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A New Drug in the Treatment of Radiation Sickness: The parallelism between the lassitude, nausea and vomiting, anorexia, and malaise of seasickness and airsickness, and those of radiation sickness suggested the use of dramamine in radiation sickness. Also, because dramamine has a definite antihistaminic action (benadryl plus 8-chlorotheophyllin - designed to eliminate drowsiness) it was felt that its use would be of benefit if histamine toxicity were an etiologic factor as postulated by Ellinger and co-workers and by Lofstrom and Nurnberger. The latter authors used benadryl in this condition with good results.

This is a preliminary report of the authors' experience with 82 patients who had radiation sickness in either moderate or severe degree. Marked nausea was present in every case and vomiting was present in 53 cases. Each patient was seen every day immediately before or after treatment and the complaints and general condition of the patient, as well as the side effects of the drug, if any, were noted. At the completion of the series of roentgen treatments the results were tabulated as excellent, when there was cessation of vomiting, decided relief of nausea and prostration, and no other evidence of radiation sickness; as good, when vomiting had been eliminated but an occasional bit of nausea persisted; as fair, when symptoms were reduced but nausea and vomiting were present in sufficient degree to produce mild discomfort; and poor, when only slight or no relief was obtained.

Accurate evaluation of any therapeutic agent in radiation sickness is very difficult because it must be based mainly on the report of the patient. Most of the patients had conditions of a malignant nature which tended to conceal the degree of pure radiation sickness.

A control series of 23 patients was run, the patients in this group believing that the therapeutic drug was being administered. Radiation sickness was present in every instance prior to the starting of the placebo. The placebo was continued for at least 4 days or until it was obvious that further continuation of the placebo in the face of severe radiation sickness would necessitate cessation of roentgen treatment. With this comparatively small group thus treated, the results showed that the percentage of apparently good or excellent results was much higher in the group receiving dramamine, namely 79 percent as compared to 13 percent in the group receiving placebos.

The dosage was varied in the beginning of the series in order to determine the most effective therapeutic plan. Maximal effectiveness was obtained when dramamine in the amount of 100 mg. was given from 30 to 60 minutes before treatment, and repeated one and one-half hours after treatment and again in 3 hours, making a total of 300 mg. Some patients required a total dosage of only 200 mg., others needed 400 mg. In 4 of the patients classified as having a poor result, there was failure to retain and absorb the tablets because of

intervening vomiting. This might possibly have been eliminated by giving the drug rectally, although this was not attempted in any case in this series.

There were certain side reactions, as shown in the table below, associated with use of the drug. Several of the patients complained of more than one side reaction or distressing feature, but the proportion of such patients was small. Drowsiness was an objectionable feature in a few instances and 3 patients in the series declined to take the tablets after from 3 to 4 days of continued sleepiness. It should be mentioned that several of the patients receiving only the placebo complained of dizziness and drowsiness due, no doubt, to the effects of the roentgen therapy or their own poor nutritional state. In 6 of the patients in whom the symptoms were controlled by the dramamine, the placebo was substituted for the dramamine without the patients' knowledge and all had recurrence of symptoms, with subsequent control in each instance upon resumption of the use of dramamine. In those patients with the most severe degree of nausea and vomiting, especially when the epigastric fields were treated, a combination of intravenously administered pyridoxine (200 mg.) and dramamine in the dosage already mentioned, gave better results than either drug alone. (Proc. Staff Meet. Mayo Clin., 14 Sept. '49, J. W. Beller et al.)

Side Effects on 82 Patients Treated With Dramamine

Complaint	Cases
Drowsiness	15
"Bad taste"	8
Paresthesias	2
Nausea	1

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Staphylococcal Cross-Infection: The first advance in the classification of the staphylococci was the recognition that all potentially pathogenic strains, whether or not they produced golden-brown pigment, were capable of coagulating human plasma; but in the search for the source of outbreaks it was found that from 40 to 50 percent of contacts carried coagulase-positive staphylococci in the nose and upwards of 20 percent on the hands. It was therefore necessary to subdivide pathogenic staphylococci as Griffith had done with Lancefield group-A streptococci. This has been attempted, and in large part accomplished, by both serological and phage typing. These technics, which require much care and experience, are still being used in only a few laboratories; but already they are yielding results of great significance. It has been established that skin carriers of staphylococci are usually persistent nasal carriers of the same type, and that the skin is most probably contaminated from the primary focus of colonization in the squamous epithelium of the nasal vestibule, although the occasional heavy skin carrier, and the profuse growth of staphylococci from healing scars, suggest that the hands may sometimes be the focus and not merely the vehicle for disseminating the organism. With superficial staphylococcal lesions like sycosis barbae, boils, and infected wounds, the staphylococcus is often derived from the nose or skin of the patient himself, and sterilization of the

nasal vestibule or the skin surrounding a wound helps to prevent the occurrence or recurrence of such infections.

