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Summary of Antimalarial Drugs: At least a dozen chemical compounds, commercially obtainable or under large-scale investigative use, are currently being recommended for the management of malaria. All of these, except quinacrine, pamaquine and the cinchona alkaloids, have been introduced during the past 5 to 10 years. Because the new drugs have appeared in medical literature under a variety of synonyms, including numbers and proprietary names, much confusion prevails concerning the identity and relative merits of the available antimalarial agents.

This summary is not intended to be a critical review of all recent advances in the chemotherapy of malaria. Original references should be consulted for detailed descriptions of the various drugs and for evidence to support the generalizations which are necessary in a summary. Those familiar with the problems of making definitive comparisons of therapeutically active compounds will appreciate the need for many qualifying statements throughout the appraisals. As the characteristics of the predominant strains of malarial parasites in a given area may greatly influence the choice of drug regimens, dosage recommendations are intended to be merely representative. In all cases they refer to the oral dosage for an average adult.

It is now accepted that the early development of sporozoite-induced malaria in man takes place in fixed-tissue cells, as has been demonstrated for Plasmodium vivax. It is further believed that persistent fixed-tissue forms, not yet actually demonstrated histologically, are responsible for the repeated relapses of P. vivax and P. malariae infections, but that such persistent forms do not occur in P. falciparum infections. In malaria caused by P. vivax and P. malariae, drugs which are active only against the asexual erythrocytic parasites will stop acute attacks, or will suppress parasites and fever as long as administered, but will not prevent relapses. The actual relapse rates following such noncurative therapy will be determined by a variety of factors, including strain of parasite, intensity of exposure, and status of host resistance.

Curative chemotherapy of malaria caused by P. vivax or P. malariae implies a significant reduction in the relapse rate, as contrasted with that following noncurative therapy, and presumably results from partial or complete destruction of persistent fixed-tissue parasites.

Protective treatment may achieve either causative prophylaxis or suppression. Causative prophylaxis implies action against the sporozoites or the succeeding pre-erythrocytic stages, prior to the first invasion of erythrocytes, and if complete, permanently prevents infection. Suppression implies action, usually against asexual erythrocytic parasites, sufficient to keep an infection latent at least as long as the drug is being administered. It may be carried out during a period of active exposure to infection, or it may follow treatment of an acute attack.

Gametocytocidal action indicates activity against the sexual erythrocytic parasites, which are necessary for the infection of mosquitoes. Such action, theoretically of public health value, does not in itself appear to affect the clinical course of malaria in the patient being treated.

All of the antimalarial drugs included in the summary are rapidly absorbed from the gastro-intestinal tract. In the description of each drug a brief

statement will be made concerning its tissue localization, i. e., its tendency to become concentrated in certain cells of the body, and its rate of elimination, either by excretion or degradation. In general, a compound which is markedly localized in tissues is more effective if loading or priming doses are given at the start of therapy. Such a compound, particularly if its rate of elimination is slow, will be long retained in the body, permitting wider spacing of individual doses, shorter courses of treatment, and prolonged periods of protection against relapse immediately following therapy.

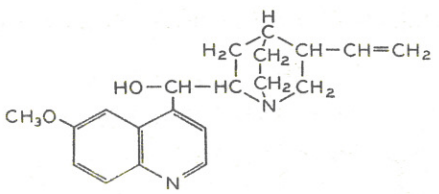
Names included in the U. S. Pharmacopoeia or approved by the Council on Pharmacy and Chemistry of the American Medical Association, will be used as principal designations. Official designations in other countries, code numbers, and proprietary names will be included as synonyms (without capitalization).

Data will be presented on the following:

Cinchona products: quinine, totaquine.
Acridine compounds: quinacrine.
4-aminoquinolines: chloroquine, oxychloroquine, sontochin, SN 10,751.
Biguanides: chlorguanide.
8-aminoquinolines: pamaquine, pentaquine, isopentaquine.

Quinine

6-methoxy-α-(5-vinyl-2-quinuclidyl)-4-quinolinemethanol



Salts: Sulfate of U. S. P. XIII (83 percent base) is the salt most commonly used in the United States; dihydrochloride (82 percent base) is the most soluble salt and is used parenterally. There are many other official and proprietary preparations.

Dosage:

Therapeutic: 2 grams per day (0.65 gram, or 10 grains, three times daily) for 7 days.

Suppressive: 0.65 gram (10 grains) per day.

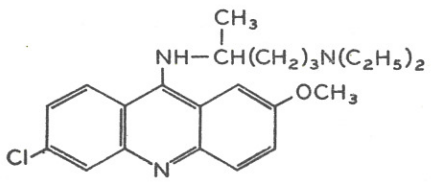
Quinine is only slightly localized and is rapidly metabolized; plasma concentrations drop 90 percent within 24 hours after dosage. The most important antimalarial action of quinine is against asexual erythrocytic parasites. This stops acute attacks, but clearance of parasites and subsidence of fever are often not as rapid as with large doses of quinacrine, or the better 4-aminoquinolines. P. vivax malaria may relapse as early as one or two weeks after therapy. Quinine has limited effect upon gametocytes of P. vivax and P. malariae but no effect on gametocytes of P. falciparum. Quinine has no causative prophylactic action. When given protectively, it will usually suppress P. vivax and P. malariae, but parasites appear after drug is discontinued. It is less efficient as a suppressant of P. falciparum. Quinine is also important

because of the potentiation observed when it is given in combination with certain 8-aminoquinoline drugs, resulting in lowered relapse rates in P. vivax malaria. Quinine may be given intravenously, but should be given slowly in a large volume of fluid. It is not well absorbed from muscle and may cause local necrosis. Therapeutic doses commonly cause cinchonism, with tinnitus, vertigo, partial deafness, visual disturbances, headache, and nausea. An occasional individual with idiosyncrasy may have severe cinchonism, urticaria or angioneurotic edema from a single small dose.

Totaquine is a standardized mixture of cinchona alkaloids, which according to U. S. P. XIII contains "not less than 10 percent of anhydrous quinine and not less than 70 percent and not more than 80 percent of total anhydrous crystallizable cinchona alkaloids, the remainder consisting substantially of diluents." A typical currently obtainable preparation contains 50 percent cinchonine, 18 percent cinchonidine, and 10 percent quinine. As all of these alkaloids possess antimalarial activity, treatment with totaquine results in more economical use of the active ingredients of cinchona bark. Dosage is similar to that of quinine, and the therapeutic efficacy is essentially the same. It can only be given orally. Some preparations may produce nausea and vomiting more frequently than does quinine.

Quinacrine

6-chloro-2-methoxy-9(4-diethylamino-1-methylbutylamino)acridine



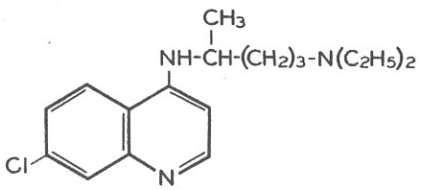
Synonyms: atabrine, atebrin, acriquine, chemiochin, chinacrin, crinodora, erion, haffkinine, italchina, mepacrine B. P., metoquina, metoquine.
Salts: hydrochloride of U. S. P. XIII is the dihydrochloride, dihydrate (79 percent base).
Dosage:
Therapeutic: 0.2 gram of salt x 5 (every 6 hours) on day 1; then 0.1 gram three times daily for 6 days, a total of 2.8 grams in 7 days.
Suppressive: 0.1 gram of salt per day.

Quinacrine is markedly localized, especially in leukocytes, liver, spleen, heart, and lungs. It is slowly eliminated, so that plasma concentrations drop only about 50 percent per week after the last dose. The principal action of quinacrine is against asexual erythrocytic parasites. When loading doses are given, it stops acute attacks of malaria at least as rapidly as does quinine. Persistent exoerythrocytic stages of P. vivax are not affected; so P. vivax malaria will relapse, but parasites usually do not reappear until at least from 4 to 6 weeks after treatment. Quinacrine resembles quinine in being ineffective

against gametocytes of P. falciparum. When given protectively, quinacrine has no causative prophylactic action, but it effectively suppresses erythrocytic parasites. Such suppression, continued for a sufficient time after exposure (e. g., 4 weeks) permanently prevents P. falciparum malaria, although resistant strains have been demonstrated. Infections caused by P. vivax (and probably P. malariae) appear after drug is discontinued. Quinacrine may be given intramuscularly in dosage of 0.4 gram. With rigid precautions it may be administered intravenously. Although in recommended dosage quinacrine is usually well tolerated, more undesirable reactions occur than accompany treatment with 4-aminoquinolines or chlorguanide. It temporarily dyes the skin yellow, but this is not a toxic reaction. It may produce anorexia, nausea, vomiting, and diarrhea, especially at the start of therapy. It is a cortical stimulant and in susceptible subjects may cause temporary mental symptoms. In a small proportion of cases, serious skin reactions occur.

Chloroquine

7-chloro-4-(4-diethylamino-1-methylbutylamino)quinoline



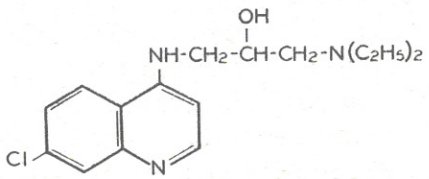
Synonyms: aralen, resochin, nivaquine B, tanakán, SN 7618, 3377 RP.
Salts: diphosphate (62 percent base) for oral use; hydrochloride (89 percent base) for parenteral use. Nivaquine B is chloroquine sulfate.
Dosage:
Therapeutic: 1.0 gram of diphosphate (0.6 gram of base) as initial dose, followed in 6 hours by 0.5 gram (0.3 gram of base), then 0.5 gram (0.3 gram of base) once daily for 2 days, making a total of 2.5 grams of salt (1.5 grams of base) in 3 days.[1]
Suppressive: 0.5 gram of salt (0.3 gram of base) once weekly.

Chloroquine is markedly localized in liver, spleen, kidney, lungs, and white blood cells. Degradation and excretion are slow; plasma concentrations drop only about 60 percent per week after last dose. The principal action of chloroquine is against asexual erythrocytic parasites. It stops acute attacks of malaria promptly. It does not affect persistent exoerythrocytic stages, but P. vivax relapses are usually delayed until at least from 7 to 10 weeks after treatment. Infections caused by P. falciparum are usually cured. No data are available on quartan relapses. Gametocytes of P. falciparum resist chloroquine. There is no action against pre-erythrocytic forms. Protective treatment suppresses parasites of all three species; P. vivax (and probably P. malariae) may appear after drug is stopped. Chloroquine hydrochloride may be given intramuscularly in dosage of from 0.2 to 0.3 gram of base. Very slow intravenous injection is still in an experimental stage. Chloroquine produces few side-actions

in recommended dosages. It does not discolor the skin. Blurring of vision, pruritus, mild headache, and gastro-intestinal complaints have been reported.

Oxychloroquine

7-chloro-4-(3-diethylamino-2-hydroxypropylamino)quinoline

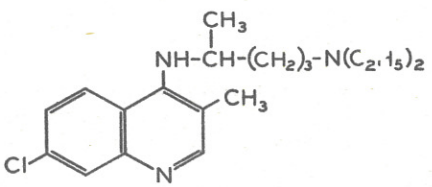


Synonym: SN 8137.
Salt: diphosphate (62 percent base).
Dosage: Not established.

