NavMed 369

UNITED STATES NAVY

MEDICAL NEWS LETTER

Editor - Captain F. W. Farrar, MC, USN

Vol. 12 Friday, 13 August 1948 No. 4

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A Penicillin Preparation with Prolonged Action: This study concerns the pharmacodynamic properties of a penicillin mixture for clinical use which has the advantage of prolonged action, high fluidity, and readiness for injection with an ordinary syringe. The standard preparation recommended for human use consists of a suspension of 300,000 u. crystalline potassium penicillin in 1 c.c. vegetable oil containing 0.3 mg. epinephrine. This is a milky suspension, available in vials and ampules, which can be injected with a 20- or 21-gauge needle.

A clinical evaluation of the efficiency of this suspension in cases of male gonorrhea, conducted by Cohn and Kornblith (see following article), confirmed the advantages claimed. Investigations on the activity of this penicillin composition in other infections are in progress, and it is anticipated that the clinical results will be parallel to those of Cohn and Kornblith, i. e., increased activity, determined by the repository effect.

In this study 1 or 2 c.c. of the material was usually injected intramuscularly into the buttocks of the dog, rabbit, and man. In the rat 0.1 c.c. was always injected intramuscularly. Blood samples were withdrawn at various intervals after injection and their penicillin content determined by the serial dilution method, using rabbit blood as an indicator for the growth of Streptococcus haemolyticus, Type A, Group 3. Approximately 200 experiments on dogs, 120 on man, 50 on rabbits, and 400 on rats were carried out.

When injected in oily suspension, the effect of epinephrine on the blood pressure is noticeably diminished, but its delaying action on the absorption of penicillin remains extremely high. The latter effect, which depends on a local ischemic reaction, appears with doses of from 0.05 to 0.1 mg., i. e., about from one twentieth to one fortieth of the dose required for eliciting a systemic vasopressor action.

The duration of the blood penicillin level cannot be prolonged beyond a certain ceiling period (26 hours) by increasing the dose of epinephrine and penicillin above a definite amount. The "ceiling duration dose" for epinephrine is approximately 0.2 mg., but for penicillin it varies with the species. The existence of a ceiling dose for epinephrine is apparently related to the production of a maximal ischemic action on the surrounding tissue. It is more difficult, however, to advance reasons for the "ceiling duration dose" of penicillin. This is probably determined by various factors: an end-point in the epinephrine effect, the dispersion of the oily material, and the instability of penicillin. An additional factor might be represented by the rate of absorption of penicillin from the deposit. When penicillin is given in oil epinephrine, there is some justification for the assumption that the fraction of penicillin absorbed in equal intervals of time does not change with the absolute amount of the antibiotic in the tissues. Assuming that half of the penicillin present in the tissue is absorbed in from 2 to 3 hours, doubling of the dose would cause an increase of the duration by from 2 to 3 hours only.

With the larger relative doses required to produce an equal duration in the smaller species, the amounts of penicillin absorbed during the same period of time are correspondingly larger with resulting higher blood concentrations. In fact, the relation in the peak concentrations reached with a 300,000 u. dose, which gives a one-day duration in man and in dog, is proportional to their weight differences: from 0.5 to 1 u. in man, and from 5 to 20 u. in dogs. Similarly, an increase in dosage from 300,000 to 600,000 u. in man results in correspondingly higher blood levels. These differences in duration, according to species and relative weight, are important from a methodologic standpoint.

The experimental work on rats reveals that the prolongation of the presence of penicillin in the liver and kidney outlasts by long periods the duration of the demonstrable blood penicillin level following injections in oil with vasoconstrictor. It might be assumed that the penicillin present in the organs after its presence in the blood is no longer detectable is of some therapeutic significance. A certain number of experiments carried out in the authors' laboratory would indicate that the accumulation of penicillin in the organs, such as observed following treatment with the suspension in oil with vasoconstrictor, cannot be obtained with high doses of penicillin given repeatedly in saline.

The experimental data suggest that the therapeutic advantages of the new penicillin preparation investigated depend on the protracted duration of the antibiotic in the tissues, and on the long "plateau" of the high initial concentrations.

The therapeutic value of this "plateau" of high blood levels appears from the following consideration based on the clinical results of Cohn and co-workers in the treatment of gonorrhea. The active intramuscular dose which cures 97 percent of the cases of male gonorrhea is 0.5 c.c. of the authors' standard preparation, corresponding to 150,000 u. of penicillin. The "duration" of detectable blood level following such an injection is from 8 to 12 hours. Twice this dose, i. e., 300,000 u. of penicillin, injected in saline, results, on the other hand, in an unsatisfactory rate of cure, though the duration of the detectable blood level is similar, from 8 to 9 hours, and the initial (very transitory) peaks are even higher.

Therefore, a comparison of the duration of blood penicillin levels obtained with these 2 treatments does not provide a satisfactory explanation of the therapeutic differences. The curative effect of the 150,000-u. preparation, in contrast with the non-curative effect of the 300,000 u. given in saline, is due probably to the plateau effect at relatively high blood levels.

The more prolonged retention of the penicillin in the organs, as indicated by the urine levels, is probably an additional factor responsible for the increased therapeutic effectiveness of the suspension in oil with vasoconstrictor.

Compared to the duration of the blood levels for approximately one day, the urines of the subjects treated with 300,000 units of penicillin (in oil + vasoconstrictor) contained penicillin up to from 2 and 1/2 to 3 days. In experimental

animals the administration of this penicillin preparation resulted in durations in the organs about twice as long as in the blood.

Prophylactic experiments in mice infected with pneumococcus Type II indicate also an increased duration of therapeutic effectiveness of the penicillin preparation in oil and vasoconstrictor. (Am. J. M. Sc., May '48 - N. Ercoli et al.)

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Single Injection Treatment of Gonorrhea with Potassium Penicillin Suspension in Oil-Containing Epinephrine: In the present clinical investigation a suspension of crystalline penicillin-in-oil containing epinephrine was used in a single injection for the treatment of gonorrhea. This mixture is stable at room temperature and after brief shaking of the ampoule is ready for aspiration and injection; it flows readily. A total of 300 consecutive ambulatory male patients with acute gonococcic infections were treated with this preparation. The diagnosis was established by routine bacteriologic examinations of urethral smears and cultures. The preparation used for the major portion of the investigation was supplied in ampoules containing 300,000 units of potassium penicillin and 0.3 mg. of epinephrine in 1 c.c. of a vegetable oil. The doses, injected intramuscularly into the buttocks or subcutaneously into the upper outer quadrant of the gluteal region, varied between 0.25, 0.5, and 1 c.c. Only exceptionally were 2-c.c. doses used.

The criteria of cure were the following: (1) the absence of urethral discharge; (2) clear urine in the two-glass tests; (3) at least 2 negative cultures of both urethral and prostatic secretions during a period of at least 2 weeks (37 cases). In the majority of the cases in which follow-up was complete, 3 prostatic cultures were taken during a period of 3 weeks. Peizer's medium was used for cultures; the identification of the gonococcus was confirmed in each case by sugar fermentation tests.

Out of the 300 patients treated with various doses of the preparation investigated, a total of 154 could be followed up for from 2 to 3 weeks for the final determination of cure. The remaining 146 patients (48.7 percent) were delinquent.

The results obtained indicate that a single injection of 0.5 c.c. of the oily suspension, containing 150,000 units of penicillin and 0.15 mg. of epinephrine, is sufficient to cure gonorrhea in the male. The bacteriologic and clinical examination of 100 patients so treated and followed up for from 2 to 3 weeks indicated a rate of cure of 97 percent. Two of the 3 patients who relapsed showed transitory negative bacteriologic findings for a period of 24 hours and relapsed soon thereafter. Since these patients definitely denied any exposure, a diagnosis of relapse was made.

A single injection of 0.25 c.c. of the suspension containing 75,000 units and from 0.075 to 0.15 mg. of epinephrine cured 7 out of 9 patients. In spite of the

small number of patients in this group, it is considered justifiable to conclude that this dose is insufficient for therapy. A single injection of 1 or 2 c.c. of the suspension containing from 200,000 to 600,000 units cured all of 46 patients followed up.

It is noteworthy that 3 patients who relapsed following treatment with 0.5 c.c. per 150,000 units dose responded promptly to a second injection of the same dose. One patient who relapsed following the administration of a 0.25-c.c. dose (containing 75,000 units) was successfully treated with 0.5 c.c. (150,000 units) given by single injection. (The other patient who relapsed following the 75,000-unit treatment was delinquent.)

After probable cure and admitted sex exposure, 9 patients were diagnosed as having reinfections. Five of these patients were retreated with the original dose used, i. e., 0.5 c.c. (150,000 units) in 4, and 1 c.c. (200,000 units) in the fifth. All of these patients were promptly cured. The 4 remaining were delinquent.