Different workers have found that from 40 to 60 percent of staphylococci from hospital cases are resistant to one or more units of penicillin, and that a similar high rate of resistant strains prevails in nasal carriers among the hospital staff, whereas the incidence of resistant staphylococci in the general community is still around from 5 to 10 percent. In the hospital cases cultures were sometimes obtained from the lesion after penicillin had been used; so the resistant strain may have been present in small numbers from the onset. However, Rountree and Thomson report from Sydney that of 91 hospital patients infected with penicillin-resistant staphylococci, the organism was derived from an outside source in at least 54, and that only 8 patients out of a total of 196 had primary infections with penicillin-resistant strains. Both the Australian workers and Barber and Whitehead have found that most penicillin-resistant hospital strains belong to 2 phage types, although the sensitive staphylococci are distributed among many different types, a finding which substantiates the view that staphylococcal infections in hospitals are mostly cross-infections with the prevalent types.

The next step was to trace the mode of spread, and a pointer is the close correspondence, found by Rountree and Thomson, between the phage types in the noses of the staff and in the lesions of the cross-infected patients. The high nasal-carrier rate of the epidemic strains among them may simply reflect a staphylococcus-contaminated environment in which ward-dust and bed-linen may be important reservoirs and the air a means of dissemination. It seems likely, although apparently this was not investigated, that a fair number of the patients were also nasal carriers of the prevalent types and may themselves have infected their various lesions. The data so far indicate that staphylococcal cross-infection may be common in hospitals and call for better standards in medical and nursing practice. Casualty departments, surgical and maternity units, and the ear, nose, and throat wards are those most vitally concerned. (Lancet, 17 Sept. '49)

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Serologic Relationships of Mumps and Newcastle Disease: The presence of neutralizing and antihemagglutinating factors against Newcastle disease virus (NDV) in half of a group of patients convalescing from mumps suggests a possible relationship between the 2 viral agents. These cross-reacting factors were first observed in the course of an outbreak of mild meningoencephalitis, suggestive of Newcastle disease because the epidemiologic and clinical findings fitted descriptions by Howitt et al. of a disease in man which led to the formation of NDV neutralizing antibodies. Paired sera from patients with mild cases of meningoencephalitis showed little or no rise of neutralizing

capacity against NDV, but a few pairs of mumps sera included as controls exhibited a sharp rise against this virus. Accordingly neutralization tests and calculation of neutralization indices of mumps sera were made by methods similar to those described by Howitt et al. The California strain No. 11,914 of NDV was employed throughout. Twenty-two patients with mumps were studied, along with 23 control patients, 17 from the outbreak of mild meningoencephalitis, and 6 having a clinical diagnosis of nonparalytic poliomyelitis. Thirteen of the mumps patients developed neutralization indices over 250, 10 having indices of 1,000 and above, whereas only 3 of the sera from control patients showed neutralization indices over 250 and none went over 800. Antihemagglutination tests with mumps sera against NDV likewise demonstrated serologic relationships. Seven of 20 pairs of heat-inactivated mumps sera showed a rise of from 4- to 64-fold of titer between the acute and convalescent phases. Four others showed titers of from 1:64 to 1:256 in convalescent phase sera, titers well above those encountered in 20 pairs of sera from the control group of patients, none of which showed a rise of antihemagglutinating capacity against NDV. In addition to confirmatory epidemiologic and clinical findings, all of the patients showed evidence of recent mumps infection by complement fixation or by antihemagglutination tests, using the Enders strain of mumps virus. Mumps virus was isolated from the saliva or spinal fluid of 11 patients.

The positive results obtained in 2 types of serological tests against NDV in the sera of patients experiencing infection with mumps virus suggests that a diagnosis of Newcastle disease in human beings should be made with caution, especially in the absence of virus isolation. Only 5 cases of human infection with NDV, with mild conjunctivitis in each, have been known to be so confirmed. The presence of neutralizing and antihemagglutinating factors against NDV in convalescent phase mumps sera is difficult to interpret. The reactions may be due to nonspecific serum factors arising as a result of infection rather than to specific antibodies. If the factors are actually antibodies, their presence would support the hypothesis that NDV and mumps virus are closely related. Burnet first presented evidence for this in his work on receptor gradients. Kilham has recently shown that NDV has a hemolytic activity closely resembling that demonstrated by Morgan, Enders, and Wagley for the mumps virus. Further studies are needed to elucidate the full meaning of serologic and other relationships which appear to exist between NDV and mumps virus. (Science, 30 Sept. '49, E. Jungherr et al.)