Oxychloroquine, or SN 8137, resembles chloroquine in many respects. Although it is less toxic in man it is also slightly less active as an antimalarial. Small-scale trials in experimental and naturally-acquired malaria have not shown any advantages over chloroquine. It has not been given definitive trial as a suppressant. Oxychloroquine is not commercially available.

Sontochin

7-chloro-4-(4-diethylamino-1-methylbutylamino)-3-methylquinoline



Synonyms: SN 6911, 3038 RP, sontoquine, santoquine, santochin, nivaquine (except nivaquine B, which is a salt of chloroquine).
Salts: disulfate, monohydrate (61 percent base) has been most widely used in the United States. French investigators have used various other salts (*47*), of which nivaquine C, the dihydrochloride, is preferred.

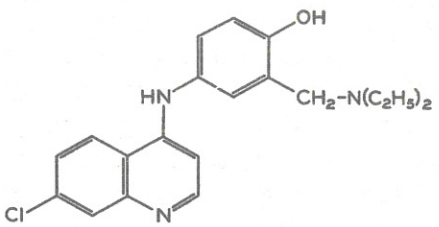
Dosage:
Therapeutic: Dosages of base corresponding to those of chloroquine.
Suppressive: 0.1 gram of base per day; 0.3 gram twice weekly; or 0.3 gram once weekly (*48*).

Sontochin, like quinacrine and chloroquine, becomes concentrated in leukocytes, liver, spleen, and certain other body tissues; plasma concentrations decline about 25 percent per day after the last dose. Like the other 4-aminoquinolines, sontochin acts against asexual erythrocytic parasites and alleviates acute attacks of malaria. Relapses of malaria caused by P. vivax can be expected at about the same intervals as after treatment with quinacrine,

or sooner. It is not gametocytocidal against P. falciparum. Sontochin is not a causative prophylactic, but is an effective suppressant. Sontochin does not stain the skin and is well tolerated at recommended dosages. Parenteral use has been reported, but details are not available. Sontochin is not commercially available in the United States.

SN 10,751

7-chloro-4-(3-diethylaminomethyl-4-hydroxyanilino)quinoline

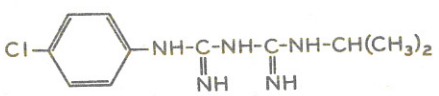


Synonyms: amodiaquin, camoquin, miaquin, CAM–AQ1.
Salt: dihydrochloride, dihydrate (77 percent base).
Dosage:
Therapeutic: Dosages of base corresponding to those of chloroquine.
Suppressive: Dosages of base corresponding to those of chloroquine; 0.6 gram of base every 2 weeks has also been provisionally suggested.

The drug is rapidly metabolized in the body. The degradation products are chemotherapeutically active and are slowly eliminated, plasma concentrations declining at the rate of about 60 percent per week. The antimalarial activity of this drug appears to be analogous to that of chloroquine. In controlled studies, relapses of malaria caused by P. vivax are delayed after SN 10,751 almost as long as after chloroquine. Infections produced by P. falciparum are apparently cured. In practical application, SN 10,751 has been shown to be well tolerated. Lassitude, anorexia, and insomnia have been described with long-continued high daily dosage. This drug is not commercially available in the United States.

Chlorguanide

N_1-(p-chlorophenyl)-N_5-isopropyl biguanide

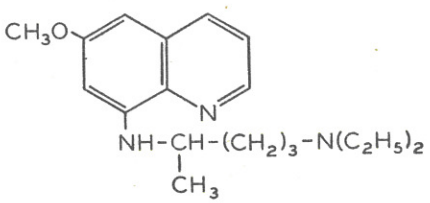


Synonyms: paludrine, proguanil B. P., M. 4888, guanatol, drinupal, palusil, tirian.
Salt: monohydrochloride (87 percent base) is commonly given orally. The acetate and lactate are more soluble and are recommended for parenteral use.
Dosage:
Therapeutic: 0.6 gram of hydrochloride per day (0.3 gram twice daily) for 10 days; alternative regimen (for *P. vivax* only), single dose of 0.3 gram, followed by suppressive course.
Suppressive: 0.3 gram of salt once weekly; 0.2 gram twice weekly; or 0.1 gram daily.

There is considerable localization of chlorguanide in erythrocytes, leucocytes, kidney, and liver. Chlorguanide as such disappears rapidly from the blood plasma after dosage, but there is evidence that at least part of it is converted into an active metabolic product. In P. falciparum infections, chlorguanide acts as a causative prophylactic and usually cures. Some strains of P. falciparum show resistance to the drug to a degree which has prompted the suggestion that a more rapidly effective drug such as quinacrine be used for first day of treatment and that 0.1 gram of chlorguanide be taken daily for 6 weeks after therapy. Chlorguanide is an effective suppressant of P. vivax, and there is evidence of action against pre-erythrocytic stages. All parasites are not eradicated, so that infections appear after suppression is discontinued. It alleviates acute attacks of P. vivax malaria over a wide dosage range, but this effect is often relatively slow. Relapses of P. vivax malaria occur at about the same rate and time as after quinacrine. Chlorguanide stops acute attacks of quartan malaria; no data are available on prophylaxis or cure. Chlorguanide renders gametocytes of P. falciparum noninfective to mosquitoes. Acquired resistance to chlorguanide has been conclusively demonstrated in the malarias of lower animals and will soon be reported for human malaria. Chlorguanide acetate has been given intravenously in doses up to 100 mg. or 400 mg. Intramuscular injection has also been reported as well tolerated, although studies in lower animals provide evidence of local tissue damage. The toxicity of chlorguanide is low. Dosages of from 1.0 to 1.4 gram per day have been tolerated for from 14 to 28 days without permanent ill-effects. With such high dosages, nausea, vomiting, diarrhea, and mild hematuria have been described.

Pamaquine

6-methoxy-8-(4-diethylamino-1-methylbutylamino) quinoline



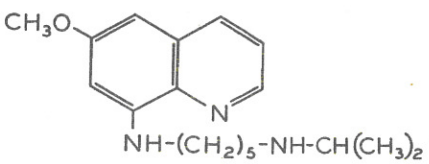
Synonyms: plasmochin, plasmoquine, praequine, gamefar, quipenyl.
Salts: naphthoate (approximately 45 percent base), monohydrochloride (90 percent base).
Dosage:
Therapeutic: 30 mg. of base per day (10 mg. three times daily) concurrent with quinine sulfate, 2 grams per day (0.65 gram three times daily) for 14 days.
Suppressive: Not used.

Pamaquine is localized only to a moderate degree in liver, lungs, and brain, and it is quickly metabolized. Its physiological disposition is markedly

altered by concurrent quinacrine or chlorguanide, leading to much higher plasma concentrations than with corresponding doses of pamaquine alone. Pamaquine has relatively weak action on asexual erythrocytic parasites. Its practical usefulness results from the fact that it will destroy the persistent forms responsible for P. vivax relapses, an effect which is enhanced by the concurrent administration of quinine. Dosage of the order recommended above reduces relapse rates of naturally acquired P. vivax malaria but will not cure early heavy infections. In toxic dosage pamaquine will destroy the pre-erythrocytic forms of P. vivax and P. falciparum, but this action is only of theoretical interest, as an effective dosage cannot be long tolerated. Small doses of pamaquine (e. g., 10 mg. three times daily for 5 days) will eliminate gametocytes of P. falciparum. Pamaquine regularly produces methemoglobinemia which, if of sufficient degree (from 5 to 10 percent of total hemoglobin), will be accompanied by cyanosis; abdominal cramps are common. Acute intravas r hemolysis is an infrequent but serious reaction, more common in Negroes. Concurrent quinacrine or sulfonamides should be avoided with all 8-amino-quinolines.

Pentaquine

6-methoxy-8-(5-isopropylaminoamylamino) quinoline



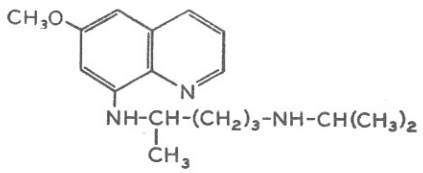
Synonyms: SN 13,276.
Salt: phosphate (75 percent base).
Dosage:
Therapeutic: 60 mg. of base per day (10 mg. every 4 hours) or 30 mg. of base per day (10 mg. every 8 hours), given concurrently with quinine sulfate 2 grams per day (0.65 gram three times daily), for 14 days.
Suppressive: Not used.

Like pamaquine, pentaquine is rapidly degraded in the body. There is apparently only slight tissue localization. Concurrent quinine results in slightly higher plasma levels, but concurrent quinacrine produces greatly elevated plasma concentrations of pentaquine. Although pentaquine has activity against the asexual erythocytic parasites of P. vivax, its real usefulness depends upon its ability, especially when given in combination with quinine, to lower the relapse rate of P. vivax malaria. The higher dosage given above is necessary for cure of heavy early experimental infections but the lower dosage has lowered relapse rates of late, naturally acquired infections. The optimal dosage of concurrent quinine is not yet defined. In very high dosage, pentaquine is a causative prophylactic against P. vivax, but its unsuitability for prolonged administration precludes such use in the field. Pentaquine will produce a moderate elevation

in methemoglobin, roughly proportional to dosage, so that some patients will exhibit cyanosis. Abdominal cramps, anorexia, nausea, vomiting, or drug fever may occur. Acute intravascular hemolysis is a potential hazard. Patients on the higher dosage should be hospitalized; those on the lower dosage may be ambulatory, but should be closely observed.

Isopentaquine

6-methoxy-8-(4-isopropylamino-1-methylbutylamino)-quinoline



Synonyms: SN 13,274.
Salt: mono-oxalate (74–79 percent base).
Dosage:
Therapeutic: Same as that of pentaquine.
Suppressive: Not used.

Isopentaquine is a close analogue of pentaquine. When given concurrently with quinine it is equal to pentaquine in reducing the relapse rate of experimental P. vivax infections and is somewhat less toxic. It is not commercially available.

Most of the newer compounds have not been studied under sufficiently varied conditions to warrant final conclusions concerning their relative merits, but several of them appear to be superior to either quinacrine or quinine. The data at hand permit the following conclusions:

Treatment of acute attacks of malaria. Quinine, quinacrine, chloroquine (and analogous 4-aminoquinolines) and chlorguanide, when given in adequate dosage, will nearly always stop acute attacks of malaria. Choice of drug, therefore, depends upon such factors as rapidity of effect, incidence of side-actions, length of treatment period, incidence of P. falciparum relapses, latent periods before P. vivax relapses, natural or acquired strain-resistance, and the cost and availability of drug. Chloroquine is superior in most of these respects and is currently regarded as the drug of choice for routine therapy.

Suppression of malaria. The aforementioned drugs, when given in properly spaced doses, will usually keep malaria latent under conditions of exposure in the field or following therapy of an acute attack. Choice of drug depends upon the incidence of break-throughs and of undesirable side-actions, the required frequency of dosage, and the persistence of protection if doses are missed, as well as upon cost and availability. Chloroquine in weekly dosage has proved to be a satisfactory suppressant, but further comparative trials are needed to determine the relative merits of chloroquine, chlorguanide, and the less well known 4-aminoquinolines.

