was found that the boundaries of the central scotomas of right and left eyes were nearly identical in both subjects. It is suggested that this symmetry of retinal pattern of the two eyes is intimately associated with the mechanism of binocular summation and binocular convergence in the dark-adapted eye. (Proj. X-467, Rep. No. 1, 21 July '47, Nav. Med. Res. Inst., Bethesda, Md. - R. H. Lee and R. H. Draeger)

Dye Injection Method for Determination of Cardiac Output. Because a method for determining the cardiac output of subjects exposed to simulated high altitude in the low pressure chamber was urgently needed, and because it was desired to explore the possibility of using the dye injection technic as a clinical research tool, this method was set up at Pensacola in 1946. The dye selected was brilliant vital red.

The dye injection method for determination of cardiac output is based on analysis of the time-concentration curve of dye in the arterial blood during its first circulation after rapid intravenous injection. Technical difficulties included selection and preparation of dye for injection, the proper placement of arterial and venous needles, the collection of adequate samples at one-second intervals, the prevention of clotting and hemolysis, and the colorimetric determination of dye concentration.

Determinations of cardiac output in normal resting subjects at sea level gave values of approximately 5 liters per minute. Two technically satisfactory determinations were performed in the low pressure chamber at a simulated altitude of 20,000 feet. In one the subject was not far from a basal state, and the cardiac output was calculated to be 9.8 liters per minute. In the other the subject was apprehensive, and the cardiac output was 16.8 liters per minute.

An estimate of cardiac output was of particular interest in analyzing the adaptations occurring at high altitude since such an estimate made possible the calculation of an approximate value for the oxyhemoglobin saturation of mixed venous blood. From a knowledge of arterial and mixed venous oxyhemoglobin saturations an estimate of mean capillary $pO_2$ was made. This value represented a closer approach to mean tissue $pO_2$ than had previously been available and was therefore helpful in analyzing the effects of high altitude upon tissue oxygenation.

This work constitutes preliminary use and evaluation of the dye-injection method. Results are to be considered as only approximate. Further evaluation is in progress. (Proj. X-726(Av-380-r), Rep. No. 1 (Final), 24 Sept. '47, Nav. School Aviation Med. and Res., NAS, Pensacola, Fla. - R. L. Riley and J. W. Remington)

NOTE: Those interested in seeing copies of the complete reports should address their request to the research activity from which the report originates. Reference may be made to those reports in the same way as to published articles, noting authors, title, source, date, project number, and report number.

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The Diagnosis, No Disease (Terminal Leave), in Error: Attention is invited to the fact that an amendment to the Armed Forces Leave Act of 1946, approved 4 August 1947, abolished terminal leave as such, substituting lump sum payments for accrued leave. It is therefore no longer appropriate for patients to be carried on the sick list with a diagnosis of No Disease (Terminal Leave), or for Fa cards to be submitted with that diagnosis. Alnav 531-46, which promulgated instructions for the use of the diagnosis was cancelled by BuPers-BuSandA joint letter of 25 August 1947, NDB of 31 August. (Medical Statistics Div., BuMed)

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NAVMED-785 (Rev. 4-47), Semiannual Dental Officer Personnel Report: Paragraph 1381 in the Manual of the Medical Department requires that all responsible dental officers submit a NAVMED-785 (Rev. 4-47), SEMIANNUAL DENTAL OFFICER PERSONNEL REPORT, to the Chief of the Bureau of Medicine and Surgery on 1 January and 1 July of each year. The responsible dental officers include district and staff dental officers, dental officers in command and in charge, heads of dental departments, chiefs of dental services, and senior dental officers of dental divisions and other dental activities, including those of Fleet Aircraft Service Squadrons, Night Composite Development Squadrons, and similar commands.

Because the Personnel Allocation Plan of the Bureau of Naval Personnel determines the distribution of dental officers and the commands to which they are assigned for duty, it is necessary that a NAVMED-785 (Rev. 4-47) be required from the responsible dental officer of each command to which dental officers are attached. Reports regarding dental officers attached to receiving stations, FASRONS, and similar commands for primary duty must not be included in those submitted by dental activities of other commands where they happen to be located or from which they are receiving logistic support and to which they are not attached by official orders from the Bureau of Naval Personnel.

Each and every dental officer on active duty in the Navy must be accounted for in a NAVMED-785 (Rev. 4-47) semiannually, even though there is but one dental officer assigned to an activity, and regardless of the duty which he is performing or the length of time he has been attached to a command. The reports should reflect the categories of duty which the dental officers are performing on 1 January and 1 July as determined from the experience of the previous six months, and also a dependable estimate of the number of dental officers required as of the date of the report.