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Antihistamines in Nausea and Vomiting Induced by Pregnancy or by Administration of Synthetic Estrogens: In previously published research, the author has recorded considerable proof that the nausea and vomiting of early pregnancy are due to an allergic reaction of the patient to the secretion of her own gravid corpus luteum. He has also shown that the nausea and vomiting

which occur following the administration of diethylstilbestrol represent an allergy and are similar to, if not identical with, the nausea and vomiting of pregnancy, occurring in the same individuals who have had nausea and vomiting of pregnancy and in the same degree.

Of a group of 29 patients with nausea and vomiting of pregnancy, 18 were treated with benadryl and 11 were treated with histadyl. Twenty-seven patients were completely relieved, one was improved, and one was unimproved.

Three of the cases were classified as plus 4 (pernicious vomiting). These patients were tertigravidas, one aged 24 years, one 29, and one 32. One woman, at about 8 weeks' gestation, had been vomiting almost all ingested food and fluid for 2 weeks. Intravenous benadryl in doses of 50 mg. every 3 hours did not alter her course any appreciable amount, although she was given, in addition, intravenous glucose and saline solution, pyridoxine hydrochloride, thiamine, and adequate sedation. She continued to vomit until she aborted 5 days later. The other 2 patients, each at about 6 weeks' gestation, had been nauseated 8 or 10 days and vomiting incessantly for 2 days. They stopped vomiting within 24 hours with 50 mg. benadryl intravenously every 4 hours and were then maintained symptom-free with 100 mg. orally 4 times a day. After 5 days this dosage was reduced to 50 mg. orally 3 times daily until they were well into the fourth months of pregnancy, when it was discontinued. In their sixth month of pregnancy they were still progressing normally. Eight cases were classified as plus 3 (nauseated all day long and vomiting 3 or 4 times daily). These patients were given 50 mg. of benadryl intravenously 4 times the first day, which stopped the vomiting in each case, and then 100 mg. benadryl or histadyl orally 3 times a day until all nausea ceased, at which time they were instructed to reduce the dose gradually as their symptoms permitted; most of them were able to reduce the dosage to 50 mg. twice daily within a 10-day period and keep symptom-free on that small dosage, leaving it off entirely by the time they entered their second trimester. Twelve cases, at about 6 or 7 weeks' gestation, were classified as plus 2 (nauseated all day long and vomiting from none to 2 times daily). These patients were given benadryl or histadyl in 50 mg. doses 3 times a day and told to double the dose if they needed it. Eleven were totally relieved within 3 days. The other patient was partially relieved but an increase in the dose caused dizziness and drowsiness of which she complained more than the nausea. She was tried on both drugs but the side effects were the same. She was given 100 mg. pyridoxine hydrochloride intravenously 3 times a week for 2 weeks following which time she was placed on 50 mg. histadyl at bedtime and after 3 weeks of this therapy, having been maintained symptom-free except for occasional morning nausea, the drug was discontinued. Six cases, at from 4 to 7 weeks' gestation, were classified as plus 1 (severe morning nausea without vomiting). All 6 of these patients were totally relieved within 24 hours by 50 mg. histadyl or benadryl morning and night and after a week were able to reduce the dosage to 50 mg. at bedtime for

another week and then were told to take it only as their symptoms indicated. Five were able to discontinue the drug entirely and the sixth patient found the 50 mg. at bedtime necessary for relief.

Because it had been shown that the nausea and vomiting caused by the synthetic estrogens, especially diethylstilbestrol, are also allergic in nature, it was believed that the antihistaminic compounds also should prevent such nausea and vomiting.

Eleven patients, known to have severe vomiting after the ingestion or injection of ordinary doses of diethylstilbestrol and 10 patients known to be allergic to hexestrol were given antihistaminic compounds with each dose of estrogenic drug and in each case a full therapeutic dose of the estrogen was tolerated with no side effects. One patient, a nullipara, aged 29 years, has been under observation for several years because of severe metrorrhagia. This woman is very allergic to progesterone, developing large bullous hives following its administration. She has a plus 4 skin reaction to intradermally injected natural corpus luteum extracts. Both diethylstilbestrol and hexestrol in ordinary doses cause severe nausea and vomiting, although these 2 drugs in large doses, apparently by dilating the spiral arterioles of the endometrium, check her severe hemorrhaging promptly. They have been used repeatedly, during the past several years, to prevent the frequent need for currettage, even though the nausea they induce is most severe. Upon the last hospital admission this patient was bleeding severely. Ten mg. diethylstilbestrol were given parenterally and repeated in 3 hours. With the first dose, 100 mg. benadryl were given orally and repeated at 4-hour intervals. Menstruation was checked markedly within a few hours and the patient was then given 18 mg. hexestrol and 300 mg. benadryl daily (orally) for the following 3 days by which time bleeding had ceased. During the entire time from admission to cessation of flow the patient experienced absolutely no nausea or vomiting, much to her surprise, for she was not advised of any change in medication from that given during previous periods of hemorrhaging. Seven days before her next menstruation was due this patient was given 10 mg. progesterone in oil and 150 mg. benadryl daily for 5 days. Two days later she had a normal type menstruation but had no hives for the first time with such therapy.