Immediate reaction to intramuscular injections of the suspension were similar to those observed when aqueous penicillin solutions are injected. They consisted chiefly of a transient sensation of burning pain which began about 20 seconds after the injection and lasted for about from 2 to 3 minutes. Sometimes it radiated downwards and subsided gradually within 5 minutes. Subcutaneous injection produced no radiating pain, but in some cases a transient sensation of burning pain was felt for from 2 to 3 minutes. The site of injection was examined repeatedly during the course of the follow-up period, and no local infiltration or other abnormalities were found except in 2 patients in whom subcutaneous indurations of 3 cm. diameter developed and lasted for about 28 days. One of these patients had been given a large dose of epinephrine - 2 mg. in 2 c.c.

Among 15 patients whose blood pressures were taken before and after the administration of varying amounts of the mixture containing epinephrine, 8 showed no rise or fall in blood pressure. Six showed a drop up to 16 mm. of mercury within 15 minutes of the injection and one a rise of the blood pressure up to 14 mm. of mercury. Thus, there appeared to be no significant effect on the blood pressure. There was no rise in the pulse rate. There were 2 patients who showed exacerbations of a pre-existing dermatophytosis of the feet and a Tinea cruris infection.

The foregoing observations indicate that the minimal effective dose for the treatment of gonorrhea by single injection with a preparation of penicillin in an oily suspension containing vasoconstrictor, consists of 0.5 c.c. of the oily suspension containing 150,000 units of crystalline penicillin and 0.15 mg. of epinephrine.

These results of therapy compare favorably with those following the administration of 150,000 units of penicillin in 4.5 c.c. of a water-in-oil emulsion (cure rate 96.2 percent) and with multiple injections of penicillin in aqueous solution (cure rate from 96.5 to 100 percent).

The prolongation of the penicillin effect by using epinephrine-in-oil as a vehicle for penicillin is probably responsible for the successful therapeutic results. Comparing these clinical findings with the figures on blood levels given by Ercoli et al. (see foregoing article), it would seem that the therapeutic dose of 150,000 units yields detectable amounts of penicillin in the serum of the patient for a period of approximately 12 hours. (Am. J. M. Sc., May '48 - A. Cohn and B. A. Kornblith)

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Osteoporosis Occurring During Potassium Thiocyanate Therapy for Hypertensive Disease: Because occasional instances of osteoporosis and arthralgia were noted at the Mayo Clinic after the extensive use of potassium thiocyanate in the treatment of hypertension, an investigation was undertaken of this previously unreported phenomenon.

The records of 5,000 consecutive patients with hypertension who had been seen on two or more occasions at the clinic in the period from 1939 through 1944 were reviewed. It was found that potassium thiocyanate had been given to 360 patients of this group and that unexplained osteoporosis had occurred in 7 of these, or an incidence of 2 percent. Since 1944 there have been 4 additional patients with this syndrome. No history of trauma or injury at onset could be elicited from these patients. One or more extremities, usually the lower, was involved. Patients with involvement of the spine or pelvis were not included, because senile osteoporosis could not be excluded. Similarly omitted were those who had a diagnosis of chronic infectious arthritis, periarthritis, rheumatoid arthritis or fibrositis. Unexplained osteoporosis was not observed in the group of more than 5,000 patients with hypertension who were not receiving potassium thiocyanate.

Of the total of 11 patients with osteoporosis, 6 were women and 5 were men. Their age ranged from 46 to 68 years, or an average of 56.5. The dosage of the drug varied considerably during the course of treatment, but was usually in the range of from 6 to 9 grains daily. The symptoms associated with the osteoporosis generally began from 3 to 6 months after the drug had been administered. They consisted of (1) pain on use of the extremity which began insidiously and gradually increased in severity, and (2) subsequent mild swelling of the joint or joints involved, but with no acute inflammatory reaction. The severe cases simulated those of extensive post-traumatic osteoporosis. Roentgenograms, which were limited to the involved regions, revealed from mild to marked diffuse osteoporosis.

Case	Onset of Symptoms After Beginning Thiocyanate	Parts of Body Involved
1	6 mos.	Right lower extremity
2	4 "	Right hip
3	4 "	Both ankles, right hip and knee
4	4 "	Feet and ankles
5	20 "	Forearms, wrists, left knee
6	3 "	Ankles
7	4 "	Feet and ankles
8	3 "	Left lower extremity
9	5 "	Feet and ankles
10	6 "	Right foot and ankles
11	5 "	Left lower extremity

Active therapeutic measures directed toward the osteoporosis were carried out in 7 cases while thiocyanate therapy was being continued. These consisted of active and passive movement, shoe corrections, walking-casts, elastic bandages, and preparations of calcium and phosphate for oral use. Symptoms continued to progress despite these measures in 6 cases but slight improvement over a period of several months was noted in the 7th and the rate of improvement was accelerated when the administration of potassium thiocyanate was stopped.

In fact, cessation of potassium thiocyanate therapy was followed by relief in every one of the 11 cases whether or not specific measures of treatment were used. Improvement was generally evident in from 2 to 3 months, and recovery was complete in from 5 to 7 months. Administration of the drug was resumed in 4 instances. In 2 cases there was no recurrence of symptoms or of osteoporosis. Symptoms recurred in the other 2 but were again relieved when thiocyanate therapy was once more discontinued.

The following evidence suggests that the osteoporosis was a result of thiocyanate therapy: (1) there was a sufficient time interval between the institution of the use of the drug and the onset of symptoms; (2) improvement was noted in a reasonable period of time after discontinuance of the drug, whether or not therapy was directed at the osteoporosis; (3) in 6 of the 7 cases the usual specific therapeutic measures failed to halt progression of the osteoporosis as long as potassium thiocyanate therapy was continued; (4) increase in dosage of the drug in one instance resulted in an aggravation of symptoms within a few weeks; and (5) resumption of use of the drug after recovery produced recurrence of symptoms in 2 of 4 cases, with relief after the drug was again discontinued.

A mode of action of the potassium thiocyanate must still be postulated. No marked lowering of blood pressure was noted consistently. The osteoporosis occurred far too infrequently to be the result of a direct action of the drug on bone itself.

Potassium thiocyanate therapy has been used in more than 100 cases of severe migraine without the production of any syndrome such as that of osteoporosis. Evidence at present seems to favor the concept of a slight but prolonged interference with calcium metabolism as the mechanism of the production of the osteoporosis. In the presence of adequate calcium intake and normal metabolism, it would seem that such a slight interference with calcium metabolism would scarcely be sufficient to produce osteoporosis, and it has not occurred in the migrainous patients who represent a younger age group. However, should there be a tendency to a negative calcium balance, which is so often found in individuals of the age group with which this report deals, then any additional deficiency in calcium metabolism could produce osteoporosis. The finding of subnormal values for serum calcium in 2 cases and of a Grade 4 reaction to the Sulkowitch test in one case was further suggestive evidence of this mechanism. Thus all known factors, including the time element both for production of and recovery from this syndrome, the infrequency of occurrence of the syndrome, the dosage of the drug, and the group of individuals dealt with, were consistent with the concept of a minor additional interference with calcium metabolism. Further investigation along these lines is being carried out at present.

Regardless of the mechanism of production of osteoporosis, one should be cognizant of the occasional occurrence of this condition and should ensure an adequate calcium intake in individuals who are taking potassium thiocyanate. The use of this drug in the presence of a fracture may be inadvisable, not because of any interference with the union of fracture locally, but because any interference with calcium metabolism in the presence of an increased calcium requirement might precipitate osteoporosis. Similarly, potassium thiocyanate therapy may be contraindicated in the presence of bone malacia, such as senile osteoporosis or osteitis deformans, since use of the drug could cause further increase of decalcification and aggravation of symptoms. (Am. J. M. Sc., May '48 - J. J. Hinchey et al.)

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The Relationship of Bone Trauma to the Development of Acute Gastroduodenal Lesions in Experimental Animals and in Man: The occurrence of fat embolism following trauma in man was first recognized in 1862 by Zenker who described a case of fat embolism of the pulmonary capillaries in a laborer who died following a crush injury with multiple fractures of the ribs. That fat embolism in the lung and brain are common occurrences in patients who die soon after fracture of long bones is well known. Warthin, in an extensive review of the subject in 1913, stated that, "it is highly probable that in every case of amputation or fracture of the long bones some fat is set free from the ruptured fat-cells and . . . enters the blood stream to cause fat-embolism in the pulmonary capillaries, or, passing the lungs, in the capillaries of some other organ . . . The gravity of the condition will depend upon the anatomical importance of the capillaries blocked by the fat-emboli." He reported, in addition, 12 cases

of fat embolism, 9 of which followed fracture of the long bones, out of a relatively small postmortem service of 560 autopsies. Of the fracture cases terminating fatally, postmortem examination in all showed a marked degree of fatty embolism as the cause of death.

Warthin stated that the mechanism of fat embolism following fracture is a release of liquid fat from the marrow of the fracture site which gains entrance into the vascular system by virtue of increased tension at the site of injury forcing the fat into the open veins of the bone. In addition, there is entrance of free fat into the lymphatics; this occurs later than the direct entrance of fat into the circulation. The fat droplets enter the thoracic duct and then pass through the venous circulation into the lungs, constituting a second supply of fat to reach the lungs.