Cure of P. vivax malaria. In relapsing P. vivax malaria, concurrent treatment with quinine and an 8-aminoquinoline, such as pamaquine, pentaquine, or isopentaquine, offers the best chance of radical cure. Pentaquine and isopentaquine afford greater margins of safety between effective and toxic dosages. (Pub. Health Reps., 10 June '49, W. C. Cooper)

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Aureomycin in Acute Peritonitis: This paper is a preliminary report on the use of aureomycin in the treatment of 52 unselected Harlem Hospital patients with acute peritonitis associated with appendicitis, perforated ulcers (gastric or duodenal), and one case of perforated sigmoid diverticulum. The group of patients was representative of patients found in the average municipal hospital, comprising that section of the population which is economically insecure, nutritionally deficient, physically impaired, and, in most instances, deprived of adequate educational opportunities.

Using previously known antibiotics and a standardized postoperative regimen the over-all mortality in 406 cases of acute appendicitis at Harlem Hospital for the years 1946 and 1947 was found by Maynard to be 4.18 percent. There were 145 cases of acute peritonitis in this group with 15 deaths, a mortality rate of 10.3 percent. In 40 cases of perforated gastroduodenal ulcers during the same period there were 7 deaths, a mortality rate of 17 percent. These patients received penicillin and sulfadiazine postoperatively. According to Maingot the current mortality rate in perforated ulcers in the average general hospital varies from 8 to 15 percent. Olsen and Nogore report a 21-percent surgical mortality rate in perforated ulcers for the 7 years, from 1938 to 1944. Luer, covering a 10-year period, showed an 18.2 percent mortality rate. Recent reports on appendicitis with peritonitis show a reduction of mortality rate to between 3 and 4 percent and lower.

All but one of the 52 patients in this study were treated by surgical intervention in an effort to remove the offending disorder and prevent further seeding of the already invaded peritoneal cavity. Drainage was instituted in 95 percent of these cases. The surgery was performed by the resident staff under the supervision of assistant visiting surgeons. The age of the patients with appendical peritonitis ranged from 4 to 68 years, and of those with perforated ulcers from 28 to 65 years. For the purpose of this paper the type of peritonitis encountered was divided into two large categories, localized, and spreading or generalized. In the appendicitis group there were 19 cases of localized and 16 cases of generalized peritonitis, with perforation found in 75 percent of the cases. There were 16 cases of generalized peritonitis in the ulcer group; in the case of the perforated sigmoid diverticulum the peritonitis was localized at the time of operation.

In this series of 52 cases there were 4 deaths. Two of these are included in the final mortality figures as possibly not having responded to the

antibiotic although these deaths occurred early in the study at which time relatively low intramuscular dosages were used. The remaining two are excluded because postmortem findings proved them to be surgical mortalities. In the initial phases of this study cases were alternated for control purposes, using penicillin and other antibiotics in one group and aureomycin in the second group. After approximately 24 cases were followed in this manner, results with aureomycin were sufficiently impressive to warrant its use in all cases of peritonitis.

In addition to determining the identity of the bacteria present at operation, cultures were obtained at frequent intervals from the in-dwelling abdominal drain until its time of removal. As anticipated, Escherichia coli was the predominant organism isolated from appendical peritonitis. In all but one case it appeared in combination with one or more organisms, usually streptococci. Although anaerobes were found in some cases, the incidence was not as frequent as has been reported in some other studies. In this type of disease a mixed flora was found far more commonly than was a pure culture; no single grouping of organisms predominated. On the other hand, pure cultures were the rule rather than the exception in perforated ulcers; probably because of early surgical intervention and the location of the lesion in the gastro-intestinal tract, E. coli was found in only 3 cases, two of which were fatal. The significance of these findings is not clearly evident at present because there appears to be no clear-cut correlation between the bacteria present and the clinical course. The percentage of negative cultures was considered to be high, particularly in peritonitis due to appendicitis. Partial explanation of these findings is related to inadequate culturing at the time of operation. In the future the authors hope to reduce the number of negative cultures by taking swabs from the pathologic lesion in addition to those of the abdominal fluid.

Failure to control or prevent the fatal termination was the basis of evaluation in the 4 deaths. Thus, two deaths were automatically dropped from the fatality percentage because both were proven to be surgical deaths at postmortem examination. One death resulted from a blow-out of the appendical stump, and in the second case two patent ulcers were found on the posterior wall of the first part of the duodenum and were feeding the peritoneal cavity from a retroperitoneal abscess. Of the other two deaths, one occurred in a 45-year-old colored male with a perforated appendix who died suddenly 3 and 1/2 days postoperatively from a pulmonary embolus. The diagnosis was made by x-ray and clinical findings; no postmortem examination was obtained. The second death was in a 65-year-old white female, acutely ill, with a perforated gastric ulcer, estimated at about 86 hours' duration prior to operation. The patient lived for 40 hours after operative intervention during which period aureomycin was administered. The inclusion of two deaths in the series to date gives an over-all mortality of 4 percent; a 2.94 percent mortality in appendical peritonitis; and a 6.67 percent mortality in perforated ulcer cases. Although this series is

too small as yet to draw any definite conclusions regarding the efficacy of aureomycin, comparison with previous mortality figures at the Harlem Hospital is very encouraging and further studies with the drug are indicated.

Aureomycin can be administered by the intramuscular, intravenous or oral route, apparently being clinically effective regardless of the method used. Initially, only intramuscular aureomycin was available and the search for an optimum dosage level began with this form of the drug. It was quickly apparent that the original dosages were too low, for, despite clinical improvement morbidity was often prolonged. Clinical response to the drug was used as the basis for increasing the dosage. As soon as sufficient amounts of the antibiotic became available, the intravenous and oral methods were used by choice. Since instituting the combined intravenous and oral regimen there have been no fatalities.

In the first patients treated by the intravenous route, the daily dosage ranged up to 2 Gm. in an effort to find the minimal dose giving optimum clinical response. When it was determined that clinical results were very good with 1 Gm. of drug daily, the authors established the standardized routine described below which has been followed in all of their later cases. Immediately after operation the patient is given an intravenous dose of 500 mg. and this is repeated every 12 hours thereafter for generally 48 hours. On the third postoperative day the Wangensteen suction is clamped off and two 250 mg. capsules are given orally every 12 hours for an average period of from 7 to 10 days depending upon clinical indications. In children, the same general scheme has been followed but dosage has been cut approximately in half. For intravenous use the dry powder is dissolved in a 500 cc. flask of 5-percent glucose in distilled water and introduced within an hour. This is given as part of the usual postoperative intravenous administration of fluids. In the authors' hands this has proven to be a simple and efficient means for administering the drug.

To date there have been no toxic responses to the drug severe enough to cause cessation of therapy, regardless of the route of administration. When the intramuscular route is used, the only reaction has been some slight pain on injection. When given intravenously, a chemical phlebitis has developed in 10 out of 22 cases, and it has ranged from mild to moderately severe. This complication did not alter the usual course of the disease nor prolong morbidity. With oral administration the authors have not seen the nausea and vomiting or the type of diarrhea seen occasionally in other patients who have been treated in this hospital for ulcerative colitis (15 cases), various wound infections (60 cases), compound fractures (10 cases) and genito-urinary infections (12 cases). In two cases there was mild nausea and some vomiting, but an interpretation of this was difficult because of the peritonitis present. Laboratory studies have shown no changes in blood chemistry, and urine studies have shown no evidence of kidney damage. Blood levels of aureomycin have been determined in several

cases and demonstrable levels have been found at all times when using both the oral and intravenous route. At present, no conclusions have been reached concerning the optimum therapeutic blood level.

This work is still in progress and a detailed report will be published at a later date. (Am..J. Surg., July '49, L. T. Wright et al.)

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Fate of Cardiac Foreign Bodies: Among the many problems to receive renewed interest as a result of World War II was that of the fate of metallic foreign bodies in and about the heart, and of the advisability of their removal. During the interval between the first and second World Wars, thoracic surgery had advanced to the point where, technically, it was quite feasible to explore the pleural or pericardial cavities and, indeed, to operate upon the heart itself. Until the advent of World War II there were few reported cases of the successful removal of retained cardiac foreign bodies. It is only natural that thoracic surgeons, meeting this problem for the first time in military hospitals and without the background of established procedure, should, therefore, solve it according to their individual daring and ingenuity. Moreover, the number of such cases was fortunately small, and thus a single surgeon's experience was limited. The majority of American, British, and German surgeons, including Beck, Edwards, and Sauerbruch, favored removal of the foreign body for prophylactic purposes, whether or not the patient was having signs or symptoms of cardiac dysfunction.

Harken, in describing the removal of 55 pericardial and 13 intracardiac missiles, stated that more foreign bodies, presumably within the heart, were allowed to remain undisturbed than were removed. However, he advanced the following four points as justification for surgical intervention as a prophylactic measure: (1) prevention of embolism by the foreign body or of an associated thrombus, (2) reduction of danger of bacterial endocarditis, (3) prevention of recurrent pericardial effusions, (4) diminution of the incidence of myocardial damage.

According to Schaefer and Satinsky the danger of permitting a foreign body to remain in the musculature of the heart is threefold: (1) cardiac rupture, especially the rupture of a cardiac aneurysm, (2) migration into the adjacent cavity with embolism formation or interference with capacity of function of the chamber, (3) injury to a coronary vessel.

It is true that these complications have a definite theoretical basis, and scattered examples of their occurrence can be gleaned from the literature. The majority of reported cases, however, do not present such sequelae.

Indeed, that these projectiles often may be permitted to remain undisturbed without endangering the life of the patient has been reported by a number of writers. The most extensive case reports have come from Russian literature. Four separate surgeons reported a total of 128 cases in which there were no serious clinical or subjective findings during the period observed. It is true that the period of observation was only from 4 to 8 months in the majority of instances, but a significant number of patients was followed for from one to 52 years after the initial wound. In the English literature, Bland reported 8 cases in which metallic foreign bodies in and about the heart were not removed and in which the patients had only minimal subjective symptoms during the observation periods of from 4 to 7 months.

From these and other reports it would appear that most patients with retained foreign bodies in and about the heart, excluding those obviously in need of immediate surgery to stop hemorrhage and cardiac tamponade, etc., may be grouped in 3 categories. A small group had no signs or symptoms whatsoever, the foreign body being picked up on routine x-ray examination, usually at the time of discharge from Service. Another small group had definite signs of impaired cardiac function. The majority, however, presented from minimal to mild subjective symptoms without objective signs of any real cardiac dysfunction. It is to be stressed, however, that observation after return to normal routine and work is necessary to evaluate the condition in these patients. Not infrequently with increased load on the heart, symptoms such as mild precordial pain, tachycardia, and extrasystole become manifest. Many of the investigators mentioned reported this to be especially true in cases in which the foreign body lies in the pericardial sac.

Another point which is repeatedly stressed is the profound psychologic effect upon the patient of the knowledge of a retained foreign body embedded in the heart combined with minimal symptoms. Not infrequently these patients are anxious to accept a serious surgical risk to gain peace of mind. Without precedent of established routine, the surgeon's decision to intervene may be swayed by such a psychologic factor. On the other hand if the surgeon could be sure in his own mind that there was little likelihood of serious sequelae, he would be in a much better position to reassure the patient.