It is most important that the NAVMED-785 (Rev. 4-47) be submitted promptly on the date on which it is due in order that the compilation of the data which it contains, showing the distribution of duties for all dental officers, can be completed by the first of the month following the due date.

All responsible dental officers should study the instructions for accomplishing the NAVMED-785 (Rev. 4-47) which are printed on the form. It is highly important that all entries be as accurate as possible. It is expected that dental officers who sign the reports will be able to verify and justify their entries when called upon to do so.

The entries on the "PRESENT" line in the upper tabulation section must balance with the entries under "ROSTER" in the lower tabulation section which are made opposite the names of the dental officers. They should total 1.0 for each dental officer in both tabulation sections.

The entries on the line "REQUIRED" in the upper tabulation section should be carefully determined. They should constitute an accurate and conservative estimate of the total number of dental officers required and the decimal fractions of time they would devote to each category of duty.

The NAVMED-785 (Rev. 4-47) does not provide a column titled "DIAGNOSIS & EXAMINING" in the lower tabulation section. It is therefore requested that the decimal fraction or whole number for that entry on the "PRESENT" line in the upper tabulation section be included under "OTHER" in the lower tabulation section and explained on the reverse side of the form under "REMARKS". Many categories of duty may be accounted for under "OTHER": for example, diagnosis and examining, general court martial, summary court martial, coding, welfare, recreation, athletic, hospital corps examining, survey board, mess treasurer, attendance on postgraduate courses, additional temporary duty, etc. A detailed explanation should be included under "REMARKS" whenever entries are made under "OTHER": for example, if the entry under "OTHER" on the "PRESENT" line is .9, it may represent .3 diagnosing and examining, .1 general court martial, .1 coding, .15 Hospital Corps examining, .05 athletic officer, .1 postgraduate instruction, .1 mess treasurer. The explanatory entry under "REMARKS" should be in the following form if for entries under "OTHER" on the "PRESENT" line in the upper tabulation section:

"PRESENT", "OTHER" includes:

.3 diagnosing and examining
.1 general court martial
.1 coding
.15 Hospital Corps examining
.05 athletic officer
.1 postgraduate instruction
.1 mess treasurer
.9 total

The word "REQUIRED" should be used instead of "PRESENT" when an explanation is written under "REMARKS" for entries under "OTHER" on the "REQUIRED" line in the upper tabulation section.

It should be noted that the instructions on the form require that entries in "ADMINISTRATION", "RESEARCH", and "OTHER" columns should be explained on the reverse side. Explanatory notes should always be included under "REMARKS" whenever they appear to be necessary for clarification of the report. (Dental Div., BuMed)

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To: All Ships and Stations 15 October 1947

Subj: U. S. Naval Dental Prosthetic Clinic, Naval Gun Factory, Washington, D. C., Establishment of

1. The following activity is hereby established under a dental officer in command:

U. S. Naval Dental Prosthetic Clinic
Naval Gun Factory
Washington 25, D. C. 2748-960

This activity is under the military command and coordination control of the Commandant, Potomac River Naval Command, and is under the management control of the Bureau of Medicine and Surgery.

2. Logistic support for the naval personnel of this activity will be provided by the U. S. Naval Receiving Station, Washington, D. C.

3. Bureaus and offices concerned take necessary action.

--SecNav. John L. Sullivan

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ALNAV 242 13 November 1947

Subj: Physical Standards for Enlistment, Modification of

Effective immediately physical standards for enlistment and reenlistment in the regular Navy and class V-6 Naval Reserve are modified as follows.

(a) Dental Requirements: Applicants must be well nourished and have good musculature, be free from gross dental infections and have a minimum requirement of an edentulous upper jaw and/or an endentulous lower jaw corrected or correctible by a full denture or dentures.

(b) Vision: Visual acuity without glasses not less than 2/20 in each eye if vision is correctible to 20/20 in each eye and provided the defective vision is not due to active or progressive organic disease. Color perception test will be administered for record purposes only. Defective color perception is not disqualifying.

(c) Height: Minimum sixty inches maximum seventy-eight inches.

The foregoing modifications temporarily suspend specific corresponding standards of respective sections of Part II, Manual of the Medical Department. The possibility of subsequent disability claim will be considered in examining applicants with questionable defects. All minor and questionable defects will be recorded. Present mental standards remain effective.