Fat embolism of clinical importance occurs most commonly following fractures of the bones containing fatty marrow. It is caused less frequently by injury to adipose tissue. Osteoporotic bones in old people, or in young individuals who possess atrophic bones from non-use, are especially likely to yield, on injury, a sufficient amount of fat to cause lipemia and embolism. Fractures of the tibia and femur are the most frequent causes of fat embolism. Scriba calculated the amount of fat present in the average adult femur to be 71 Gm. In studies relating to experimental fat embolism he calculated that the femur of a dog weighing 17 kilograms contains on the average 12.7 Gm. of fat, and that the femur of a rabbit weighing 2 kilograms contains an average of 1.3 Gm. of fat.

Of the numerous accounts of fat embolism of the lung, brain, and kidney following fracture, only occasional reference is made in the literature to the occurrence of embolic phenomena involving the capillaries of the gastro-intestinal tract. Scriba, in 1879, noted fatty emboli with capillary hemorrhage in the mucosa of the stomach and intestine. LeCount and Gauss noted, at autopsy, fat emboli in the vessels of the gastric mucosa in some of their 14 cases of fat embolism associated with fractures. Warthin stated that there is not a single organ or tissue in the body that does not get some fat in its capillaries when fat embolism occurs and he has found emboli of fat present in the capillaries of the stomach and intestine.

Furthermore, the only allusion to the occurrence of gastro-intestinal erosion and/or ulcer following fracture, other than that made by one of the authors in 1945, is to be found in a discussion of a paper by Sternberg in 1907. Schridde, in this discussion, stated that at post mortem in fracture cases he had twice observed fat embolism affecting the submucosal gastric arteries. In one patient, a 70-year-old man, there were numerous erosions and twenty superficial ulcers. The patient died in coma which had continued following the fracture. Schmorl, in a six-line discussion at the same meeting of the German Pathological Society, stated that he too had observed punctate hemorrhages in the gastric mucosa due to fat embolism following fractures and severe bodily contusions. Vale and Cameron, in a paper concerning the occurrence of gastric and duodenal perforation during hospital treatment, reported a case of a 55-year-old man who,

21 days after fracture of the clavicle and compound fracture of the right leg, and while on a regimen of bed rest and a soft diet, developed a perforated duodenal ulcer which was surgically closed. They stated that "trauma sustained at the time of injury may be mentioned as a possible causative factor."

Brooke reported gastro-intestinal bleeding on a psychic or emotional basis following minor surgical procedures in 4 cases. Herbut observed 5 patients in whom acute peptic ulcers developed following distant operations. He stated that the causes of the ulcers were not apparent.

Experimentally, Magendie, during the years from 1821 to 1836, before the occurrence of pathologic fat embolism in man was known, performed many experiments upon animals to determine the effects of the injection of oil into the circulating blood, and discovered that the fluid fat would not pass the smaller vessels, but blocked them mechanically. Lower, in 1669, had injected large amounts of milk intravenously into dogs. Scriba (1879) pointed out that a drop of fat could pass through the lungs without difficulty. Lehman and Moore in 1927 presented experimental evidence suggesting a nontraumatic origin of fat embolism, the source of fat being the ultramicroscopic emulsion of fat in the normal blood plasma which, due to physical or chemical alterations in the blood, may form fat droplets which act as emboli. Virchow in 1862 showed that the experimental injection of minutely emulsified fat was not followed by embolism. He was one of the first to foster the theory of vascular blocking in the genesis of peptic ulcer, a deduction made from observing the funnel-shaped character of many ulcers.

Experimental studies concerning the relationship of fracture of long bones to gastroduodenal pathology have been reported in abstract form previously from the clinic at the University of Minnesota. Those studies have been enlarged upon. This presentation embodies a series of studies concerning the relative incidence of acute gastroduodenal ulcer and/or erosions complicating fractures and amputations of long bones in patients dying early after fracture or amputation and submitted to necropsy, as well as two patients who recovered following fracture. In addition, experimental evidence is presented concerning the occurrence of similar gastroduodenal lesions in animals subjected to operative fracture or the administration of nonemulsified fat intravenously.

The records from the files of the Department of Pathology of the University of Minnesota showed that over a period of 27 years (extending from 1920 to August, 1947) there were 1,432 autopsies performed on individuals who died following fractures of bones, excluding skull fractures. The etiologic factors involved in the occurrence of peptic ulcer in head trauma may be complex, particularly, as Cushing has suggested, if the diencephalon is involved. Also, those cases in which there was a question of postmortem autolysis of tissue or evidence of chronicity of the ulcers, clinically or pathologically, are not included in the study.

In a series of 1000 consecutive autopsies of patients dying of all causes, it was noted by one of the authors that forty patients demonstrated gastroduodenal

ulceration, eight of whom died of peptic ulcer per se and its complications. Thus, thirty-two patients presented coincidental gastroduodenal ulceration (acute and chronic, but excluding healed scars of ulcers); however, in six of these cases it was not possible to rule out entirely changes due to autolysis and postmortem digestion. The incidence of coincidental acute and chronic ulcers, then, is between 2.6 and 3.2 percent among routine autopsies.

Of 27 cases in which acute or subacute ulceration or erosion of the stomach and/or duodenum following fracture were demonstrated at autopsy, 23 presented definite ulceration, 8 gastric, 14 duodenal, and one both gastric and duodenal. In the 4 remaining cases definite erosions and petechial bleeding points were observed in the stomach and duodenum. The age of the patients ranged from 17 to 93 years, the majority being about 55. The time of death after fracture varied from one to eighty-three days, death occurring within three weeks from the time of fracture in all but five cases. Two patients who recovered were included in this study. Hemorrhage from the gastro-intestinal tract, recognized clinically and recorded as hematemesis or melena, was observed in 12 of the 29 cases tabulated; in 5 additional instances autopsy revealed evidence of bleeding not recognized clinically. Ulcer therapy was instituted in 7 cases diagnosed clinically; two of these patients recovered completely. One patient, a 36-year-old man, having sustained multiple fresh fractures in an automobile accident, was admitted to the University Hospital on 10 December 1940; fat was demonstrated in the urine of the patient the day following admission, but no abnormal lipemia was observed. He suffered one episode of dyspnea. On the twenty-second hospital day hematemesis occurred, followed by melena, which continued for one week, necessitating blood transfusions. The prothrombin time and vitamin C level in the blood were normal. The patient eventually recovered. There had been no antecedent story of ulcer or bleeding. Another patient, a 68-year-old man, was admitted to the University Hospital on 27 March 1942; melena occurred 35 days after a fresh fracture of the neck of the right femur. Associated with the onset of melena, a sudden and marked drop in hemoglobin occurred, for which blood transfusions were given. The stools were consistently positive for blood for two weeks. Gastric aspiration without histamine stimulation revealed 18 degrees free acidity and 34 degrees total acidity. The patient had undergone gastrojejunostomy elsewhere 18 years previously for duodenal ulcer. He had experienced only mild epigastric distress infrequently in the intervening years. X-ray examination of the gastro-intestinal tract with a barium meal sixty days after the fracture revealed a large stomal ulcer 2 cm. in diameter. The patient did well on an ulcer regimen and was dismissed from the hospital on crutches. X-ray examination three months later demonstrated healing of the stomal ulcer. There has been no recurrence of ulcer symptoms since the fracture. It was felt that this episode represented an acute ulceration associated with fat embolism following fracture.

Gastroduodenal ulcers and/or erosions were produced in experimental animals by operative fracture or curettage of the bone marrow; the incidence of such erosions or ulcers is markedly increased when histamine administration

accompanies the fracture, especially in dogs. Experimental fracture of long bones abets the ulcer diathesis.

Gastroduodenal ulcers and/or erosions were produced in experimental animals by the intravenous injection of small amounts of fat; the reproduction of this phenomenon of fat embolism also increases the susceptibility of the laboratory animal to the histamine-provoked ulcer.

Emboli of fat were demonstrated in the submucosal and mucosal vessels of the stomach and duodenum in experimental animals subjected to operative fracture.

The rate of disappearance of the fat from the tissues is rapid.

The mechanism of the occurrence of gastroduodenal ulcer and/or erosions following fractures or amputations of long bones is undoubtedly one of embolic occlusion of the vessels to the mucosa by fat released from the fracture site; the resultant anemic areas in the mucosa become susceptible to the acid-peptic digestive activity of the gastric juice. (Surgery, July '48 - S. R. Friesen et al.)