Six other patients in this series, with the menopausal syndrome, all multiparas, varying in age from 42 to 49 years, all having experienced severe nausea and vomiting with pregnancies and all having had previous nausea from diethylstilbestrol, were given 1 mg. diethylstilbestrol and 150 mg. antihistaminic compound (3 patients treated with benadryl and 3 with histadyl) daily. Each patient was relieved of her varied menopausal symptoms and none of the 6 had any nausea from the estrogen. Four other patients, aged from 17 to 19 years, each a virgin with severe dysmenorrhea, were given 2 mg. stilbestrol and 150 mg. benadryl daily to suppress ovulation and thus obtain a painless anovulatory

menstruation. This had been tried previously but the nausea from the estrogenic drug was so intense that it had to be withdrawn. With the addition of the antihistaminic there was no nausea experienced and each patient was given a painless withdrawal-type bleeding for 3 consecutive months while this treatment was being employed.

In another series of 10 patients, who had been previously unable to take hexestrol because of nausea, one woman, aged 26 years, who had had severe nausea with her one pregnancy 7 years before, was given 6 mg. hexestrol daily for secondary amenorrhea but was severely nauseated by it. She volunteered to take hexestrol with histadyl experimentally to see if it would prevent the nausea. She was given 200 mg. histadyl daily and was able to take as much as 18 mg. hexestrol daily without any nausea. After this experimental dosage, the drug was reduced to 3 mg. twice daily which she was able to take without any side effects as long as she continued 50 mg. histadyl twice daily. Five nulliparas, aged from 19 to 24 years, who had previously been unable to take hexestrol for their dysmenorrhea, were all able to tolerate 18 mg. daily without nausea as long as they were given from 150 to 200 mg. antihistaminic compound. Four women, from 45 to 49 years of age, all with previous nausea and vomiting from pregnancy and from hexestrol, were able to tolerate 3 mg. of this drug daily, which was adequate for relief from their menopausal symptoms, as long as they were given 50 mg. of either histadyl or benadryl with the hexestrol.

Results using benadryl or histadyl were equally good, several patients being given both drugs at different times. A few patients complained slightly more of drowsiness or dizziness from benadryl when it was first started but within 2 or 3 days they developed a tolerance to it. To prevent any side effects from the antihistaminics, the author now starts the patient with 50 mg. of the drug at bedtime, then has her increase the dose by 50 mg. each day until her symptoms are relieved. In this way the dosage is kept to a minimum and the side-effects are almost totally prevented. (Am. J. Obstet. and Gynec., Sept. '49, J. W. Finch)

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Control of Stilbestrol Vomiting: Use of diethylstilbestrol has been hampered by the side effect of nausea and vomiting. Other estrogenic drugs are satisfactory in treatment of the menopause, but in therapy of the functional ovarian disorders in younger women stilbestrol (as it is commonly called) remains valuable. It is economical in the large doses required and apparently more beneficial than some of the other drugs. The author has had excellent results in treating patients with menorrhagia, pelvic pain, and cystic ovaries with 5 mg. doses of stilbestrol. A survey of 107 such cases was published in 1945. The findings in a second series of 86 cases were published recently. In the first series, 50 percent had some nausea and 9.3 percent had to stop the drug because of vomiting.

Because of the similarity of this nausea and vomiting to that seen in pregnancy, it was decided to use the drug which has been so successful in treatment in the vomiting of pregnancy. A single dose of from 50 to 100 mg. of pyridoxine was given intravenously to all patients who complained of severe nausea or of vomiting after starting the 20-day oral course of 5 mg. stilbestrol daily. Twenty of the 86 patients requested pyridoxine. This is higher than the 9.3 percent of the control series who could not take the drug, but some of these 20 patients could have continued to take the drug despite their discomfort, had pyridoxine been withheld. Three, or 3.5 percent of the 86 continued to vomit after the pyridoxine when they resumed taking the stilbestrol. This compares with the 9.3 percent of the control series who discontinued stilbestrol because of vomiting.

As a second control group, 18 pregnant women to whom vomiting was quite troublesome were given from 50 to 100 mg. pyridoxine intravenously. Fourteen obtained relief and 4 were unrelieved. This is very similar to the treatment in the stilbestrol induced vomiting cases described above in which 17 were relieved and 3 were not.