In addition, as pointed out by Harken, one must be cautious in evaluating straight statistical studies of reported cases. In his series one half the patients referred to the thoracic center as having foreign bodies in the heart were found not to have these missiles in the heart when careful fluoroscopic examination was done. Furthermore, one third of the missiles previously considered to be intracardiac were not found in the heart at surgical exploration.

An experimental study was undertaken to determine the fate of metallic foreign bodies introduced in and about the heart. By the study of such experimental lesions, in conjunction with statistical analyses of clinical cases, it was

hoped that more definite indications and contraindications for surgical intervention might be postulated. Young dogs weighing from 6 to 15 kilograms were used. The foreign bodies were irregularly shaped fragments of metal, cast iron or brass for the most part, from 3 to 10 mm in diameter and weighing from 0.15 to 5.0 Gm. A definite attempt was made to simulate bomb or grenade fragments. In addition, actual 0.30 caliber rifle slugs were used in a few cases. Using intratracheal, positive pressure ether anesthesia, the dog's chest was opened aseptically and the fragments were introduced into the pericardial sac, into the right and left myocardium, and also directly into the right and left auricular and ventricular cavities. The animals were x-rayed or fluoroscoped as soon as the chest was closed and at frequent intervals during the period of observation. In some animals with foreign bodies in the pericardium and myocardium electrocardiographic studies were done before, during, and at intervals up to 3 months following operation. All animals were re-operated upon or sacrificed at regular intervals up to 12 weeks after operation. In every case autopsies were performed and sections made for pathologic study.

Altogether, 62 dogs were used, only 3 of which died as a result of the foreign body, two of these being from embolism and occlusion of a systemic artery and one from infection. Foreign bodies introduced into the pericardium produced minimal local reaction and were well encapsulated by 8 weeks. In animals pain is hard to evaluate. On the basis of these experiments the pain in similar clinical cases cannot be explained. Only 3 out of 35 foreign bodies introduced directly into the chambers of the heart remained within the heart. Apparently these had been mechanically caught between chordae. No untoward findings were noted in these 3 cases. The remaining 33 were quickly embolized to the pulmonic or systemic circulation. Those embolized from the right side of the heart lodged in the primary pulmonary artery to a more dependent lobe. Only rarely was an infarct produced. Those embolized from the left side of the heart lodged for the most part at the bifurcation of the aorta. The site of their lodgment in the systemic circulation apparently was due to the proportionate size of the foreign body.

Of the 18 foreign bodies placed in the myocardium, only two caused serious results; one because of infection and one because of concomitant extensive infarction of the myocardium due to injury to the coronary artery at the time of surgery. The other 16 caused only minimal local reaction and were firmly encapsulated in a fibrous scar by 8 weeks. Indeed, the removal of these foreign bodies from the myocardium was accomplished rather by additional myocardial damage. There were no cases of migration of a foreign body from the myocardium into the chamber of the heart.

It seems reasonable to conclude therefore that the majority of foreign bodies retained in or about the heart, as long as they are not producing symptoms or signs of cardiac dysfunction, may be permitted to remain undisturbed. The authors feel that it is not necessary to remove such foreign bodies for prophylactic purposes. (Surgery, June '49, J. M. Fritz et al.)

A Simple Questionnaire for the Taking of Histories in Cases of Cancer:

In the course of his postgraduate hospital training the intern, resident or fellow probably does not remain long in a position where his duties include the taking of histories. As he reaches the senior positions on the house staff this traditionally somewhat onerous task is usually passed on down to successive junior members of the house staff. The result is that clinical histories in cancer cases, as they accumulate over a period of years, will have been taken by a succession of postgraduate trainees at a time when they are just beginning their hospital experience. The junior house officer can hardly be expected to exercise reasonably good discrimination or to have attained sufficient insight regarding the type of questions which are essential in cancer cases. At any rate, without some specific directives the clinical records will hardly be complete or uniformly arranged. Although in some of the cases the histories may be excellent, in others the information will be so meager or so confused as to vitiate the over-all value of the greater mass of recorded data.

In highly specialized institutions such as cancer hospitals or tumor clinics one solution to the problem of the clinical history of the present illness would be to provide a set of instructions in the form of a questionnaire which would always be before the intern when he is actually taking the history. It seems reasonable to make such a questionnaire simple and concise so that it would provide a logical sequence of questions which would fully bring out in chronologic order the more important features in the history of the present illness and suggest the directions in which further inquiries might be made.

The following is a questionnaire which, if consistently and routinely employed, would tend to bring out the more significant points in a cancer history, many of which might otherwise be omitted. It is to be noted that all questions begin with and often include the specific interrogations, when, what, and how. After recording the family history and past medical history according to the usual routine, use the following questions for the present illness:

(1) When did you first notice anything wrong or abnormal in connection with your present complaint? (If the patient gives an indefinite answer such as "about 3 months," recheck by asking the exact month. Record the exact month and year in the history.)

(2) What symptom or difficulty did you notice first and what other symptoms followed and when? (It is important to ascertain the exact first symptom. Some discretion may be used in recording the character and order of symptoms. Some are obviously entirely irrelevant.)

The following are the most significant symptoms (not necessarily the only ones) in the various anatomic forms of cancer. Their presence or absence should always be recorded.

Skin and subcutaneous tissues: The lesion itself - ulcer - swelling.
Mouth: The lesion itself - pain - cervical metastasis.
Nasopharynx: Cervical metastasis - unilateral deafness or tinnitus.
Oral and hypopharynx and extrinsic larynx: Dysphagia - cervical metastasis.
Intrinsic larynx (vocal cords): Hoarseness.
Esophagus: Dysphagia.
Lung: Cough - hemoptysis - pain.
Breast: Tumor mass - deformity - nipple bleeding.
Stomach and small intestine: Indigestion - anorexia - vomiting - weight loss.
G. U. system: Hematuria - dysuria - frequency.
Gyn. viscera: Bleeding - discharge - pelvic pain.
Large intestine and rectum: Change of bowel habit - bleeding.
Blood (leukemias): Fatiguability - bleeding tendency.

(3) What did you first believe caused your trouble? (The patients opinion regarding the cause of the growth is always of interest even though illogical.)

(4) When and how long after the first symptom did you consult your doctor or dentist? (Include cultists and irregular practitioners.) (Always record the names and addresses of all doctors or dentists consulted. If only the last name and the street address (without the number) can be obtained, that information is nevertheless of value.)

(5) What examination did the doctor make? Did he make a rectal or vaginal examination? Did he use an endoscope or throat mirror? Did he take a specimen for examination or make a blood test? What treatment did he give or prescribe for you? (It is essential to record the method of examination and subsequent management of a cancer case in order to understand the delay in diagnosis and treatment.)

(6) What advice did the doctor or dentist give you in regard to the necessity for further examination either by himself or by some other doctor? Did he tell you the name of your disease? (The attitude of the first physician or dentist consulted in regard to advice and treatment is an excellent indication of their tentative diagnoses.)

(7) What did you do in carrying out the doctor's advice? (Continue interrogating the patient in regard to subsequent doctors consulted, treatment, operations, etc.)

(8) Who finally referred you to this hospital or clinic and when was this advice first given? (Attempts should be made to obtain accurate and specific information concerning the name and address of the referring doctor or clinic. These parties often have biopsy slides, records of treatment, and furthermore expect to be informed of the patient's admission and progress under treatment.)

Under question 2, it should be noted that specific symptoms are listed in the order of their importance and would apply particularly to each of the major anatomic sites in which cancer is likely to occur. These symptoms are of such importance that they should be recorded both when present and when absent. This list was obtained by checking with a number of surgeons and internists, each of whom had had many years of experience in one or another anatomic form of cancer. Each was asked to name the 3 most important symptoms in the order of their significance in a particular clinical field. It is to be noted that in certain diseases such as cancer of the intrinsic larynx and esophagus, a single symptom (hoarseness and dysphagia, respectively) stands out as being so constant and unique that no other symptoms need be listed under this particular heading.

In the Memorial Hospital this questionnarie has been found so useful that it is printed on the reverse side of the clinical history sheet so that it may be before the questioner at all times when taking and recording histories. (Am. J. Surg., July '49, Editorial, H. Martin)

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Clinical Manifestations of the Sympathetic Reflex Arc: During London's 1941 air raids physicians found that victims whose legs had been pinned under timbers and masonry for several hours died mysteriously of kidney failure. This strange condition was called crush syndrome. Injuries to the vessels of the crushed extremity reflected the blood vessels of the kidneys into spasm and thus caused anuria. A gradual increase in the blood pressure followed. This clinical syndrome has been studied intensively during the past few years by pathologists. Although pathologists still talk about the release of toxic substances by crushing injuries to the muscles of the limb and about some unknown muscle-endocrine mechanism responsible for the observed intense vasoconstriction and ischemia of the glomerular tuft, they agree that vasoconstriction of the kidneys is always present in the postglomerular arterioles. The steady rise of the blood pressure is a result of this vasoconstriction. Experimental data are now available which confirm the early appearance of vasoconstriction in crush wounds as seen by Keele and Slome following release of complete ischemia maintained for 4 hours in an extremity of a cat. Of course, one must admit that the vasoconstriction initiated and caused by a crushed or ischemic limb is limited not only to the kidneys but it is in the kidneys that this vasoconstriction manifests itself most alarmingly. Considering all these proven facts it is logical and scientifically sound that repeated sympathetic blocking should take preference over all other measures in the treatment of a patient with a crush syndrome. Vasodilatation of the kidney arterioles and glomerular tufts is the first clear-cut aim of the clinician. Not all clinicians handling traumatic surgical material will see many cases of a well expressed crush syndrome but all have seen many borderline cases in which in more or less extensive

injuries to an extremity the patient shows numerous unexplained complications of a systemic nature despite good, conventional care. It should be an established rule that along with the management of the injured limb, a prompt and repeated blocking of the sympathetic is a condition without which the management is deficient. This is especially true in patients with a labile sympathetic system, the one with cyanotic, clammy hands who is subject to instantaneous vasospastic reactions.

Another field in which many individual observations have not been fully understood is the field of vasospastic heart disease. When a traumatized heart is exposed for repair, the most difficult task is to control the irritability of the heart muscle. It was found that spraying the exposed heart with a solution of novocain relieves this irritability. The novocain, by blocking the sympathetics, abolishes the spasm of the numerous small blood vessels of the exposed myocardium.