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Administration of Penicillin and Streptomycin by Means of the Hypospray Apparatus (Jet Injection); Absorption, Toxicity, and Stability: Recently a device for the parenteral administration of solutions or suspensions of drugs known as the Microjet or Hypospray became available for study. Preliminary reports on its use clinically have been published by Hingson and Hughes and by Hingson and associates. The principle upon which the instrument is based is that an extremely fine high-pressure jet of liquid is capable of piercing the human skin with, at most, only slight pain. The instrument injects the drug in solution or suspension by means of high pressure obtained through the release, by means of a button, of a previously wound calibrated high-tension spring which is attached to a plunger. The material to be injected is placed in a metal ampoule (Metapule) which has a capacity of 0.25 c.c., is shaped like a blunt-nosed bullet with an orifice 0.003 inch in diameter in the rounded tip, and is stoppered with a rubber plug at the butt end. The tip of the Metapule is held against the skin at the site of the injection with the base locked securely in the apparatus. The plunger explodes against this rubber stopper which forces the material out of the Metapule and through the skin as a fine spray. The material is deposited subcutaneously and intramuscularly to depths varying from 0.2 to 2 cm., depending on the tension of the spring and the site of injection. Since the orifice in the Metapule through which the medication is expelled is only 0.003 inch, the size of a human hair, pain is either nonexistent or slight because there is little trauma to the tissues and a minimum of pain nerve fibers is stimulated. Another advantage attributed to this instrument is that it eliminates the fear incident to injection by needle and syringe.

The maximum amount of drug that could be dissolved in 0.25 c.c. of solution, the capacity of a Metapule, was found to be 200,000 units in the case of penicillin and 0.1 Gm. of streptomycin.

In order to compare the height and duration of the concentration of penicillin in the blood following administration by the Hypospray with that by the needle and syringe, 50,000 units were given to a group of patients by both methods, and blood for penicillin assay was taken two, three and 4 hours thereafter. The volume of the penicillin solution was 1.5 c.c. when given by needle and syringe, and 0.25 c.c. when the Hypospray was employed. The concentrations obtained with the Hypospray were somewhat higher and more prolonged than those obtained with the use of the needle and syringe. Although the volumes of the solution injection were not the same, it is believed that that does not account for the differences. In the opinion of the authors the differences may be due to the fact that part of the penicillin injected with the Hypospray is deposited subcutaneously. It has been demonstrated that the concentrations of penicillin in the blood are prolonged following subcutaneous injection as compared with the other methods of parenteral injection.

After the administration of 0.05 Gm. of streptomycin at 4, 8, and 12 hours, the mean concentrations in the blood were 1.25, 0.62, and 0.31 micrograms per cubic centimeter of serum respectively. Following the injection of 0.1 Gm., the mean concentrations were 2.5, 1.25, and 0.625 micrograms per cubic centimeter of serum at the same times.

Since significant concentrations were obtained 12 hours following the injection of 0.1 Gm. of streptomycin, it was decided to investigate the results of repeated injections of this dose at 12-hour intervals and also to compare these results with the same dose given by needle and syringe. For this study, blood for streptomycin assay was taken every 12 hours, immediately before the next injection (12 hours following the preceding injection), over a period of 4 days. No added effect from repeated injections was observed and the concentrations in the blood at the twelfth hour were at a plateau. Furthermore, there was essentially no difference in the results obtained with the two methods of administration. Several patients were given 0.1 Gm. of streptomycin every 4 hours 5 times a day by means of the Hypospray. Assay of the blood at the fourth hour (immediately before the next injection) revealed constant concentrations at that hour, indicating no increment of streptomycin in the blood as a result of repeated injections.

The instrument employed in these studies had a spring which when released exerted a static pressure of 2,300 pounds per square inch on the skin. Although it has been shown that the depth and spread of the injected material varies with the site of injection and the race of the patient, no differences in the blood concentrations of these antibiotics were noted in this series despite the fact that the sites of injection were varied (flexor and extensor aspects of arms, thighs, and buttocks) and both white and Negro patients were studied.

Most patients complained of momentary stinging at the site of injection, particularly with the larger doses of penicillin and streptomycin. Of the 60 patients in this series, only 4 showed an unfavorable reaction. In one patient a

small area of induration developed at the site of injection after 24 hours, but abated following treatment with warm, wet dressings for 24 hours. In two patients small hematomas developed at the sites of injection. In a fourth patient a small, subcutaneous nodule developed at the site of injection several days after administration. This persisted for a period of two weeks. Although it is relatively simple to master the technic of administration with the Hypospray, small linear cuts, blister formation, and bleeding resulted from improper handling during the early use of this instrument. The area prepared for injection should be allowed to dry before administration is attempted in order to prevent the instrument from slipping on the skin.

One patient with tuberculosis was treated daily with 5 injections of 0.1-Gm. streptomycin every 4 hours. Using the posterior aspects of the arms and thighs, the site of injection was rotated. After about 10 days of therapy, small nodules developed at the site of injection within 24 hours after each injection. It is believed that these reactions were the result of repeated subcutaneous depositions of part of the streptomycin during administration with the Hypospray apparatus. Supporting this are the results of absorption studies, reported herein, which indicate that some of the drug was deposited subcutaneously. There is also evidence to indicate that the high concentrations of both streptomycin and penicillin may have been a factor in the development of the few untoward local reactions observed with the use of the Hypospray in this series.

Aqueous solutions of penicillin stored in Metapules are unstable.

Dispensing penicillin in solution in Metapules commercially for general use with the present design of the apparatus is impractical. With the available instrument the dose of the antibiotics is limited by the size of the Metapule. This method of administration is not feasible, particularly in the treatment of infections requiring large doses of streptomycin. It appears, however, that the problem of dispensing penicillin and streptomycin will be solved. The instrument has been improved so that it will discharge the contents of Metapules with capacities of 0.5 and 1 c.c.

The possibility of drugs being deposited in blood vessels during the course of injection with the Hypospray was anticipated. In spite of deliberate efforts to deposit some of the injected drugs directly into blood vessels, this was accomplished only once when injection was made directly over a vein. With most drugs this would be relatively unimportant, but serious consequences would follow injection of some drugs directly into the circulation. Further investigation is necessary to resolve this problem completely. (J. Lab. and Clin. Med., July '48 - H. L. Hirsh et al.)

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U. S. Marine Corps Casualties in World War II: The war casualties in the U. S. Marine Corps during the period from 7 December 1941 through 31 December 1946, numbered 74,964, 70,813 enlisted personnel and 4,151 officers.

These figures were compiled from a special file on war casualties set up in the Medical Statistics Division from Fa-cards (Individual Statistical Reports of Patient), NavMed N's (Certificates of Death), NavMed M's (Reports of Medical Survey), action reports, health records, and various other sources. Additional information is being received from time to time from certificates of death and Army clinical records for individuals taken up at Army medical facilities, but for all practical purposes, the file is considered almost complete, and it is not expected that minor changes yet to be made will appreciably alter the currently available data.

The accompanying tables, on pages 16 and 17, present war casualty data for both officers and enlisted personnel by type of disposition and by place of action.

In this study war casualties are defined as those incurred during, or as a direct result of, action against an organized enemy. The data compiled included (with the exception of a few diagnoses) only injuries and poisonings under Class XXV and Class XXVI of the Diagnostic Nomenclature of the Medical Department of the Navy. Therefore, combat fatigue and war neuroses are excluded. The category "killed in action" includes both those killed at the place of action and those missing in action and later declared legally dead.

In the compilation of the data on the disposition of the casualties, those who were wounded and subsequently died (after 24 or more hours on the sick list) are listed with the disposition "Dead;" they are therefore excluded from the total wounded. When these casualties are included with the total individuals wounded, the figures show that 2.82 percent of all U.S. Marine Corps personnel wounded in World War II died subsequently as a result of those wounds (2.80 percent enlisted personnel and 3.45 percent officers); this figure may be compared with an over-all figure of approximately 11.1 percent of the total Navy and Marine Corps wounded of World War I who subsequently died of wounds. It is considered that this comparison reflects clearly the effectiveness of improved methods of treatment, including the use of quantities of whole blood and blood derivatives, the employment of medical personnel in advanced areas, and air evacuation.

It may be noted that the large majority of the wounded who survived returned to duty, 80.2 percent of the enlisted men and 96.8 percent of the officers. Of the wounded enlisted men who lived, 19.0 percent were invalided from the Service as compared with 1.6 percent of the officers. The disposition "other" (439 enlisted and 43 officer), as listed in the tables, includes individuals who were wounded and lived and who are either still on the sick list, who deserted while on the sick list or whose records are still incomplete.