In summary, it appears that the use of 100 mg. pyridoxine intravenously will reduce by two thirds the number of patients who are unable to take stilbestrol because of vomiting. (Am. J. Obstet. and Gynec., Sept. '49, G. D. Patton)

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Crystalline Toxic Factor from Agenized Flour: Mellanby's discovery that flour prepared with nitrogen trichloride (agene) can cause canine hysteria has been followed by an intensive investigation of its possible adverse effect on man. This study has so far brought to light no substantial evidence that it harms man, but workers have been hampered by their ignorance of the responsible factor.

Moran found that this factor was associated with the protein fraction of flour, and now he and his colleagues at the Cereals Research Station appear to have isolated the factor itself. This is a crystalline material, giving a constant atypical ninhydrin reaction. Twice recrystallized from aqueous ethanol, the material retains the same degree of toxicity. The needle-like crystals melt sharply with decomposition at 232° C. A preliminary qualitative test has revealed an appreciable sulfur content. Identical crystals have been prepared from separate batches of agenized flour, but have been absent from unagenized flour treated as for the isolation of the crystals. The substance is highly toxic to rabbits, in which it produces convulsive fits. (Lancet, 17 Sept. '49, Annotation)

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Studies on the Relation of Pituitary-Adrenal Function to Rheumatic Disease: During the past few years it has become increasingly evident that the adrenal cortical hormones exert a marked influence on a wide variety of metabolic processes in man. The over-all effects exerted by these hormones may be divided into 3 general groups: (1) an electrolyte-regulating effect; (2) the regulation of the rate of utilization of carbohydrate, protein and fat; and (3) an androgenic and anabolic effect.

Electrolyte-Regulating Effect of Adrenal Cortical Steroids. This is characterized by urinary retention of sodium and chloride, increased excretion of potassium, increased plasma and extracellular fluid volume. It has also been shown that desoxycorticosterone-like steroids decrease the concentration of sodium and chloride in sweat. The most potent electrolyte-regulating adrenal steroid is 11-desoxycorticosterone, which has been synthesized. The 11,17-oxysteroids (Compounds E and F) exert a relatively weak sodium-retaining effect.

Unfortunately, there is no direct method for the measurement of circulating salt hormone. Therefore, the activity of such steroids must be estimated indirectly, by changes in the renal excretion of sodium, chloride and potassium, by alteration in the mineral composition of thermal sweat and by changes in hematocrit and body weight.

Regulation of Intermediary Metabolism by 11-Oxysteroids and 11,17-Oxysteroids. The second group of metabolic activities modified by the adrenal cortex involves the regulation of carbohydrate, protein and fat utilization, control of lymphoid tissue and circulating eosinophils. The administration of this type of compound is characterized by the following effects:

1. An increase in blood glucose level and liver glycogen stores.

2. An increased conversion of protein to carbohydrate (increased gluconeogenesis). Recent studies indicate that this effect is accomplished, not by an increased catabolism of body protein, but rather by diverting amino acid radicals to pyruvic acid and glucose (antianabolic effect).

3. An increased mobilization of depot fat and its enhanced utilization, thus sparing carbohydrate. An increased intestinal absorption of fat has been observed after the administration of this group of steroids, and although relatively unimportant calorically, it is of theoretical interest.

4. An increase in the renal clearance of uric acid, resulting in the excretion of large quantities of urate, both in normal subjects and in patients with gout.

5. A lysis of fixed lymphoid tissue and a transitory decrease in circulating lymphocytes. A somewhat more permanent effect is observed on the

circulating eosinophils, which almost completely disappear from the blood during the period of action of the hormone.

Examples of the carbohydrate-regulating adrenal cortical steroids or S hormone are the 11-oxysteroids, Kendall's Compounds A (11- dehydrocorticosterone) and B (Corticosterone) and the much more active 11,17-oxysteroids, Kendall's Compounds E (17-hydroxy-11-dehydrocorticosterone) and F (17-hydroxycorticosterone). The effects on lymphoid tissue and eosinophils are exerted only by the 11,17-oxysteroids. In all but electrolyte effects, the latter substances are superior to the 11-oxysteroids and to 11-desoxycorticosterone. Although the salt-retaining effect of the 11,17-oxysteroids is approximately one thirtieth that of 11-desoxycorticosterone, adequate salt retention may be obtained by the use of relatively large quantities of these substances. It is therefore possible, with Compounds E and F, to maintain a satisfactory electrolyte balance in Addison's disease if adequate quantities of either of these hormones are administered. It appears that Compounds E and F may compete with 11-desoxycorticosterone in its action on electrolyte regulation. Thus, in the presence of excessive sodium retention induced by desoxycorticosterone acetate, treatment with large doses of Compound E may result, not in further sodium retention, but in increased sodium excretion.