Maguire and Friswold noticed that a seemingly trivial wound piercing the right ventricle near the atrioventricular groove without damage to the left coronary artery will cause electrocardiographic tracings consistent with a diagnosis of anterior infraction in 100 percent of the cases. These typical tracings disappeared in from 7 to 10 days. This observation is explained by the distribution of the sympathetic system in the heart. The heart muscle shows an abundant supply of nerve fibers in the pectinate muscles, the trabeculae carneae and in the papillary muscles. Incomparably more abundantly supplied is the region of the heart along the coronary sulci and the atrioventricular groove. There the heart is thickly covered with widely ramified bundles of the sympathetic nerves for at least one inch to each side of the groove or sulcus. Therefore, even a seemingly trivial wound in the neighborhood of the atrioventricular groove divides numerous sympathetic bundles causing an immediate and widespread spasm of the coronary ramifications with the typical electrocardiographic tracings. To some degree an analogous observation is seen in coronary disease when even a small ischemic area in the myocardium initiates a further spread through the sympathetic of a reflex spasm and leads to an aggravation of the disease. It is only logical, therefore, to suggest that measures aiming at vasodilatation through blocking of the sympathetic arc in the myocardium should follow immediately after the conventional administration of analgesics and oxygen in the treatment of coronary disease. Such a sympathetic block is not to be viewed as a pain-relieving measure only, as it is at present. It also follows that whenever time permits, a sympathetic block should precede any surgery on the myocardium.

The role of the sympathetic reflex arc may be studied in cases of vagotomy. The gastro-intestinal tract is innervated by both the sympathetic and parasympathetic systems. The parasympathetic system consists of the vagus nerves and of the splenic nerve which is the sacral division of the parasympathetic system. The vagi supply the gastro-intestinal tract down to the splenic flexure of the

colon and the pelvic nerve supplies the descending colon. When the vagus nerves are cut in the chest or about their exit from the thorax, the sympathetic system is left without an antagonist from the stomach down to the splenic flexure of the colon. The postvagotomy complications naturally are the result of sympathetic irritability. In other words there is a sympathetic reflex arc which is as unimpeded as the knee jerk in an upper neuron lesion. Irritations, which under normal conditions would become neutralized by the antagonistic action of the vagus, lead to serious complications in the absence of this antagonist.

In May 1947 the author underwent a vagotomy in the course of an esophagectomy. Immediately following the vagotomy a number of complications appear which confuse the patient. After a few weeks the complications assert themselves and crystallize. These complications appear in episodes or bouts and are more frequent in cold or damp weather. Exposure or chilling of the long thoracotomy scar immediately reflects in a new bout of eructations, regurgitations, nausea, occasional vomiting of white, foamy, gastric secretion, abdominal distention and pain in the right lower quadrant and throughout the lower abdomen. The eructation and regurgitation result from a dilation of the stomach through contraction of the pylorus by the inhibiting action of the sympathetic system. Inhibition of the movements of the small gut and the proximal two thirds of the colon by the sympathetic leads to stasis. The overfilled, small gut causes pain typical of an intestinal obstruction with loud borborygmus. This may persist for days until a whistling sound of escape of intestinal gas through the splenic flexure of the colon gives full relief. This terminates the episode but not for long. An exposure to cold of the author's frostbitten finger or even an arduous argument or outburst of temper again reflects in a new bout of sympathetic crises. During the bout, turning from his back to his side and the consequent falling of the intestines to the dependent side, immediately exacerbates the pain. This is then accompanied by profuse perspiration (a sympathetic reaction), chill and tingling of the skin. Even loud talk and noises of various kinds increase the colicky abdominal pain. The author not only does not recommend vagotomy but believes that even in esophagectomy the surgeon should make a real effort to save the vagus nerves.

Recently clinicians have reported rapid control of eclampsia by means of sympathetic block achieved by spinal or high caudal anesthesia. This observation supports the suggestion that the pathologic physiology of eclampsia is mainly sympathetic vaso-spasm of the kidneys. Another recent observation is that paravertebral sympathetic block relieves the swollen hands and feet, muscle spasm and tenderness of polio victims. Although it is known that spasm is not the most damaging effect of the disease, it is logical to believe that a sympathetic block will accomplish more with less in relieving this spasm than the time and effort-consuming Kenny method.

The author has previously expressed the view that the presupposed decussation in the pons cerebri of <u>all</u> post-ganglionic sympathetic fibers destined

for the blood vessels is not borne out clinically. Recently Gilbert and de Takats, in treating cerebral vascular insult (another manifestation of vasospasm) with blocking of the sympathetic in the stellate ganglion, insist upon blocking the ipsolateral ganglion. This observation is in direct support of the author's view on decussation of the sympathetic fibers.

The field of pathologic physiology centering about the sympathetic reflex arc is an enormous field which requires intensive study, analysis, correlation, and systematization. (Am. J. Surg., July '49, A. Kolodny)

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The Use of Pyrogens in the Treatment of Lower Nephron Nephrosis: Transfusion reactions, blackwater fever, hemolytic reactions due to sulfonamides, hemolytic reactions following burns, the intravenous injection of distilled water, any intravascular hemolysis, or extensive destruction of tissue may precipitate a syndrome characterized clinically by chills, fever, nausea and vomiting, dyspnea, shock, then oliguria and anuria, heme pigment excretion, azotemia, hypertension, and uremia. The mortality cannot accurately be determined because many patients who recover are not reported, but this syndrome was the most frequent form of fatal kidney disorder encountered among military personnel during the recent war.

Pathologically there is found a large, pale kidney that microscopically shows degeneration and necrosis of the distal convoluted tubules, edema (or extravasated glomerular filtrate) and leukocytic infiltration of adjacent stroma, pigment precipitation in the tubule cells which have often been sloughed into the lumina, and relatively normal appearing glomeruli. Autopsies on patients expiring at varying intervals from 3 hours to 10 days after onset reveal progressive changes. Tubular necrosis becomes evident on the third day. Red pigment is seen in the lining cells of the distal convoluted tubules. Interstitial edema is presented by the sixth day, when tubular cell desquamation is marked. Attempts at repair are noted by the seventh day. Cellular and pigment casts are numerous on the tenth day.

Vascular changes in the kidney of the crush syndrome (included in this group of lower nephron nephrosis) have been intensively studied by Goormaghtigh in his studies of the relation of the juxtaglomerular apparatus to renal hypertension. Autopsy material includes the kidneys of patients who expired from the fourth to the ninth day following injury. Vasoconstriction of the efferent arteriole is observed early, with later extension back to the glomerular tuft. He explains the elevation of blood pressure by an increase of vasopressive endocrine function of the afferent arteriole wall, following deterioration of circulation in the tufts, efferent arterioles, and intertubular capillaries. There is an increase of afibrillar cells of the media of the preglomerular arterioles,

which acquire cytological features of glandular activity and are considered to participate in the formation of a vasopressive substance. He concludes that renal deficiency in the crush syndrome is to a great extent the result of vasoconstriction, first of the efferent arterioles and later the capillary tufts. This implies an ischemia.

Until recently, oliguria in the lower nephron nephrosis was believed to be the result of tubular block by pigment casts. Many histologic studies, however, invalidate this explanation. Currently, renal ischemia and, consequently, anoxia are believed to be of fundamental importance in the pathogenesis. Yuile has shown in animals that tubular necrosis due to anoxia results in extensive precipitation of hemoglobin in the tubular cells. Tubular degeneration causes loss of tubular function, and unselective resorption of the glomerular filtrate occurs; the filtered, concentrated blood in the efferent arteriole by its increased osmotic pressure resorbs most of the glomerular filtrate through a nonfunctioning tubule acting now only as a semipermeable membrane. As anoxia persists, the tubular lining cells necrose and slough. Interstitial extravasation of urine follows. These two mechanisms of urinary suppression, initiated and augmented by diminished renal blood flow, appear to explain adequately anuria in lower nephron nephrosis. Van Slyke divides the effects of renal ischemia into 3 stages, depending on its duration: (1) reduced kidney function without damage to nephrons, (2) reversible damage to nephrons, and (3) irreversible damage with subsequent death in uremia. All 3 stages may occur in man.

The critical period is approximately 2 weeks, and patients who survive generally resume adequate renal function. Therapy today is supportive. Sufficient evidence has not yet been advanced to credit the recovery of the patient to any one mode of treatment. When considering the problems of therapy, it appears necessary to examine the primary functional disturbance, the altered renal blood flow, which in a normal patient is relatively constant and approximately 1200 cc. per minute. In his studies of renal blood flow, Homer Smith has demonstrated the remarkable constancy of the glomerular filtration rate and its control by the tone of the efferent arterioles. These vessels constrict when the renal blood flow diminishes, thus causing an increase in filtration fraction and thereby maintaining a constant filtration rate. Renal hyperemia is accompanied by a decreased filtration fraction (and constant rate), indicating that it is a result of dilation of the efferent arterioles.

In endeavoring to increase renal blood flow, pyrogens were discovered to be effective, causing the flow in one normal subject to increase 244 percent and at least 75 percent in other subjects. No drug was found to increase renal blood flow. The primary change resulting from intravenous administration of one hundred million killed typhoid organisms, used as a strong pyrogenic agent, is peripheral vasodilation, a relatively greater vasodilation occurs in the renal vascular bed than elsewhere. In addition, cardiac output is increased. By the use of amidopyrine all other pyrogenic effects (headache, lumbar pain, nausea,

and fever) were blocked, but increased renal blood flow was still obtained; and in the experimental animal the denervated kidney showed identical change in response to pyrogens; indicating that either the pyrogen acts directly on the renal arterioles, or it causes the secretion of some vasodilator humoral agent. In the treatment of lower nephron nephrosis it appears physiologically sound to attempt to increase the renal blood flow before irreversible ischemic necrosis of the tubules is widespread.

In an attempt to reverse the syndrome of renal shutdown by increasing the renal blood flow with pyrogens, an oliguria was produced in 8 rabbits by use of sterile water injected intravenously. This oliguria persisted at least 3 days in the controls. In the 4 rabbits whose treatments with thyphoid vaccine were started 18 hours after onset and repeated at 12-hour intervals, normal urinary output was resumed on the second day; however, because of its efficient reticuloendothelial system, the rabbit may not be the most desirable experimental animal to use for studying this problem. (J. Urol., June '49, L. J. Scheinman)

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Recent Developments re Bacitracin: The Tracey strain of Bacillus subtilis, which produces bacitracin, was discovered in May 1943 in the Bacteriological Research Laboratory of the Department of Surgery of Columbia University during a study of wound infection under a contract with the Office of Scientific Research and Development (OSRD). The development of bacitracin was carried to the point where it was demonstrated to have a wide antibacterial spectrum covering the hemolytic and nonhemolytic streptococci, staphylococci, pneumococci, meningococci, gonococci, the anaerobic clostridia and cocci, the diphtheria organisms, and the spirochete of syphilis. It was found to be of low toxicity and to be capable of controlling experimental infections in animals and clinical infections in man. On 1 January 1946, the Surgeon General's Office of the Army undertook the support of the further research and development of bacitracin.

During the gradual improvement in the commercial production of bacitracin, in which difficulties similar to those met with in the production of penicillin and streptomycin were encountered, the relatively impure antibiotic was used in over 200 cases of localized surgical infections by the injection of the solution or the application of an ointment containing the antibiotic, and favorable results were recorded in 87 percent of these cases. Similar gratifying results were obtained in dermatological and ophthalmologic infections by local application of ointments or solutions. In its relatively crude state it was effective when applied to local infections, but it had not yet become standardized nor had it been obtained in a sufficiently pure state to warrant its systemic administration.