--SecNav

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Circular Letter 47-157 18 November 1947

To: MedOfCom, U. S. Naval Hospitals

Subj: Establishment of Positions as Ward Attendants (Group II) and Hospital Attendants (Group IVb) in the Dependents' Services of Naval Hospitals,

1. Correspondence reaching the Bureau has indicated that there is some confusion as to duties that can be assigned properly to graded and ungraded civilian positions in the Dependents' Services. In some instances, duties which properly belong in classified positions have been included in job descriptions for Ward Attendants in the unclassified service.

2. In general, the distinction between classified and unclassified positions in this category of work depends largely on the extent which the employee will be expected to participate in the care and treatment of patients. Such duties as feeding, bathing, dressing and undressing patients, taking and recording temperatures, pulse and respiration, assembling materials for and giving enemas,

answering patients' calls, etc., should not be assigned to unclassified positions as Ward Attendants. These are all duties that belong in classified (Group IVb) positions in the Subprofessional Service, under the Hospital Attendant Series.

3. Duties considered appropriate for assignment to Ward Attendant positions in the unclassified service include such items as: serving, distributing and collecting trays; fixing the patients' flowers; cleaning and polishing; washing out and sponging linens; making and wrapping surgical supplies; washing windows; dusting and mopping, etc.

4. In order that the Bureau will have accurate data as to the number of civilian employees engaged in ward duties in the Dependents' Service, it is desired that all employees performing such duties be classified either as Hospital Attendants or Ward Attendants. Action should be taken at the earliest possible date to reclassify all civilian employees otherwise classified who are performing ward duties.

--BuMed. H. L. Pugh

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Circular Letter 47-158 20 November 1947

To: (Activities Having An Allotment for Care of the Dead)

Subj: Program Allotments for Care of the Dead, Appropriation 1781102 Medical Department, Navy, 1948.

Ref: (a) Advance notice of Change 5, Instruction Memorandum 5-3, Volume IV, BuSandA Manual dated 20 October 1947

Encl: 1. (HW) Allotment authorization decreasing program allotment for Care of the Dead

This letter from the Chief of BuMed (1) rescinds funds granted under subject allotments for the transportation of remains (Obligations incurred for transportation of remains will be chargeable to an allotment administered directly by BuMed.); (2) directs that expenditures and/or obligations outstanding for transportation of remains reported on the Status of Allotment Reports be cancelled; (3) prescribes the appropriate accounting data to be inscribed on transportation requests and/or bills of lading; (4) provides cost accounting instruction insofar as concerns the recording of the estimated cost of transportation of remains in cost accounting records (NavMed 569 for naval hospitals and NavMed E for other shore stations); (5) directs attention to Advance Notice of BuSandA Manual Change #5 which establishes the procedure whereby issues of clothing and small stores for the burial of the dead will be charged to subject appropriation on the NavSandA Form 870 as an issue from the Naval Stock Account.

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Circular Letter 47-159 21 November 1947

To: MedOfsCom, NavHosps, Continental U. S.

Subj: Standard Admission Card, Proposed Adoption of

Encl: A. (HW) Proposed Standard Admission Card (reduced size).
B. (HW) Proposed Standard Staff Locator Card.

This letter from the Chief of BuMed states that the Bureau has reviewed the admission cards and admission procedures in use at several naval hospitals, and that the analyses indicate an urgent need for the development of a standard admission card to be used in establishing uniform admission procedures in naval hospitals. An outline of the use of the card is given. Comments and suggestions regarding the suitability of the proposed standard admission card (Enclosure A), particularly from the personnel and/or records officer, are requested prior to 12 December 1947. Comments are also requested on the use and the appropriateness of the content of the proposed standard Staff Locator Card (Enclosure B).

NOTE: Because of space limitations, enclosures are not copied in the News Letter.

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Circular Letter 47-160 21 November 1947

To: All Ships and Stations

Subj: Articles and Speeches on Professional and Scientific Subjects Prepared by Personnel of the Medical Department.

Ref: (a) Article 113, U. S. Navy Regulations.
(b) BuMed Circular Letter 42-95 dated 21 Oct 1942 (N.D. Bul. Cum. Ed. 1943, 42-883, p. 447).

1. Reference (b), which directed that two copies of subject material be transmitted to BuMed, is hereby canceled.

2. In the future, the provisions of reference (a) shall apply.

--BuMed. C. A. Swanson

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Circular Letter 47-161 21 November 1947

To: All Medical Department Activities

Subj: Civilian Awards Certificates, Extension of Time to Make Recommendations for

Refs: (a) BuMed Cir. Ltr. No. 47-50, 21 Apr 1947.
(b) BuMed Cir. Ltr. No. 47-108, 15 Aug 1947.