One may achieve an approximate measure of the amount of carbohydrate-regulating factors secreted by following the urinary excretion of 11-oxysteroids or cortin-like substances, more correctly called neutral reducing steroids; more simply, by noting a fall in the level of the circulating eosinophils referable to a rise in the circulating 11,17-oxysteroids, or by observing the rise in the urinary uric acid-creatinine ratio, which follows an increased blood level of 11- and 11,17-oxysteroids. Recent evidence suggests that the adrenal cortex contains predominantly Compound F.

Androgenic and Anabolic Effect of Adrenal Androgens. The third group of adrenal steroids are those referred to as the adrenal androgens or N hormone. It is assumed that these substances exert an effect similar to that of the testicular androgens, which consists of masculinization, with retention of nitrogen, phosphorus, potassium, sodium and chloride. This effect has been characterized as the androgenic or anabolic hormone effect. In the female it is evident that nearly all androgenic effect is derived from the adrenal cortical androgens, whereas in the male, the adrenal cortical androgens appear to account for only two thirds of the androgenic substances, the remainder being derived from the testes. Adrenal androgens are related in structure to testosterone, but carry an oxygen group in position 11 (adrenosterone).

The secretion of androgenic substances or the administration of such steroids is evidenced by a relatively small rise in urinary 17-ketosteroids, their excretory product.

Practical Considerations in Adrenal Hormone Therapy. Two groups of adrenal cortical hormone preparations are available commercially at the present time, namely, whole adrenal cortical extracts derived from beef or hog adrenal glands and synthetic desoxycorticosterone acetate.

In cases of adrenal insufficiency, the salt-retaining factors are easily substituted for by the administration of synthetic desoxycorticosterone acetate (DCA) in the form of a solution in oil (5 mg. per cubic centimeter), a macro-suspension in various solvents, or in the form of subcutaneously implanted tablets or pellets weighing 125 mg. or 75 mg. each. Such pellets give off 0.5 and 0.3 mg., respectively, of DCA daily. These substances are ineffective in the therapy of rheumatic diseases.

Substitution therapy with carbohydrate-regulating factors has in the past been possible by the administration of whole extracts of beef or hog adrenal glands. Such commercial extracts contain relatively small quantities of the known steroid hormones. Aqueous whole adrenal extracts are about one tenth as potent as Lipo-adrenal Cortex (Upjohn), a concentrate of hog adrenal gland in oil, each cubic centimeter of which is equivalent to 2 mg. of Compound E. In the treatment of diseases such as rheumatoid arthritis, very large quantities of whole adrenal extract will obviously be required to induce an effect comparable to that obtained from Compound E in the amount of from 50 to 100 mg. daily. By 1950 Compound E acetate should be available as a crystalline suspension in saline solution. Compound F, which has not been synthesized, is derived from hog adrenal glands. Doses of the same order of magnitude as Compound E acetate will probably be required in the treatment of rheumatoid arthritis. However, because of the greater solubility of Compound F, it will be necessary to increase the frequency of administration, as compared with Compound E acetate.

Pituitary Adrenocorticotrophic Hormone (ACTH). Since purified pituitary adrenocorticotrophic hormone has become available in quantities adequate for clinical investigation, it has been possible to study the effect of administering this trophic substance on the secretion of adrenal steroids in man. Four hours after the injection of a single dose of 25 mg. of purified ACTH (Armour Standard) there is a profound fall in circulating eosinophils and a rise in urinary uric acid excretion (increased ratio of uric acid to creatinine). Repeated administration of ACTH, in doses of 10 mg., injected intramuscularly every 6 hours, 40 mg. daily (Armour Standard) has resulted in marked sodium and chloride retention, with initial potassium loss, a rise in urinary 11-oxysteroid excretion and in the level of circulating 11,17-oxysteroids as determined by biologic assay, a rise in blood sugar level, a fall in circulating eosinophils, a rise in uric acid excretion and an increase in urinary 17-ketosteroid excretion to the upper limit of normal. Prolonged administration of the preparation gives rise to a chemical pattern and a clinical picture suggestive of mild Cushing's

syndrome. Thus, in man, it appears that, with an adrenal gland capable of responding, stimulation of the gland by ACTH is followed by an increased secretion of adrenal steroids, which give rise to all the known effects previously observed with crystalline adrenal steroid preparations. The fall in circulating eosinophils affords the most sensitive indicator of adrenal cortical activation and may change before any of the other signs of adrenal cortical activation have become manifest. In addition to increasing the adrenal hormone level in patients with intact adrenal glands, ACTH stimulation has served a very useful purpose in providing a clear-cut test for adrenal cortical insufficiency. Thus, patients with Addison's disease fail to show any of the effects mentioned above when given ACTH. Furthermore, the studies on patients with Addison's disease prove that the changes following ACTH are due to the secondary outpouring of the adrenal cortical steroids, rather than to a primary effect of ACTH itself. It is obvious, therefore, that the administration of ACTH would not be a suitable means for increasing adrenal hormone secretion in patients with adrenal cortical insufficiency due to primary disease of the adrenal gland or physiologic exhaustion.