Pharmacologic studies demonstrated that bacitracin was without toxic action to any tissue of the body of experimental animals, except for local irritation of the tubules of the kidneys of mice and to a lesser degree of monkeys. Rabbits, rats, and dogs seemed to be unaffected. The administration of bacitracin

by intramuscular and subcutaneous injection was begun cautiously and with gradually increasing confidence, as it was demonstrated that although traces of albumin and a few granular casts appeared in the urine, they disappeared in the course of treatment or shortly after its cessation. In 1947 and the spring of 1948, a gradually increasing number of patients with generalized infections were treated systemically with the product of the Ben Venue Laboratories, produced by a surface growth, in doses ranging from 3,000 to 50,000 units every 6 hours, with a control of the infection in the majority of cases.

Blood levels could be obtained and maintained for a period of 6 hours by the subcutaneous or intramuscular injection of solutions containing from 10,000 to 30,000 units per cubic centimeter and in doses ranging from 3,000 to 50,000 units, but administration by mouth in doses as high as 250,000 units seldom showed absorption into the blood stream and only minimal levels in the urine. On the other hand, high concentrations of the antibiotic could be found in the stools following oral administration. It was found that Endamoeba histolytica was susceptible to bacitracin in vitro and administration by mouth demonstrated its ability to bring the symptoms of amebiasis under control with rapid healing of the lesions.

An extraordinary synergism between bacitracin and penicillin in the treatment of experimental syphilis has been demonstrated by Dr. Harry Eagle who has treated a series of patients with bacitracin alone and with bacitracin in conjunction with penicillin. Dr. Edward Reisner has found bacitracin effective in the treatment of pneumococcic pneumonias of various types.

Bacitracin was first made by the deep tank method by the Commercial Solvents Corporation. This product became available for the first time in January 1948 and was used from January to June. Although it met the specifications that had been set up in January 1946 by the Food and Drug Administration, certain lots were found to be more toxic than the Ben Venue product and confidence in the parenteral administration of the drug was temporarily shaken, and the systemic treatment of patients was halted until this difficulty could be overcome. New, less toxic lots became available, and in the summer and fall of 1948, it was demonstrated that the product of the Commercial Solvents Corporation, meeting a toxicity level of an LD_{50} of 500 units for a 20-Gm. mouse, could be given safely in doses that were clinically effective and produced only transient or inconsequential evidences of renal toxicity.

Bacitracin has cured dogs with experimental staphylococcal meningitis, and it can be given subdurally or intrathecally in human beings in concentrations of 1,000 units per cubic centimeter and in doses of 10,000 units without signs of irritation or toxicity. Bacitracin powder can be applied to the brain surface and the solution injected into its substance without causing the irritation or convulsions characteristic of other antibiotics or antiseptics.

In September 1948, the Food and Drug Administration gave its consent for the general distribution of bacitracin to practitioners of medicine for local injection or application of the solution or ointment or for oral medication, but distribution for systemic administration is being held up until its safety has been fully demonstrated. Bacitracin is being thoroughly studied to demonstrate the nature of the residual toxic elements, and studies are being made by countercurrent, chromatographic, ultracentrifugal, electrophoretic, and chemical methods in an effort to separate the toxic factors or to nullify the toxic action. Meanwhile, clinical studies are being continued in New York, Philadelphia, New Orleans, San Antonio, and Cincinnati under carefully controlled conditions in order to demonstrate further the indications and limitations of this new antibiotic in the treatment of infections. Up to 15 February 1949, the records of 205 cases of generalized infections, exclusive of pneumonia and syphilis, had been submitted by the 5 units which had been set up for the clinical appraisal of systematically administered bacitracin, with favorable results in 64 percent of these cases. More than half of this series were cases in which there had been failure of response to penicillin, streptomycin, or the sulfonamides, either alone or in combination. Fifty-six percent of these patients have been salvaged by bacitracin, although the favorable results in cases not previously treated approached 80 percent. (From abstract in Bull. U. S. Army Med. Dept., June '49, of paper presented by F. Meleney at the Army Medical Center, Washington, D.C.)

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Opalescence of Serum After Total Body X-Irradiation as a Prognostic Sign of Death: During an investigation of the clotting reaction of blood after irradiation with 200-kv x-rays, the author noted the appearance of a marked opalescence in the serum and plasma of rabbits that died a few days after exposure to a single lethal dose of total body irradiation. This opalescence appeared within 24 hours following the exposure to radiation. In all cases, it disappeared completely 72 hours after exposure. A review of the literature has failed to reveal any mention of this phenomenon.

In all cases the opalescence, when present, was noted in both serum and plasma as a pearly white tint homogeneously distributed throughout the sample. Various degrees of intensity have occurred and can be classified as marked, moderate, and slight. All animals showing marked opalescence died as a result of radiation within 5 days following exposure. Animals having no opalescence or opalescence to a lesser degree usually survived the radiation for at least 30 days, unless death occurred from other causes. If opalescence occurred it was prominent 24 hours after radiation, and completely disappeared 3 days after radiation in all cases. No relationship was noted between its occurrence and diet or fasting. Serum obtained in nonirradiated animals either with or without fasting (20 hours) was always clear, whereas opalescence has been found in both fasting and nonfasting animals after radiation.

The absence of any red pigmentation in opalescent serum tends to rule out erythrocyte hemolysis as a causative factor. Also, there seems to be no direct relationship between opalescence and radiation dose rate. Detailed coagulation and hematological studies on these animals will be reported subsequently.

Studies are in progress with the collaboration of Dr. John Gofman to determine the chemical nature of opalescence. The opalescence can be eliminated from serum by acetone and ether extraction according to the method described by Blix. In low-speed ultracentrifugation, material that is responsible at least in part for the opalescence rises to the top, leaving a clear solution below.

At present, there is no clear explanation of the mechanism by which radiation produces this opalescence. In view of its apparent relation to death, it is believed that the phenomenon may not only provide a valuable early measurement of the effect of acute exposure to radiation, but may lead to further knowledge concerning the nature of radiation sickness and its lethal mechanisms. (Science, 8 July '49, R. L. Rosenthal)

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Influence of Sodium Chloride Upon the Actions of Desoxycorticosterone Acetate: In previous publications by the author and co-workers from the Institute of Experimental Medicine and Surgery of the University of Montreal, attention has repeatedly been called to the fact that many of the toxic actions of DCA are dependent upon the sodium chloride content of the diet. It has been shown that excessive dietary supplements of sodium chloride increase the severity of the nephrosclerosis, periarteritis nodosa, and hypertension produced by DCA although diets comparatively poor in sodium chloride tend to diminish these toxic actions of this corticoid compound. Extensive experimental work supports the view that in sodium chloride it is the sodium ion which is of importance in this connection. A variety of acidifying salts, such as ammonium chloride, ammonium nitrate, calcium chloride, and others, also counteract the toxicity of DCA presumably because these salts occasion severe losses of sodium.

It is believed that the typical morphologic lesions produced by overdosage of DCA in the presence of sodium are caused fundamentally by a derangement in the deposition of hyalin (fibrinoid) material. The characteristic hyalinization of arterioles and renal glomeruli, the formation of granulomatous nodules around hyalin plaques in the heart, and the deposition of fibrinoid material on the cardiac valves, the pericardium, the internal surface of blood vessels, and on other tissues form a syndrome which might well be described as fibrinoid diathesis or hyalinosis, just as the terms lipoidosis, calcinosis, or amyloidosis are used when excessive

lipid, calcium, or amyloid deposition occurs throughout the body. This experimental hyalinosis caused by DCA probably has its counterparts in human pathology in the form of such diseases as malignant nephrosclerosis, rheumatic arteritis, Libman-Sacks disease, diffuse collagen disease, periarteritis nodosa, thromboangiitis obliterans, and malignant arteriolosclerosis.

In this paper the authors report upon a series of observations on rats receiving DCA while on a diet completely devoid of sodium chloride. It was found that the weight of the kidney was by far highest in the rats treated with DCA and receiving sodium chloride. This renal enlargement is typical of the early stages of nephrosclerosis before secondary contraction occurs. Sodium chloride deficiency was seen to have caused some renal atrophy when the control animals on diets containing sodium chloride were compared. It is especially noteworthy that animals on a sodium chloride-free diet, even when treated with DCA showed no increase in renal weight in comparison with the corresponding rats whose sodium chloride was depleted but which were not treated with DCA.

The degree of nephrosclerosis caused by DCA in rats on the sodium chloride-containing diet was 93 percent although not even the slightest microscopic trace of such a lesion was detectable in the rats with depleted sodium chloride and receiving the same amount of DCA.

DCA caused no significant increase in heart weight in the sodium chloride-depleted animals. In fact, this substance appears to have produced a decrease, but this may not be significant. On the other hand, the rats receiving DCA on a diet containing sodium chloride had a significantly higher cardiac weight than the corresponding controls. It should be emphasized that the heart weight is a rather reliable indicator of the mean blood pressure during the entire experimental period.

Myocardial changes, with the formation of granulomas containing giant cells and hyalin deposits between the cardiac muscle cells, have been produced by DCA only in animals on the diet containing sodium chloride. Periarteritis of the mesenteric vessels likewise occurred only under the influence of DCA plus dietary sodium chloride.

The blood pressure was measured after 4 weeks of DCA treatment, that is, when the animals of all 4 groups were still on a completely sodium chloride-free diet. At this time the mean blood pressure, determined under light ether anesthesia by direct cannulation of the carotid artery, was within normal limits in all 4 groups. Previous experiments had shown that after 4 weeks of treatment with DCA, the blood pressure would have risen far above normal in rats receiving normal diets containing sodium chloride. After 9 weeks, that is, 5 weeks after a control and a test group had been placed on sodium chloride, the blood pressure remained within normal limits in all rats except in those receiving both DCA and sodium chloride. Some of these animals had subnormal blood pressures because they were practically

moribund by this time. However, the sole representative of this group which was still in good condition had a mean blood pressure of 154 mm. Hg and the high mean cardiac weight of the animals of this group clearly indicated that at one period or another during the last 5 weeks hypertension had probably also occurred in the other animals.

The mean adrenal and pituitary weight was significantly depressed by DCA in the test groups. This indicates that the well-known compensatory atrophy effect produced by DCA, which consists in diminishing adrenal cortical development caused by inhibition of production of pituitary corticotrophin, is independent of the dietary intake of sodium chloride. The thymus weight varied in all groups and a significant thymus atrophy was observed only in the animals receiving DCA plus sodium chloride. It is doubtful, however, whether this should be considered as showing that the antithymus effect of DCA is conditioned by dietary sodium chloride because atrophy of the thymus is a consequence of any type of stress and the animals in this group were obviously most severely damaged.

The plasma sodium concentration was determined by the micro modification of the method of McCance and Shipp. An extraordinarily high plasma sodium value was obtained in animals receiving DCA plus sodium chloride. In comparison with the corresponding control groups treated with DCA but kept on the diets free of sodium chloride, the increase is highly significant. It is also noteworthy that the mean plasma sodium concentration in the sodium chloride-free control was significantly lower than in the corresponding controls receiving no DCA treatment but kept on a sodium chloride-containing diet. As indicated in earlier publications, by the authors, an increased sodium/chloride ratio is rather characteristic of animals overdosed with DCA while receiving diets which contain normal or high amounts of sodium. However, this is generally the result of a marked decrease in plasma chlorides and is only accompanied by a slight increase in plasma sodium. The unusually marked increase in blood sodium observed in the group receiving DCA may be due to the preliminary sodium depletion of these animals during the first 4 weeks of the experiment.