The places of action are listed in approximately chronological order, there being a certain amount of overlapping in the dates of the various engagements. Only those places of action are listed in which Marine Corps casualties occurred among officers and enlisted men. No attempt has been made to list all of the engagements in which the Marine Corps participated. (Statistics of Navy Medicine, Aug.'48)

TABLE I - WORLD WAR II CASUALTIES - METHOD OF DISPOSITION BY PLACE OF ACTION - U. S. MARINE CORPS OFFICER PERSONNEL, 7 December 1941 - 31 December 1946

Place of action	Total casualties	Method of Disposition									
		Dead					Wounded				
		Total		Killed in action	Wounded, Died, subsequently	Died Prisoner of war	Total		Returned to Duty	Invalided from the service	Other
		Number	Percent of all casualties				Number	Percent of all casualties			
Total	4,151	1,516	36.5	1,359	91	66	2,635	63.5	2,551	41	43
Aleutian or Alaskan Area	4	-	0	-	-	-	4	100.0	4	-	-
Pacific or Asiatic Area	1	1	100.0	1	-	-	-	0	-	-	-
Attack on Pearl Harbor	5	3	60.0	3	-	-	2	40.0	2	-	-
Fall of the Philippines	52	52	100.0	6	-	46	-	0	-	-	-
Netherlands East Indies engagements	1	1	100.0	1	-	-	-	0	-	-	-
Battle of Midway	26	23	88.5	23	-	-	3	11.5	3	-	-
Guadalcanal - Tulagi landings	261	104	39.8	95	4	5	157	60.2	153	4	-
Battle of Savo Island	10	7	70.0	7	-	-	3	30.0	3	-	-
Battle of Guadalcanal	2	1	50.0	1	-	-	1	50.0	1	-	-
Capture of remaining Solomon Islands	276	139	50.4	129	1	9	137	49.6	133	-	4
Battle of Tarawa	144	58	40.3	56	2	-	86	59.7	86	-	-
Battle of Cape Gloucester	110	52	47.3	50	-	2	58	52.7	57	1	-
Invasion of Marshall Islands	97	36	37.1	36	-	-	61	62.9	59	1	1
Invasion of Marianas Islands	886	269	30.4	253	16	-	617	69.6	604	7	6
Invasion of Palau Islands	315	84	26.7	80	4	-	231	73.3	225	3	3
Bombardment of Truk	13	7	53.8	7	-	-	6	46.2	6	-	-
Return to the Philippines	79	45	57.0	43	2	-	34	43.0	34	-	-
Battle of Iwo Jima	811	263	32.4	228	35	-	548	67.6	525	15	8
Bombardment of Formosa and French Indo-China	1	1	100.0	1	-	-	-	0	-	-	-
Bombing and landings on Okinawa	757	220	29.1	194	26	-	537	70.9	514	7	16
Bombardment of Kyushu Island and Japan	20	9	45.0	9	-	-	11	55.0	10	1	-
Pacific area after 1 July 1945	7	3	42.9	3	-	-	4	57.1	3	-	1
Other or unspecified action	273	138	50.5	133	1	4	135	49.5	129	2	4

TABLE II - WORLD WAR II CASUALTIES - METHOD OF DISPOSITION BY PLACE OF ACTION - U. S. MARINE CORPS ENLISTED PERSONNEL, 7 December 1941 - 31 December 1946

Place of action	Total casualties	Method of Disposition									
		Dead					Wounded				
		Total		Killed in action	Wounded, Died, subsequently	Died prisoner of war	Total		Returned to Duty	Invalided from the service	Other
		Number	Percent of all casualties				Number	Percent of all casualties			
Total	70,813	18,070	25.5	16,105	1,521	444	52,743	74.5	42,282	10,022	439
Aleutian or Alaskan area	50	2	4.0	2	-	-	48	96.0	43	5	-
Atlantic or Caribbean area	2	1	50.0	1	-	-	1	50.0	-	1	-
Pacific or Asiatic area	26	21	80.8	20	-	1	5	19.2	4	1	-
Attack on Pearl Harbor	139	98	70.5	96	2	-	41	29.5	35	6	-
Fall of the Philippines	490	450	91.8	83	-	367	40	8.2	39	1	-
Netherlands East Indies engagements	42	42	100.0	35	-	7	-	0	-	-	-
Pacific raids	2	1	50.0	-	1	-	1	50.0	1	-	-
Battle of Coral Sea	31	21	67.7	19	2	-	10	32.3	10	-	-
Battle of Midway	31	17	54.8	16	1	-	14	45.2	13	1	-
Guadalcanal - Tulagi landings	3,607	973	27.0	897	69	7	2,634	73.0	2,267	362	5
Battle of Savo Island	67	26	38.8	26	-	-	41	61.2	39	2	-
Battle of Eastern Solomons	2	1	50.0	-	1	-	1	50.0	-	1	-
Battle of Cape Esperance	10	7	70.0	7	-	-	3	30.0	2	1	-
Battle of Santa Cruz Islands	30	15	50.0	13	2	-	15	50.0	15	-	-
Battle of Guadalcanal	31	10	32.3	9	1	-	21	67.7	13	8	-
Battle of Tassafaronga	12	-	0	-	-	-	12	100.0	12	-	-
Capture of remaining Solomons Islands	2,656	737	27.7	660	60	17	1,919	72.3	1,640	277	2
Battle of Tarawa	2,930	927	31.6	896	31	-	2,003	68.4	1,790	209	4
Battle of Cape Gloucester	1,311	309	23.6	279	30	-	1,002	76.4	843	156	3
North African landings	8	4	50.0	3	1	-	4	50.0	3	1	-
Sicilian landings	8	1	12.5	1	-	-	7	87.5	6	1	-
Invasion of France	1	-	0	-	-	-	1	100.0	1	-	-
Invasion of Marshall Islands	1,540	399	25.9	368	31	-	1,141	74.1	996	140	5
Invasion of Marianas Islands	16,275	4,072	25.0	3,770	302	-	12,203	75.0	10,029	2,131	43
Invasion of Palau Islands	6,080	1,192	19.6	1,102	89	1	4,888	80.4	4,184	678	26
Bombardment of Truk	4	-	0	-	-	-	4	100.0	3	1	-
Return to the Philippines	302	98	32.5	89	8	1	204	67.5	176	25	3
Battle of Iwo Jima	18,232	5,262	28.9	4,699	563	-	12,970	71.1	9,718	3,099	153
Bombardment of Formosa and French Indo-China	5	2	40.0	2	-	-	3	60.0	2	1	-
Bombing and landings on Okinawa	14,161	3,027	21.4	2,708	319	-	11,134	78.6	8,960	2,021	153
Bombardment of Kyushu Island and Japan	69	52	75.4	52	-	-	17	24.6	15	2	-
Pacific area after 1 July 1945	414	42	10.1	38	-	4	372	89.9	186	172	14
Other or unspecified action	2,245	261	11.6	214	8	39	1,984	88.4	1,237	719	28

Phlebitis in the U. S. Navy: In the 10-year period from 1936 through 1945, there was a consistent increase in the incidence of phlebitis in the Navy and Marine Corps. During these years there were reported 6,222 admissions and 1,131 readmissions.

The annual incidence rate increased steadily from a low of 21.7 per 100,000 average strength in 1936 to 1945, in which year approximately 63 persons out of each 100,000 in the Navy and Marine Corps were at some time on the sick list with phlebitis. The largest percentage of rate increase for any one of the 10 years occurred in 1942 when the incidence rate was 52.0 per 100,000 average strength, a jump of 45 percent above the 1941 rate of 35.8. The average annual rate for the prewar period, from 1936 through 1939, was 25.8 per 100,000 strength as compared with an average annual rate of 59.1 for the four war years from 1942 through 1945. Preliminary data for 1946, however, indicate a slight decrease in the incidence rate, 52.4 per 100,000 strength. Of the 6,222 admissions for phlebitis, it was considered that in 509, or 8.2 percent, the disease had existed prior to the individual's entry into the Service; 499 of these were admitted during the war years.

Of the total number of persons admitted with phlebitis, 532 or 8.5 percent were listed as being complications or sequelae of other conditions. Detailed data available on these conditions which preceded phlebitis for the years from 1937 through 1945, covering 528 of the 532 cases showed that appendicitis was the leading diagnosis preceding phlebitis closely followed by cellulitis, varicose veins, hernia, wounds, and pneumonia.

Data available on the distribution of the incidence of phlebitis by anatomic region for the years 1939 through 1945 showed that the veins of the lower extremities were the ones most frequently affected, accounting for 91.0 percent of the incidence.

During the 10-year period there were 7,192 dispositions from the sick list for phlebitis, including the dispositions of readmitted cases. It should be pointed out that this total does not agree with that of the incidence because of the lag due to patients remaining from previous years and to patients still on the sick list at the end of the 10-year period. For the 10 years combined, 5,804, or 80.7 percent, of the patients were returned to duty, 820 or 11.4 percent were invalided from the Service (806 of these invalidings occurred during the war years) and in 564 cases, or 7.8 percent, the patients were continued on the sick list with some other disability (either a complication or sequela, or a concurrent or intercurrent diagnosis). The other 4 dispositions are accounted for by 2 deaths and 2 desertions. Of the 5,804 patients returned to duty, 1,131, or 19.5 percent, were later readmitted for the same diagnosis. In other words, one out of 5 of those returned to duty were later readmitted for phlebitis.

From 1936 through 1942 there was a downward trend in the number of sick days per case. However, in the ensuing 3 years this trend was reversed. Prior to the war years, the noneffective ratio fluctuated between 3.3 and 4.7 per 100,000.