Epinephrine Stimulation of the Anterior-Pituitary-Adrenal-Cortical System. On the basis of earlier animal experiments by Long and others, in which it was shown that epinephrine was capable of stimulating an intact pituitary-adrenal-cortical system, studies in man were carried out.

It was observed that a single injection of 0.3 mg. of epinephrine subcutaneously, in a patient with an intact pituitary gland and adrenal cortex, was followed by a fall in the level of circulating eosinophils, most marked after 4 hours. In normal persons, this amounted to 50 percent or more; in patients with pituitary deficiency, or in patients with Addison's disease, a small or negligible fall was observed with this dose of epinephrine. The 4-hour epinephrine test is a useful screening technic for detecting both anterior pituitary ACTH or adrenal cortical insufficiency. Larger doses of epinephrine (1 mg. or more) appear to be capable of activating adrenal cortical remnants in patients with advanced Addison's disease, but not in patients with severe pituitary ACTH deficiency. Repeated injection of small quantities of epinephrine (from 0.5 to 0.8 mg.) every 6 hours over a period of weeks has resulted in a moderate stimulation of adrenal cortical steroid hormone production, as evidenced by eosinopenia, moderately increased urinary 11-oxysteroid excretion and a doubl-doubling of the urinary 17-ketosteroid excretion.

In contrast to the uninhibited stimulation of adrenal cortical hormones that follows the repeated administration of ACTH, epinephrine administration has the disadvantage of losing much of its effectiveness as an adrenal cortical stimulator because endogenous ACTH production is inhibited by a rising titer of adrenal cortical steroids. This inherent disadvantage will be found with any substance that stimulates pituitary ACTH production.

Stimulation of the Hypothalamic-Pituitary-Adrenal-Cortical System by Stress. Anterior hypothalamic centers have recently been shown to form an essential link in the activation of pituitary ACTH secretion following conditions of stress, as well as epinephrine administration. Upon nervous stimulation or contact with circulating epinephrine, a humoral substance appears to be secreted by cells of the anterior hypothalamus, which stimulates ACTH secretion. Through this neurohumoral system, the adrenal cortex may be activated to secrete 11, 17-oxysteroids by a variety of nonspecific stresses and emotional factors.

Depression of circulating eosinophils has been demonstrated in a variety of moderate stresses, but the extent to which adrenal cortical activation may be accomplished by such nonspecific means awaits further investigation. It appears that the stimulatory effect upon the central nervous system of such noxious stimuli is the basis of pituitary ACTH activation. Whereas epinephrine is a good eosinolytic agent, nor-epinephrine is practically devoid of such action and is characterized pharmacologically by the near absence of any central nervous-system stimulatory effect as compared with epinephrine.

Adrenal cortical reserve was measured by means of 4-hour and 48-hour ACTH tests, or both, in 22 patients with rheumatoid arthritis. The 4-hour ACTH test using the intramuscular injection of 25 mg. of ACTH and its effect on the circulating eosinophils 4 hours later was done on 10 patients, 8 of whom showed normal or low normal response. One patient who did not respond subsequently proved to be refractory to therapy with ACTH as well. This essentially normal response in all but one of the group suggests that the available reserve of the adrenal cortex was not noticeably impaired by the rheumatic state. This concept was confirmed by the results of the 48-hour tests, which in most cases were a continuation of the 4-hour tests and were carried out using 10 mg. of ACTH every 6 hours. All the known functions of the adrenal cortex were stimulated in all but one of the 10 patients.

The epinephrine test, which consists of the administration of 0.3 mg. of epinephrine subcutaneously and determination of the fall in eosinophils at the end of 4 hours, was carried out on 14 patients with rheumatoid arthritis. The average fall of 50 percent was slightly less than that in a similar group of normal subjects, who showed a mean 64 percent fall. However, the spread of the results in the tests on patients with rheumatoid arthritis was considerably greater than that in the normal control group. Several of the patients who failed to respond normally to epinephrine responded well to ACTH. Such a dissociation may be fortuitous or else suggests a possible deficiency in the hypothalamic-pituitary link in adrenal cortical activation.