Previous observations had shown that severe renal hypertension (produced with the endocrine kidney technic) causes the same cardiovascular changes as overdosage with DCA, but there this effect was independent of the sodium intake. It is probable, therefore, that the failure of DCA to cause lesions in the cardiovascular system, in the absence of sodium, is due to its inability to increase the production of renal pressor hormone unless sufficient sodium is available.

These observations are in agreement with that interpretation of the pathogenetic mechanism governing the production of fibrinoid diathesis, according to which DCA acts through the intermediation of the kidney. Presumably this substance increases the production of renal pressor hormones, as a result of the transformation of certain nephrons into endocrine nephrons, but this occurs only in the presence of sodium. On the other hand, excessive production of renal pressor hormone damages the cardiovascular system irrespective of the sodium intake.

In summary it can be said that rats maintained on a sodium-free and chloride-free synethtic diet tolerated otherwise fatal doses of DCA. Sodium

chloride deficiency was also most effective in preventing the renal and cardiac enlargement, nephrosclerosis, myocarditis, hypertension, and periarteritis nodosa normally caused by excessive amounts of DCA; however, it did not prevent the atrophy of the adrenal cortex and pituitary, which results from overdosage with this corticoid. From this, in conjunction with the authors' previously published observation, it is concluded that sodium is essential for the renal, and, through the intermediation of the kidney, for the cardiovascular actions of DCA. (Am. Heart J., June '49, H. Selye et al.)

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Current Morbidity from Diphtheria in the Navy: In general, the incidence of diphtheria in the Navy has been confined to sporadic outbreaks at varying locations. Data have been compiled from the Monthly Morbidity Report (NAVMED-582) for the period since July 1945 on the incidence of this disease in the entire Navy.

In February of the current year the incidence of diphtheria rose to a point higher than at any other time during the period under consideration. The majority of the cases, almost 70 percent, occurred in the first naval district, the cases being almost entirely confined to the activities at Newport, Rhode Island. In March and April of 1949, approximately 86 percent of all the cases were reported from this area.

High peaks in incidence also occurred in April and July of 1946. The great majority of the cases in April 1946 occurred at Great Lakes, Ill., where 23 or approximately 80 percent of the cases occurred. In July 1946, on the other hand, the bulk of the cases were reported from outside the continental limits, 90 percent of all the cases being reported from Alaska.

In the first 4 months of this year there were 29 cases reported whereas for the entire year 1947 there were 19 cases and for 1948 there were 23. (Statistics of Navy Medicine, July '49)

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Nephritis as a Cause of Manpower Loss in the Navy: The decrease in the incidence rates for nephritis during the period from 1936 through 1947 has been discussed in an article in the June 1949 issue of Statistics of Navy Medicine. Statistics presented here on the disposition in these cases have been compiled from the Fa card (Individual Statistical Report of Patient). The data include the diagnoses, nephritis, acute and nephritis, chronic.

One of the features of nephritis, of importance to the Service, is the permanent loss of manpower due to medical discharges (invalidings) and deaths. During the 12 year period 1936-1947 there were 1,441 invalidings from the Service and 206 deaths reported for nephritis. The loss of manpower due to medical discharges was 7 times as great as the loss due to deaths. For the entire 12-year period an average of approximately 13 persons out of each 100,000 in the Navy and Marine Corps were permanently lost for military service due to either medical discharge or death. The rates during the war years (1942-1945) were much lower than for any of the other periods. The highest over-all loss rate occurred during the immediate prewar period (1940-1941). The total rate for deaths and invalidings combined for the postwar years

1946 and 1947 and for the prewar years 1936 through 1939 are approximately the same.

Of the 1,441 invalidings, 1,400 were for chronic nephritis. These 1,400 accounted for 53.6 percent of the discharges from the sick list of all the chronic nephritis patients. For the period as a whole, however, a majority of the deaths, 123 or 59.7 percent, were for acute nephritis.

In addition to the permanent loss of manpower, there is the temporary loss caused by time spent on the sick list. For the 12 years as a whole an average of 6.3 persons out of each 100,000 were continually on the sick list with nephritis. The noneffective rates were higher for chronic than for acute nephritis. This same relationship holds true for average sick days per case. (Statistics of Navy Medicine, July '49)

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Notification of Results of Examination by American Specialty Boards: Following examination by any of the American Specialty Boards, medical officers shall forward two certified copies of the letter received from the Specialty Board notifying them of the results of examination to the Chief of Naval Personnel via the Chief of the Bureau of Medicine and Surgery. (Professional Div., BuMed)

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Training in Industrial Health: A limited number of medical officers of the regular Navy may receive an academic year of instruction commencing in late September 1949 covering the subject of industrial health at the Harvard School of Public Health, Harvard University, Boston, Massachusetts. Those who successfully complete this course will be awarded the newly-established degree, Master of Industrial Health.

The course has been designed to include orientation in the basic disciplines of Public Health with special emphasis on the problems of industrial health and medical care; it encompasses knowledge of occupational hazards, industrial hygiene, sanitation, safety engineering, insurance compensation, placement examinations, labor relations, industrial organization, rehabilitation, disability evaluation, and the assessment of medical needs of organizations.

The course will operate under the direction of the Department of Industrial Health of the Harvard University School of Public Health. Related teaching and research facilities of Harvard University, including certain special facilities at the Massachusetts Institute of Technology and other cooperating institutions, will be available to supplement the instruction.

Requests are desired from interested medical officers of the regular Navy in all ranks and must reach BuMed not later than 1 September 1949 to receive consideration by the Bureau Advisory Board on Postgraduate Education. Each request must contain a service agreement not to resign during the course and to serve for a period of 3 years in the U. S. Navy upon completion of the period of training.

Requests may be made by dispatch if the time element involved requires such action. Dispatch requests must be confirmed by a following official letter. (Professional Div., BuMed)

Convention of the Military Surgeons of the United States Planned to be of Interest to Reserve Medical and Dental Officers: At the meeting of the Association of Military Surgeons of the United States, to be held in Washington on 10, 11, and 12 November, the professional program is being planned so that the last day will be devoted entirely to the problems of officers of the Reserve of the Medical and Dental Corps of the Army, Navy, and Air Force. On that day the meeting will be conducted by Captain Wendell Scott, MC, USNR, of St. Louis, Missouri. It is planned that the Director of the Medical Corps Reserve Section in BuMed and the Director of the Dental Corps Reserve in BuMed will speak at the meeting and present information concerning the present situation and future plans. Following the presentation of these papers the remainder of the meeting will be devoted to answering questions submitted by members of the Association who will attend the convention.

The guest speakers scheduled for this convention are all eminent, and authorities in their individual fields. Because many members of the association throughout the country have signified their intention to attend the convention, it is suggested that those who have not yet made hotel reservations write to Captain R. L. Ware, MC, USN, Reservation Chairman, at the Bureau of Medicine and Surgery, Navy Department, Washington 25, D. C.

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Course in Medical Aspects of Special Weapons and Radioactive Isotopes Available to Reserve Medical Officers: The Bureau of Medicine and Surgery announces the establishment at the Naval Medical School, National Naval Medical Center, Bethesda, Md. of two courses of instruction for inactive medical officers of the Naval Reserve in medical aspects of special weapons and radioactive isotopes. The first course is to commence on 26 September 1949, and will continue through 1 October 1949. The second course is to commence on 10 November 1949, continuing through 19 November 1949.

The speakers scheduled are outstanding men in their respective fields, hence an interesting and informative course is assured.

Inactive medical officers of the Naval Reserve who desire to attend one of these courses should submit a request for training duty to the commandant of their naval district. Requests for the September course should reach the commandant's office not later than 29 August 1949. Requests for the November course should reach the commandant's office prior to 15 October 1949.

The facilities at the National Naval Medical Center make it necessary to restrict the number in attendance for each course to 210. District quotas will be established by the Bureau of Naval Personnel. A limited number of sleeping quarters will be available at the National Naval Medical Center to those who wish such accommodations. Full messing facilities will be available. (Reserve Div., BuMed)

Correspondence Courses Administered by the Bureau of Medicine and Surgery for Regular and Reserves, Officers and Enlisted: The following correspondence courses are now available for distribution and may be obtained from the Bureau of Medicine and Surgery by qualified personnel upon request:

Title of Course	Promotion Units	Retirement Points	Eligible Personnel
Clinical Laboratory Procedures	3	36	MC, DC, MSC, NC, HC (officers and enlisted)
Special Clinical Services - General	2-1/2	32	MC, DC, MSC, NC, HC (officers and enlisted)
Tropical Medicine in the Field	2-1/2	32	MC, DC, MSC, NC, HC (officers only)
Combat and Field Medicine Practice	2-1/2	32	MC, DC, MSC, NC, HC (officers only)

All officers of the Medical Corps, Dental Corps, Medical Service Corps, Nurse Corps, and Hospital Corps of the regular Navy and Naval Reserve are eligible to enroll in any one of the above listed courses. Enlisted personnel of the Hospital Corps are eligible to enroll for the Clinical Laboratory Procedures course and for the Special Clinical Services - General, course.

Application for enrollment should be made to the Bureau of Medicine and Surgery via appropriate official channels and may be made either on NavPers-992 (application for enrollment in officer's correspondence courses), or by letter request. Applications must include the full name of the applicant, rank or rate, corps, file or service number, and the address to which the material is to be forwarded.

Members of the Medical Department may enroll in only one of these courses under the sponsorship of the Bureau of Medicine and Surgery at a time. This does not preclude simultaneous enrollment in one of the correspondence courses administered by the Bureau of Naval Personnel if the individual desires to do so. Additional correspondence courses are now in process of preparation by the Bureau of Medicine and Surgery; announcement of their availability will be made from time to time. (Reserve Div., BuMed)

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Disposition of Standard Form 88 (Report of Medical Examination) and Health Records, Upon Discharge of USNEV Personnel: In connection with

BuPers C/L 111-49 of 7 July 1949, which appears as 49-496 in the Navy Department Bulletin of 15 July 1949, the following instructions relative to the disposition of Standard Form 88 (Report of Medical Examination) and terminated health records are effective upon discharge of USNEV personnel:

A. Discharge and transfer to the U. S. Naval Reserve. The physical examination is to be conducted on the actual date of discharge from the Service and recorded on Standard Form 88 (in duplicate) on which an additional entry shall be made in the upper right hand corner showing to which naval district the records have been forwarded. The health record is to be terminated, and NAVMED H-2, NAVMED H-4, and all NAVMED H-8's removed therefrom. The original Standard Form 88 is to be folded lengthwise. The sheets removed from the health record shall be placed in chronological sequence with NAVMED H-2 uppermost, stapled together with the original Standard Form 88 at the bottom, and then forwarded to the Bureau of Medicine and Surgery. A NEW HEALTH RECORD SHALL NOT BE OPENED. The remainder of the health record (minus NAVMED H-2, NAVMED H-4, and NAVMED H-8's) with a copy of Standard Form 88 folded between the health record cover, shall be forwarded with the service record to the Commandant of the cognizant naval district.