From a low of 3.3 in 1941, the noneffective ratio increased steadily until in 1945 approximately 7 out of each 100,000 persons in the Navy and Marine Corps were continually on the sick list with phlebitis. (Statistics of Navy Medicine, Aug. '48)

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Acute Gastro-Enteritis Aboard Ships of the U. S. Navy: For the 16-month period from February 1947 through May 1948, data have been assembled from the Monthly Morbidity Report (NavMed 582) on the incidence of acute gastro-enteritis aboard ships in the Navy. These data indicate that the highest rate for this condition aboard ships occurred in November of 1947. The incidence rates since February of this year are approximately the same as for the corresponding months a year ago.

In general, the highest rates for the various ship commands are reported from the larger vessels (aircraft carrier commands, and the battleship-cruiser commands). This is true of both the Atlantic and the Pacific fleets. During the period under discussion the battleship-cruiser command of the Pacific fleet had the highest incidence rates of any of the ship commands, 96.2 per 1,000 strength having been reached in November 1947 and 70.6 in February of this year.

The incidence rates are based upon those cases admitted as A's (New Admission), ACD's (Admitted Contributory Disability), AD's (Additional Diagnosis), and EC's (Diagnosis Established or Corrected). The incidence rates reported for acute gastro-enteritis may be somewhat lower than the actual occurrence of the disease because there are, undoubtedly, many patients whose cases are of too mild a nature and too short duration to be admitted to the sick list. It should be kept in mind, therefore, that the incidence rates represent only those cases which were sufficiently severe to be reported (i. e., the patient was on the sick list for more than 24 hours). (Statistics of Navy Medicine, Aug. '48)

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Selection of Samples in a Statistical Study: In setting up a statistical study concerned with large numbers of human beings it is frequently impractical, from the standpoint of time and expense involved, to work with the entire population covered by the study. In such cases, sampling devices may be employed, wherein a representative sample is drawn from the total population, thus enabling certain impressions to be derived regarding the total population. If listings of the entire population are available, it is possible to work out sampling procedures that are efficient and in which the sampling error may be accurately measured.

The random selection sample method is generally used when the entire population concerned is treated as a whole. In such a sample the chance of any unit

in the group being selected must be the same as that of every other unit. For example, a random sample of a card file or a register might consist of pulling every nth card or selecting every nth name on the register, if the arrangement of the file or register did not bias the sample for the characteristic under consideration.

For certain purposes, however, the simple random sample is less efficient than other methods. If a card file containing data on all Navy and Marine Corps personnel were used in an attempt to measure a characteristic that was correlated with the age of the individual, for example, a random sample of the entire file would not give the most reliable results. Rather, it would be necessary first to divide the population into age groups and then take a random sample in each of the subgroups. This method of sampling a population broken down into subgroups or strata is known as stratified random selection. The size of each of the subsamples should be conditioned by the relative size or importance of the subgroup from which the sample is taken.

Another method of selecting the sample is purposive selection wherein the sample, by design, has the same characteristics as the population under study in respect to one or more factors which are relevant to the problem being studied. Stratified sampling may also be used with this method by breaking the population up into subgroups and then applying purposive selection to each of the subgroup samples.

The selection procedures and the size of the sample are major factors in determining the reliability of the results. However, even after the sample has been secured and analyzed it must be remembered that it is only a selected part of the universe. Many of the problems encountered in sampling records among a civilian population are absent in sampling from medical records of the Navy, for the Navy population is a select group and therefore a fairly homogeneous one as far as health is concerned. (Statistics of Navy Medicine, Aug. '48)

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B Vitamin Requirements with Advancing Age: Two years ago the author and coworkers reported a markedly increased thiamine requirement (in mgm. per kgm. of diet) with advancing age in rats. Since then, Rafsky and Newman have described an apparent thiamine deficiency in aged people on diets which are qualitatively quite adequate for young adults. Low blood thiamine levels and low urinary output in elderly people on what was formerly considered an adequate thiamine intake led these authors to conclude that diets for the aged need enrichment.

During the last two years a group of rats have been followed from weaning time to old age, and periodically tested for their requirement of one B vitamin after another needed for optimal growth. In this way it was hoped to discover any other changes in requirement similar to that for thiamine. No changes were found except for verification of the marked rise of thiamine requirement in old

age. Dietary concentrations of the other B vitamins adequate for optimal growth in young animals remain similarly adequate throughout life.

These findings, in conjunction with the studies on aged people provide ample reason to recommend thiamine supplementation for elderly people. There is no basis yet for supplementing the normal dietary intake of other members of the B group for elderly people. (Am. J. Physiol., 1 April '48 - C. A. Mills)

* * * * * *

Hypoxia and Body Temperature Regulation: Kottke et al., working in the Department of Physiology and the Hospital Laboratories of the University of Minnesota, summarize a recent study on the effect of hypoxia upon temperature regulation of mice, dogs, and man as follows:

Hypoxia decreases the ability of mice, dogs, and men to control body temperature during exposure to cold. The loss of temperature control and fall in body temperature is most marked in the mouse and least marked in man. Hypoxia inhibits shivering in all three species studied. In man exposed to cold the suppression of an increased oxygen consumption by the hypoxia was demonstrated. In addition to this effect of hypoxia on heat generation it was also shown for man that hypoxia results in a greater dissipation of heat from the skin in a cold environment. Decreased environmental and body temperature favored survival of mice exposed to progressive hypoxia; between 37° C. and 20° C., the survival ceiling increased approximately 1000 feet per 1° C. drop in temperature. (Am. J. Physiol., 1 April '48)

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Intravenous Cholecystography with Tetraiodophthalic Fluorescein: The advantages of intravenous cholecystography are that a known quantity of dye is injected directly into the blood stream, the variable factor of intestinal absorption is circumvented, and the interval before the gall bladder can be visualized is shortened.

It was considered that a report of an additional dye for intravenous cholecystography would be of interest.

Sodium tetraiodophthalic fluorescein was first employed at the clinic of the University of Minnesota Medical School in an attempt to increase the radiopacity of certain intracranial lesions. Since it was known that sodium fluorescein itself was largely excreted in the bile, incidental attempts were made to obtain cholecystograms. Thus, several of the first patients received much more dye than would be necessary for gall bladder visualization alone.

The final method worked out for visualization of the gall bladder consisted of the rapid intravenous injection of approximately 40 mg. of dye per kilogram of body weight, so that the total dose given adults ranged from 2 to 3 Gm. The dye solution was adjusted so that a convenient volume (15 c.c.) contained an individual dose. Direct intravenous injection was made within a period of from one to two minutes. A light, fat-free breakfast was given on the morning of the examination; no other preparations were made. The first x-ray view was usually obtained two hours after the injection. If this showed a gall bladder shadow, a

fatty meal was administered, and a second view (40 minutes later) of the gall bladder was obtained in order to show the contractility of the organ. If a poor or questionable shadow resulted, an additional roentgenogram was made in three hours. Oblique and upright views were obtained if necessary.

Selection of an interval of from 2 to 3 hours for gall bladder visualization was based upon studies made in which radioactive iodine was substituted in a similar dye and counts were made over the gall bladder with a Geiger counter. A marked increase in the counts over the gall bladder region was noted beginning 45 minutes after injection.

Originally, tetraiodophthalic fluorescein prepared by the authors frequently caused nausea and severe intestinal contractions, but later use of more purified samples of the dye (supplied in part through Abbott Laboratories, North Chicago, Ill.) resulted in transient nausea in only two patients. There were no instances of vomiting nor did the patients complain of diarrhea which not infrequently follows the use of tetraiodophenolphthalein.

In three patients who received large amounts (from 9 to 10 Gm.) of tetraiodophthalic fluorescein over a prolonged period, acute thrombophlebitis of the veins developed proximally to the site of injection. This complication, which was not encountered subsequently, was probably due to the long exposure of the intima to the alkaline dye solution (pH 10.0).

In two instances appreciable amounts of dye (estimated 30 c.c. of a 5-percent solution) infiltrated into the subcutaneous tissue. Although local pain and some redness developed at the site of the infiltration, the transient inflammation regressed rapidly without therapy.

It was noted that all patients were tinted a light flesh-pink color by the dye, and that this color remained visible in the skin for several hours.

Twenty-two patients, some with gastric or biliary symptoms and some without, were examined by this method. Two patients had pyloric obstruction, and intravenous cholecystography was necessary to visualize the gall bladder which previously could not be visualized after oral administration of Priodax. The results were (1) good visualization of the gall bladder in the majority of the patients, (2) nonvisualization of the gall bladder in 4, and (3) nonvisualization of the common duct in a patient whose gall bladder had been removed previously. In the other four instances the gall bladder was assumed to be diseased; this was correlated with the clinical findings and was verified in two cases by subsequent surgery. (Surgery, July '48 - G. E. Moore and M. J. Smith)

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Excessive Hypertension of Long Duration: There is little available information on which to base a prognosis in patients with excessive hypertension,

including systolic pressures from 200 to 300 and diastolic pressures over 120, with evidence that the condition is not progressive, with retinal changes that are minimal, and with no indications of cardiac and renal damage.

In order to add to the presently available information the author made a study of the records of private patients seen since 1914.