This letter from the Chief of BuMed extends to 31 December the final date for submission of recommendations for the awarding of certificates to civilians (nonemployees) and civilian organizations in recognition of outstanding services rendered to the Medical Department of the Navy during World War II.

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Circular Letter 47-162 25 November 1947

To: MedOfCom, NavHosps

Subj: Christmas Greetings to Hospital Patients by the American Legion

This letter from the Chief of BuMed states that the Navy Department has again offered cooperation to the American Legion in its annual program of sending Christmas greeting cards to patients in naval hospitals. Besides containing information related to the carrying out of this project, the letter states that these cooperative arrangements are not to be interpreted as excluding other worthy patriotic, fraternal, and religious groups from participation in the celebration of Christmas, and that addressees will coordinate, within their commands, the program of The American Legion with that of the American Red Cross and such other organizations as may be indicated locally, to the end that the spirit of the season may be adequately and effectively met.

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Circular Letter 47-163 25 November 1947

To: U. S. Naval Hospitals

Subj: Graduate Medical Training Program - Essentials of Approved Residencies and Fellowships

Refs: (a) Essentials of Approved Residencies and Fellowships dtd June 1947 (Rev. to June 1947. Reprint from JAMA, Vol. 134 No. 16, dtd 16 Aug 1947).

Refs: (b) Report of Reserve Consultants Board to the Bureau of Medicine and Surgery dtd 16 June 1947 (available in BuMed).
(c) Par. 5129A, Manual Medical Dept.
(d) Par. 5129C, " " "
(e) Essentials of an Approved Internship, JAMA 118: 1497, 1942.
(f) Internships, JAMA 127: 783, 1945.
(g) NavMed 762 revised 21 June 1946.
(h) Outline of Graduate Medical Training Program in the U. S. Navy (May 1, 1946), and revised (Nov 15, 1947).

1. The pamphlet "Essentials of Approved Residencies and Fellowships," originally published in March 1928, was revised at the last meeting of the House of Delegates of the American Medical Association. Ref. (a) has been published and is hereby approved as the standard for approved residencies in naval hospitals.

2. Ref. (g) is hereby cancelled and superseded.

3. Medical Officers in Command of naval hospitals are enjoined to use refs (e) and (f) as the standard and basis of approval for intern training.

4. The Graduate Training Committee in naval hospitals conducting residency training shall carry out functions as required in ref. (h).

5. The submission of the reports (NavMed 949 and NavMed 1048) required in refs. (c) and (d) shall continue.

6. Ref. (b) is a report of the Reserve Consultants Board to the Bureau of Medicine and Surgery. One of the recommendations made was that medical officers should apply to the Bureau of Medicine and Surgery for an evaluation of previous training, and not to the Specialty Board. This was done in an effort to reduce correspondence between medical officers and the secretaries of the various specialty boards.

7. Ref. (a) is available in BuMed. Medical officers desiring copies should write to BuMed instead of the Council on Medical Education and Hospitals of the AMA. It is directed that medical officers familiarize themselves with the requirements of the specialty board prior to initiating any correspondence. Ref. (a) contains several changes, particularly Parts III, IV, and V.

8. Part III, page 29 of ref. (a) is of especial importance to residents and interns as it serves to clarify relationships. Part V is of importance to Medical Officers in Command.

9. Part IV, page 30 of ref. (a) affects every medical officer interested in obtaining credit toward certification by a specialty board. The method of keeping a "Log of Professional Assignments" is obsolete. Medical officers who have been keeping such logs should not destroy them as they may be useful in compiling data for the secretary of a specialty board. Residents in naval hospitals must

keep an accurate record of all work performed, lectures, seminars, grand rounds. Such records should be signed by the Chief of Service, Consultants, and approved by the Commanding Officer at the completion of each training period (1 year). BuMed will inform the Council on Medical Education and Hospitals, and each secretary of a specialty board annually of the names of medical officers who have completed training, either in residencies in naval hospitals or other training in civilian institutions. Medical officers should withhold correspondence with secretaries of specialty boards until advised to do so by BuMed. This represents a change in policy in that requests for admission to examination by a specialty board should be submitted via BuMed. This procedure is the same as that followed for candidates who seek admission to one of the colleges (e.g., American College of Surgeons, etc.).

10. As a statement of policy, leave during residencies should be limited to two (2) weeks except in cases of emergency. Officers assigned to residency training and to "duty under instruction in a specialty" will not be considered as having working hours. They must be regarded as being on duty 24 hours a day except that they are expected to devote most of their efforts toward acquiring a knowledge of their specialty. Medical officers shall stand such watches as ordered by the Commanding Officer.

--BuMed. C. A. Swanson

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