B. Discharge without transfer to the U. S. Naval Reserve. The physical examination is to be conducted on the actual date of discharge from the Service and recorded on Standard Form 88. The health record is to be terminated, and the cover is to be removed and destroyed. The original Standard Form 88 is to be folded lengthwise, placed at the bottom of the terminated health record which has been arranged in chronological order with NAVMED H-2 uppermost, stapled together, and then forwarded to the Bureau.

C. Reenlistment in the regular Navy on the date immediately following the effective date of discharge. The physical examination for discharge and reenlistment shall be conducted on the actual date of discharge from the Service and recorded on Standard Form 88. The old health record shall be terminated, and NAVMED H-2, NAVMED H-4, and all NAVMED H-8's removed. A new health record shall be opened and dated the day following discharge. The duplicate copies of the new NAVMED H-2, NAVMED H-4, and NAVMED H-8's shall be placed on top of the old NAVMED H-2, NAVMED H-4, and NAVMED H-8's, followed by the original Standard Form 88 which has been folded lengthwise, stapled together, and then be forwarded to the Bureau of Medicine and Surgery. (PQ and MR Div., BuMed)

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BUMED CIRCULAR LETTER 49-84 6 July 1949

To: All Holders of the Manual of the Medical Department

Subj: Report of Board of Medical Survey, NAVMED-M (Rev. 5-45); Modification of

1. Until such time as the NAVMED-M is revised, the following modifications shall be made whenever subject forms are used:

A. Front of form. In lieu of present "from" and "to" lines, substitute:

FROM: Board of Medical Survey.
TO: Bureau of Medicine and Surgery.
VIA: Commanding Officer

B. Back of form. Immediately under the third set of double lines, insert the word, ENDORSEMENT.

--BuMed. C. A. Swanson

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BUMED CIRCULAR LETTER 49-85 8 July 1949

To: All Ships and Stations

Subj: Epidemic Disease Control Units and Malaria and Mosquito Control Units; Missions of

Ref: (a) SecNavLtr Serial 15P24 dtd 10 Mar 1949; ND Bul of 15 Mar 1949, 49-145.

This letter, a copy of which is contained in the Navy Department Bulletin of 15 July 1949 states that the Chief of Naval Operations has approved the mission as set forth for Epidemic Disease Control Units and Malaria and Mosquito Control Unit established by reference (a) and directs strict compliance with these functions by each unit.

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BUMED CIRCULAR LETTER 49-86 12 July 1949

To: Commandants, All Naval Districts (less 10, 15, and 17) and Commandant, Potomac River Naval Command

Subj: Dental Commissioning Allowance List for Use by Naval Reserve Dental Officers Performing Appropriate Duty; Instruction for Obtaining

Ref: (a) BuPers ltr Pers-1D9-be, Serial F: 743, dtd 29 April 1949.
(b) BuMed C/L No. 47-100, dtd 4 August 1947.

Encl: 1. (HW) Enclosure (1) of reference (b).

1. Reference (a) authorized and requested Commandants to order dental officers of the Naval Reserve, not on active duty or in drill pay status, to perform appropriate duty with pay with their consent, subject to certain limitations.

2. The dental commissioning allowance listed in reference (b), enclosure (1), should be procured by Naval Reserve Training Center for use by Reserve dental officers who are ordered to perform "appropriate duty" when other adequate dental equipment is not available. --BuMed. C. A. Swanson

Note: Enclosure consists of one page listing 9 commissioning allowance items.

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BUMED CIRCULAR LETTER 49-87 13 July 1949

To: All Stations

Subj: Insecticide Aerosol for Use on Naval Aircraft

Refs: (a) General Order No. 7, dtd 26 Aug 1947 Quarantine Regulations for Naval Aircraft
(b) BuMed Circ. Ltr. 48-36, dtd 24 Mar 1948 Disinsectization of Naval Vessels and Aircraft
(c) FSA, PHS, Ltr. to Air Line Medical Directors and others concerned, dtd 28 Mar 1949
(d) Navy Dept. Specn 51-I-5, dtd 15 Feb 1949

1. References (a) and (b) direct that naval aircraft be disinsectized just prior to departing from airports where insect vectors of disease are present. Basic requirements contained in the Public Health Service Foreign Quarantine Manual of Operations have been modified by reference (c) effective 1 July 1949, to require disinsection by aerosol containing both a stronger pyrethrin content and DDT as well.

2. All bombs procured during the war years originally contained pyrethrum-sesame oil insecticide without DDT. A new Navy specification reference (d)

consisting of both pyrethrins and DDT has been and is now being used to refill those bombs which are refillable. Standard Stock Item No. 51-C-2031-25, forty pound charging cylinders, contains this formula. Refilled bombs will contain this DDT aerosol mixture and will be marked accordingly.

3. Although this formula contains DDT, it is not quite up to the requirements of reference (c) in pyrethrin strength. Accordingly an adjustment of dosage has been authorized by the Public Health Service for Navy use until such time as universal standardization can be effected, and Navy specifications and procurement schedules modified. When Navy formula, reference (d) is used the dosage for aircraft shall be at the rate of 6 Gm. per 1000 cubic feet instead of the 5 Gm. dosage heretofore required in paragraph 2 of reference (b). This means 6 seconds of application instead of 5 seconds.

4. In the event, that aerosol insecticides that meet the specifications of reference (d) are not available, refilled bombs may be procured at the nearest refilling facility, locations of which are as follows:

USNSD, Bayonne, New Jersey
USNSD, Great Lakes, Illinois
USNSD, Mechanicsburg, Pennsylvania
USNSD, Newport, Rhode Island
USNSD, San Diego, California
USNSD, Seattle, Washington
USNSC, Oakland, California
Charleston Naval Shipyard, Naval Base, South Carolina
New York Naval Shipyard, Brooklyn 1, New York
San Francisco Naval Shipyard, San Francisco, California
Puget Sound Naval Shipyard, Bremerton, Washington
USNSC, Guam, Marianas Islands
MCAS, Cherry Point, North Carolina

--BuMed. H. L. Pugh

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BUMED CIRCULAR LETTER 49-88 14 July 1949

To: All Ships and Stations

Subj: Medical Administrative Technic - Establishment of Hospital Corps Specialization Course in.

Ref: (a) Catalog of Hospital Corps Schools and Courses - Revised 1944 (NAVMED-367).

Encl: (A) Copy of Curricula and Prerequisites for Assignment to Subject Course of Instruction.

1. A specialization course of instruction in Medical Administrative Technic for enlisted personnel of the Hospital Corps has been established at the U. S. Naval School of Hospital Administration, NNMC, Bethesda, Md., and shall be made a part of reference (a). The curriculum and prerequisites for assignment to this instruction are contained in Enclosure (A), and will be incorporated in the next revision of the Catalog of Hospital Corps Schools and Courses.

2. The purpose of establishing this course is to provide a more comprehensive curriculum of instruction in Medical Department administrative procedures primarily with a view toward increasing the general proficiency of enlisted Hospital Corps personnel in the two upper rating groups, and secondarily to provide an advanced step in the career program for the Hospital Corps in qualifying for eligibility for promotion.

3. It is not intended that completion of this course will be made a mandatory prerequisite for future consideration for appointment to higher grade in either the Hospital Corps or Medical Service Corps. Assignments to this instruction will be on Bureau quota orders to major administrative commands similarly as with assignments to other courses of Hospital Corps technical instruction.

4. The course will cover a period of nine months and classes will convene normally once each year in September. Assignments currently are restricted to Chief Hospital Corpsmen and Hospital Corpsmen First Class.

5. Students who successfully complete the course of instruction will be awarded a Certificate of Graduation and designated "Medical Administrative Technician." Assignments to duty thereafter, insofar as practical, will be made to fill vacancies in naval activity allowances for Medical Administrative Technicians, and in such other billets as indicated.

6. This course of instruction does not supersede nor cancel curricula currently in effect under the separate subjects of Clerical Procedures (CLT), Property and Accounting (PAT), or Commissary Technic (CMT).

7. Requests for designation as Medical Administrative Technician (MAT) from Hospital Corps personnel in the ratings of Chief Hospital Corpsmen and Hospital Corpsmen First Class who previously have completed the Hospital Corps Officers course of instruction in Medical Administrative Procedures at the U. S. Naval School of Hospital Administration, NNMC, Bethesda, Md., and from others of similar ratings who are considered by the Medical Officer to have had equivalent training and experience in the subjects outlined in Enclosure (A), should be addressed to the Chief of Naval Personnel via the Bureau of Medicine and Surgery for appropriate action.

8. This procedure is in accordance with the Navy Personnel Accounting System and the "Manual of Enlisted Navy Job Classifications." --BuMed. C. A. Swanson

Note: A copy of this letter with the enclosure appears in the 15 July 1949 Navy Department Bulletin.

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Op24B/cj, Serial 237P24 21 June 1949

To: All Ships and Stations

Subj: Redesignation of Naval Medical and Dental Activities

1. The following medical and dental activities are hereby redesignated:

From:	To:
Inspector of Dental Activities, USN East Coast Federal Office Bldg. 90 Church St. New York 7, N. Y. 3595-550	Inspector, Naval Dental Activities Atlantic Coast Federal Office Bldg. 90 Church St. New York 7, N. Y. 3595-550
Inspector of Dental Activities, USN West Coast 50 Fell St. San Francisco 2, Calif. 3595-750	Inspector, Naval Dental Activities Pacific Coast 50 Fell St. San Francisco 2, Calif. 3595-750
U. S. Navy Inspector, Medical Department Activities Pacific Coast Hdqtrs. Western Sea Frontier Treasure Island San Francisco, Calif. 3620-750	Inspector, Naval Medical Activities Pacific Coast Hdqtrs. Western Sea Frontier Treasure Island San Francisco, Calif. 3620-750

2. Bureaus and offices concerned take necessary action.

--SecNav. Francis P. Matthews

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ALSTACON 151545Z 15 July 1949

Subj: Status in Case of Reserves Who Suffer Disability or Death While on Active Duty

Public Law 108 81st Congress, approved 20 June provides in part that all officers, nurses, warrant officers, and enlisted men of the United States Naval Reserve or United States Marine Corps Reserve, who (a) if called or ordered into active naval or military service by the Federal Government

for extended naval or military service in excess of 30 days, suffer disability or death in line of duty from disease while so employed or (b) if called or ordered by the Federal Government to active naval or military service or to perform active duty for training or inactive-duty training for any period of time, suffer disability or death in line of duty from injury while so employed shall be deemed to have been in the active naval service during such period, and they or their beneficiaries shall be in all respects entitled to receive the same pensions, compensation, death gratuity, retirement pay, hospital benefits, and pay and allowances as are now or may hereafter be provided by law or regulation for officers, warrant officers, nurses, and enlisted men of corresponding grades and length of service of the regular Navy or Marine Corps.

The provisions of this act shall be effective from 14 August 1945.

It is noted that this law extends to Reservists injured while in training duty status the rights and benefits heretofore provided for those ordered to extended active duty in excess of thirty days with right of election as to benefits if entitled to pension or compensation from other agencies under applicable laws.

Implementing regulations will be published when developed and approved. Pending their receipt no action other than publicity is desired. --SecNav.

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NAVY DEPARTMENT
BUREAU OF MEDICINE AND SURGERY
WASHINGTON 25, D. C.

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