With a view toward finding out what happens to persons with excessive hypertension that is definitely not of the progressive malignant type, the records were selected of the first 100 patients in whom the condition had existed for at least eight years, for, this period without progression was regarded as evidence that malignant hypertension would not supervene. In these patients, retinal hemorrhages were very rare and renal failure occurred in only one; no case of malignant hypertension developed. Although many other patients with excessive hypertension of eight years' duration or longer have since been observed, it was recognized that by limiting the study to those seen earliest, the group would contain only cases in which a long follow-up study has been possible. Of the 100 patients, 90 were found to have had excessive hypertension prior to 1932, the remaining patients having first been observed in 1934, 1935, or 1936. In only 3 cases is the condition of the patient unknown at the present time. These 3 patients are reported as of their last recorded examination.

The average survival time was compared with the average life expectancy of all persons of the same age and sex. The group then was divided into three parts: the living, the dead, and the physically incapacitated. The patients then were reclassified according to age, sex, and degree of hypertension - both systolic and diastolic pressures being ascertained - so that the influence of these factors on length of life could be deduced.

At present 47 of the persons concerned in this study are still living; 53 are dead. The tables below, marked 2 and 3, give the main facts concerning the whole group. A more final judgment regarding ultimate prognosis will be possible after another ten years have elapsed at which time only a few of the patients will likely be still alive.

TABLE 2. *Status of Patients in 1947.**

STATUS OF PATIENT		NO. OF CASES
Living		47
In good health	30	
Slightly disabled	5	
Moderately disabled	3	
Markedly disabled	3	
Unknown	6	
Dead		53
Of cardiac disease	22	
Of cerebral disease	9	
Of renal disease	2	
Of unrelated cause	3	
Cause of death unknown	17	

*Thirty-two patients were from twenty-eight to fifty years of age inclusive, 39 from fifty-one to sixty, inclusive, 18 from sixty-one to seventy inclusive, and 11 from seventy to seventy-seven, inclusive.

TABLE 3. *Comparison of Actual Duration of Life with Average Expectation of Life (1947).*

STATUS OF PATIENTS	AVERAGE EXPECTANCY	ACTUAL DURATION	DEFICIT
	yr.	yr.	yr.
Living	21.6	16.9	4.7
Dead	17.8	14.2	3.6
All patients*	19.8	15.7	4.1

*The average expectancy of life was exceeded by 28 patients.

It is evident from these tables that the average person of the group lives out almost his entire life span. In the patients reported upon it is notable that every person who was sixty-five years or over when excessive hypertension first was noted has outlived his life expectancy. The corollary to this statement is that persons in whom excessive hypertension was discovered relatively early in life and whose normal expectancy is therefore relatively long are unlikely to complete their life span. Table 4, below, shows what has happened to the 32 patients in whom the condition was discovered at the age of fifty years or younger. This group is of particular interest because patients of fifty years or younger are the ones who are usually regarded as favorable subjects for

TABLE 4. *Data in Patients Twenty-Eight to Fifty Years of Age.*

Status of Patient	No. of Patients	Average Blood Pressure		Highest Blood Pressure		Life Expectancy	Actual Duration of Life	Deficit
		systolic	diastolic	systolic	diastolic			
						yr.	yr.	yr.
Living	20	220.6	121.7	160	96.7	29.4	18	11.4
Dead	12	253.7	126.7	175	94.2	26.0	15	11.0

dorsolumbar sympathectomy. Of these, the 12 patients who have died had lived an average of fifteen years, or eleven years short of their life spans. The 20 still alive have lived an average of eighteen years, or again about 11 years short of their normal expectancy, and are, all but 3, normal people who are living normal lives without symptoms. They probably will live enough longer to raise the average length of life for the group to a much more favorable figure. A question that should be considered is whether or not the long-range results of surgical treatment can be expected to be of benefit to these patients.

Regarding the influence of sex it must be admitted that a group of 20 patients is far too small to justify any definite conclusions. However, in these 20 male patients the average life expectancy for 8 patients who were still alive in 1947 was nineteen years and the actual duration of life fifteen and three-fourths years; the average expectancy for 12 dead patients was nineteen and a half years and the actual duration fifteen and a half years. The deficit for the patients still living was slightly over three years, and the deficit for those who had died was four years. The duration of life was slightly longer than the average for the 100 patients. The age at which the condition was first observed in these 20 men was one year earlier than the average for the entire group.

The influence of the degree of hypertension on the prognosis is demonstrated in Tables 5 and 6.

TABLE 5. *Influence of Systolic Blood Pressure of More than 250.**

Status	No. of Patients	Average Life Expectancy	Actual Duration of Life	Deficit
		yr.	yr.	yr.
Living	9	22.9	19.1	3.8
Dead	18	18.5	16.0	2.5

*Among 1 living and 4 dead patients with systolic pressures of more than 300, the average life expectancy was sixteen and the actual duration of life sixteen and three-fourths years.

It is evident that an elevated systolic pressure is not, of itself, an unfavorable prognostic sign. In fact, the 27 patients who showed a systolic pressure of 250 or higher at some time while they were being observed lived distinctly nearer to their life expectancy

TABLE 6. *Influence of High Diastolic Blood Pressure.*

STATUS	DIASTOLIC PRESSURE OVER 120				DIASTOLIC PRESSURE UNDER 120			
	NO. OF PATIENTS	AVERAGE LIFE EXPECTANCY	ACTUAL DURATION OF LIFE	DEFICIT	NO. OF PATIENTS	AVERAGE LIFE EXPECTANCY	ACTUAL DURATION OF LIFE	DEFICIT
		yr.	*yr.*	*yr.*		*yr.*	*yr.*	*yr.*
Living	20	24.0	17.8	6.2	27	20.0	16.2	3.8
Dead	30	21.7	14.6	7.1	23	16.6	14.7	1.9

than those in whom such high readings were never obtained. This is further emphasized by the fact that the 5 patients in whom a reading of over 300 was recorded on one or more occasions actually showed an average duration of life slightly in excess of the normal. The most probable explanation of these findings is that many of these patients with very high systolic pressures showed relatively low diastolic pressures. They belong to the group with arteriosclerotic hypertension in whom a loss of elasticity of the arteries, rather than degeneration of the arterioles, has led to excessive pulse pressures but not to marked organic damage other than cardiac hypertrophy.

The facts presented in Table 6 indicate the unfavorable influence of a high diastolic pressure. In exactly 50 patients the diastolic pressure was found to have been, on one or more occasions, 120 or higher. In these patients the actual duration of life fell short of the normal expectancy by a considerably longer period than it did in the whole group. The other 50 patients, those whose diastolic pressure was never found to reach 120, showed figures for duration of life that were correspondingly more favorable than those of the total group. It is noted that the 50 patients who had diastolic pressures above 120 were on the average several years younger than those with the lower diastolic pressures, and that the actual time of survival in the two groups was approximately the same.

This leads to a comparison of the actual survival time of these patients considered without reference to their life expectancy as shown in Table 7. The

TABLE 7. *Actual Duration of Life and Deficit in All Groups.*

GROUP	LIVING PATIENTS	DURATION OF LIFE	DEFICIT	DEAD PATIENTS	DURATION OF LIFE	DEFICIT
All cases	47	16.9	4.7	53	14.2	3.6
Patients 50 years of age or under	20	18.0	11.4	12	15.0	11.0
Male patients	8	15.9	3.0	12	15.5	4.0
Systolic pressure over 250	9	19.1	3.8	18	16.0	2.5
Diastolic pressure over 120	20	17.8	6.2	30	14.6	7.1
Diastolic pressure under 120	27	16.2	3.8	23	14.7	1.9

deficit - that is, the number of years by which this survival time falls short of normal life expectancy - for each group is also shown in Table 7, which demonstrates that the various factors discussed (age, sex, and degree of hypertension) do not cause a marked variation in the actual duration of life. Although older people tend to live up to or beyond their normal life expectancy, this is because, according to the standards in use, their life expectancy is shorter. Their average duration of life is about the same as that of the younger group. It is, of course, true that as the 47 people who are still alive (30 of whom are apparently in good

health) continue to live on, the average duration of life for the whole group will lengthen. It may be said, then, that the prognosis in hypertensive patients of the type discussed is actually more favorable than the figures indicate. The shortest duration of life recorded in the whole series, after the discovery of the hypertension, is nine years, and the longest twenty-five years.

The most frequent cause of death in these patients is cardiac failure. A cerebrovascular lesion is the next most common terminal event.

Further investigation of this subject should involve the collection of a sufficiently large number of cases to make statistical studies really significant. This could be accomplished by the collaboration of a large number of physicians who have practiced twenty-five years or longer.

It is suggested that when the physician is confronted with a patient who is not over fifty years old and in whom he finds excessive hypertension, frequent examinations should be made for evidence of progression, especially for the signs of retinal, renal or cardiac damage. In the absence of such evidence it is believed that resort to surgery may well be delayed. (New England J. Med., 15 July '48 - A. M. Burgess)

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Therapy with Vitamin B Complex in Erythema Multiforme: The purpose of this report is to suggest the possibility that nutritional deficiency is a cause of some cases of erythema multiforme.

Three male patients with painful, superficial ulcerations of lips and oral mucosa, as well as skin lesions characteristic of erythema multiforme, which had been unresponsive to previous therapy, were given large doses of vitamin B complex. Recovery was prompt and complete in all three cases. One patient, however, had a recurrence after a year, which was relieved following vitamin B complex therapy.

Two other male patients with erythema multiforme, both of whom had had gynecomastia concomitantly with the initial episode, were administered vitamin B complex. In the first case, there has been no recurrence, and in the second, it is still too early to determine whether or not another episode might occur.

A female patient had oral lesions which could not be differentiated from erythema multiforme. These occurred regularly about four or five days before the onset of menstruation. Although previous local therapy had not been effective, after treatment with vitamin B complex, she has had no recurrences to date.

The experimental work of Ziskin on the effects of estrogenic substances on oral tissues has stimulated much interest in this phase of endocrinology. Moreover, the effects of estrogen on various tissues, both in the male and the female,

are known. The experimental work of Biskind and Biskind not only showed that the liver inactivates estrogen, but proved that it requires adequate levels of the vitamin B complex in order to perform this function. (See News Letter of 14 February 1947, p. 2.) During the war erythema multiforme occurred rather frequently in patients with infectious hepatitis, thus possibly relating this syndrome to liver function. There was a high incidence of gynecomastia among prisoners at Bataan who suffered a high degree of starvation and showed widespread manifestations of beriberi. Dramatic recoveries followed treatment with vitamin B complex.

In correlating these observations and the results in the six cases described, it might be conjectured that the mechanism of the syndrome of erythema multiforme could be accounted for by nutritional deficiency leading to inadequate levels of vitamin B complex which affects liver function and causing particularly depression of the estrogen-inactivating mechanism with the resulting high estrogen level being in some way related to the development of lesions of erythema multiforme in susceptible individuals.

Although no conclusion may be drawn from so little evidence, further study along these lines might lead to a more rational treatment in erythema multiforme. (Oral Surg., Oral Med., and Oral Path., May '48 - T. I. Moe)

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Re American Specialty Board Certification: It is requested that all medical officers who receive notification that they have been certified by any of the American Specialty Boards immediately notify the Bureau of Medicine and Surgery. (Chief, BuMed)

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Training Duty for Dental Reserve Officers: Training duty, beginning 25 October 1948 and ending 5 November 1948, at the U. S. Naval Dental School, National Naval Medical Center, Bethesda, Maryland, will be available to a limited number of Reserve dental officers. The total number that can be accommodated has been apportioned among the naval districts.

Requests for assignment to this training duty should be submitted to the Commandants of the naval districts in which the officers maintain their official residences. Final approval of requests and issuance of orders will depend upon the availability of funds. (Dental Div., BuMed)

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Training Available in Medical Aspects of Radiological Defense: The Atomic Energy Commission has invited the Armed Forces to participate in the fellowship training program which it has developed. The training involved in this program will cover a period of approximately 12 months and will be composed of a basic phase and an advanced phase.

For the first phase, lasting for about six months and devoted to basic training, those assigned will be sent to one of the following regional training centers:

Durham, North Carolina, with instructors from Duke University, the University of North Carolina, the North Carolina State College, and the Bowman Gray School of Medicine.

Houston, Texas, with instructors from the Rice Institute and the Baylor School of Medicine.

Denver, Colorado, with instructors from the University of Denver, the University of Colorado School of Medicine, and the University of Colorado.

Portland, Oregon, with instructors from the University of Oregon, the University of Oregon School of Medicine, the Oregon State College, and Reed College.

These regional centers will offer a basic training course in biology, mathematics, physics, and chemistry as they apply to atomic energy. In addition, there will be

opportunity to participate in research and development in this field, combined with activities in clinical medicine and biology. The basic phase of training will start with the academic year 1948, the exact time varying with the institutions concerned.

Upon completion of the basic training phase, the students will be sent to The Institute of Nuclear Studies at Oak Ridge, Tennessee, for advanced study for a period of six months. During this phase, the students will attend conferences and participate in the laboratory program of the institute. In addition to a general coverage of the field, specialization in a particular phase of atomic energy as related to medicine will be possible.

The Bureau of Medicine and Surgery has reserved 10 places in these courses of instruction. Requests are desired immediately from medical officers of the regular Navy interested in this field. Each request must contain a three-year service agreement. Reserve medical officers may apply providing they agree to submit an application for transfer to the regular Navy, agree to accept their commission when it is delivered, and sign a three-year service agreement. Requests may be made by dispatch and must be confirmed by a following letter. (Professional Div., BuMed)

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Application for Certification in Preventive Medicine: See BuMed Circular Letter 48-84 on page 31 for information re certification by Interim Board of Preventive Medicine.

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BUMED CIRCULAR LETTER 48-80 26 July 1948

To: All Ships and Stations

Subj: Procedures for Applying Requisition Priority Indicators

Ref: (a) BuSandA ltr L8-2(1)/DM-30C, PPW, of 20 Jan 1948; Item 48-58 of Navy Department Bulletin of 31 Jan 1948.
(b) BuSandA ltr L8-2(1) (S-111/JBP:ms), of 16 June 1948; Item 48-485 of Navy Department Bulletin of 30 June 1948.

This letter (1) states that the "General Instructions on Procedures for Applying Requisition Priority Indicators," (enclosure (A) to reference (a)), as modified by reference (b), shall be implemented and carried out by Medical and Dental Department activities in the preparation and submission of all requisitions, including requisitions by dispatch, and (2) directs that priority indicators be assigned with careful consideration.

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BUMED CIRCULAR LETTER 48-81 26 July 1948

To: All Medical Department Activities

Subj: Standard Transfer Order; Use of

Ref: (a) Navy Department Bulletin All Ships and Stations Letters, Jan - Jun 1947, Item 47-108, p. 415.

This letter (1) points out that the Standard Transfer Order, NAVPERS-563/NavSandA Form 536 is now in general use as authorized and directed by reference (a), (2) cancels NavMed forms HF-3, HF-4, HF-5, and HF-7, and (3) states that a supply of the Standard Transfer Order may be requisitioned from the Publications Supply Depot, Naval Supply Center, at Oakland, California, or Norfolk, Virginia, as applicable.

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BUMED CIRCULAR LETTER 48-82 28 July 1948

To: NavHosps and Stas having Medical Dept. Installations (Continental)

Subj: Prosthetic Appliances Board; Disestablishment of

Refs: (a) BuMed Circular Letter No. 45-24
(b) Par. 5134, MMD

1. Refs (a) and (b) are hereby cancelled. Ref (b) will be deleted in the next advance change or page change to the Manual of the Medical Department.

--BuMed. C. A. Swanson

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BUMED CIRCULAR LETTER 48-83 28 July 1948

To: All Offices of Naval Officer Procurement

Subj: Aviation Classification Tests; Instructions Concerning

1. At each Office of Naval Officer Procurement where a Flight Surgeon or Aviation Medical Examiner is assigned, he will be responsible for the administration of the Flight Aptitude Tests (Aviation Classification Test, Mechanical Comprehension Test, and Biographical Inventory).

2. At Offices of Naval Officer Procurement not having a Flight Surgeon or Aviation Medical Examiner, the Senior Medical Officer will assume the responsibility for the test administration.

3. All previous instructions to the contrary are hereby modified accordingly.

--BuMed. C. A. Swanson

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BUMED CIRCULAR LETTER 48-84 29 July 1948

To: All Medical Officers on Active Duty and Retired Medical Officers

Subj: Application for Certification by Interim Board of Preventive Medicine

Encl: 1. (HW) Outline of the Qualifications for Applicants

This letter states that the Interim Board of Preventive Medicine is now ready to receive applications for examination from medical officers desiring certification as specialists in preventive medicine. It is expected that officers in all branches of preventive medical work, including administration and research, may be eligible. The Board has written its own standards and prescribed its own qualifications for examination. The Services will in no way interfere with or attempt to influence the Board in its processes of certification.

Applications to be considered by the Board at its next meeting must be received before 1 October 1948. They should be sent to:

Dr. E. L. Stebbins, Chairman
Interim Board of Preventive Medicine
c/o Division of Research Grants and Fellowships
National Institute of Health
Bethesda, Maryland

The first group of officers to be certified will consist of those selected by the Board as having considerable experience and a long record of distinguished service in responsible public health positions. For these officers the formal training and supervised experience requirements will be waived. A written examination will not be required of these officers. Applications are solicited from those officers who believe they may fall into this category. Although the Board has set no specific requirements as to age or length of experience, it is suggested that medical officers having in excess of ten years service in responsible public health or preventive medicine positions might be considered favorably.

A written and an oral examination will be held during the fall of 1948 or spring of 1949. Those officers whose training and experience meet the qualifications will be notified by the Board when to appear for examination.

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