Effect of ACTH Therapy on Rheumatoid Arthritis. After the discovery by Hench, Kendall, Slocumb and Polley of the Mayo Clinic, that Compound E, given in large doses (100 mg. per day), is effective in the treatment in rheumatoid arthritis, studies were made on the effect of the prolonged administration of

ACTH to patients with rheumatoid arthritis. Ten patients were treated for from 2 to 14 days with 40 mg. of ACTH per day, given in divided doses of 10 mg. every 6 hours. Of the patients treated, 5 were males and 5 females, varying in age from 25 to 61 years; the arthritis was severe or moderately severe in 9 cases and mild in one case; and the duration of the disease varied from 3 months to 28 years. In every case - that is, 9 - in which the adrenal cortex responded, improvement occurred. Two patients were treated for 2 weeks, and 8 for 48 hours. Within from 12 to 24 hours of the initial administration of ACTH, clinical improvement was observed, in every way similar to that reported by the Mayo Clinic group, who used 100 mg. of synthetic Compound E daily. The most characteristic immediate change was loss of stiffness in the joints. This was followed by improvement in the patient's general sense of well-being, culminating in a euphoric state. Because this is found in patients with Addison's disease on Compound E therapy it is not related solely to decreased pain on motion. With more prolonged administration, there was increased range of motion in the joints and loss of pain. Objective evidence of improvement was found in a progressive fall in the blood sedimentation rate, often reaching normal levels after about a week. Evidence for a generally increased adrenal hormone secretion in these patients given ACTH was provided by a sustained fall in the level of circulating eosinophils, by a marked rise in 17-ketosteroid excretion and by sodium retention. One patient who failed to show any improvement on 48 hours of ACTH did not have an eosinophil fall, although urinary 17-ketosteroids rose. A patient who showed only 1+ improvement was the single one of the group whose arthritis was initially mild.

Withdrawal of ACTH therapy after from 2 to 14 days of treatment in 10 patients was followed in from 12 to 24 hours by a partial return of symptoms, including stiffness and pain in the joints, a rise in sedimentation rate and a loss of the euphoria.

Patients with milder cases of rheumatoid arthritis show a somewhat more lasting effect after ACTH therapy, although the majority of patients return toward, but do not reach, their status before treatment.

The reversion to pre-treatment status may be minimized by withdrawal of the adrenal cortical stimulation gradually. Thus, after 10 mg. of ACTH intramuscularly every 6 hours, the same dose was given every 8 hours for a week, then every 12 hours for another week, and then once a day for a short period before being discontinued altogether.

Because of the limited quantities of synthetic Compound E and natural ACTH that are available, attempts were made to increase the degree of pituitary adrenal stimulation by less specific methods. Because epinephrine has been shown to stimulate ACTH production in man, patients with rheumatoid

arthritis were given a stimulating dose of epinephrine every 6 hours throughout the day and night. This therapy in 2 patients with rheumatoid arthritis resulted in a very slight but definite improvement, although, again, the maximum improvement observed was far less than that which occurred with ACTH or which might have been expected with 100 mg. of synthetic Compound E. Definite adrenal cortical activation occurred, although apparently not sufficient in terms of its beneficial effect on the rheumatoid arthritic state. The use of epinephrine at the termination of a course of ACTH holds promise as a means of increasing endogenous ACTH production and of buffering the sudden falling off in adrenal cortical activity, which invariably follows the discontinuance of ACTH. A number of methods of nonspecifically stimulating the pituitary to increase its ACTH output, and thereby the adrenal cortical secretion, are now being studied in patients with rheumatoid arthritis.

In addition to the studies carried out with ACTH and epinephrine, an attempt was made to improve the clinical condition of patients with rheumatoid arthritis by the administration of large quantities of adrenal cortical extract. Two cc. of Lipo-adrenal Cortex (Upjohn) were given intramuscularly, every 3 or 4 hours, for from one to 3 days, to 5 patients with rheumatoid arthritis. The total daily dose of Lipo-adrenal cortex was from 12 to 15 cc. This corresponds to an amount approximately between 120 and 150 cc. of aqueous whole adrenal extract. Patients with rheumatoid arthritis given this treatment showed very slight improvement, but the magnitude of change was in no way comparable to that observed after ACTH, or after Compound E as described by the Mayo Clinic group. This relative ineffectiveness appears, in all probability, to be due to the fact that the total amount of extract administered contained much less than the equivalent of 100 mg. of Compound E, or the quantity of Compound E or F released by the adrenal cortex upon stimulation by 40 mg. of ACTH.

Effect of ACTH Administration on Rheumatic Fever. The response to ACTH in patients with acute rheumatic fever is more striking than that obtained in patients with rheumatoid arthritis, in whom previous joint deformities persist in spite of ACTH-induced improvement. To date, 3 patients with acute rheumatic fever have been treated for periods varying from 8 to 14 days, with 10 mg. of ACTH given intramuscularly every 6 hours. An 11-year-old girl was given ACTH early in her second known rheumatic attack, which was associated with subcutaneous nodules, arthritis, pericarditis and myocarditis, as suggested by a protodiastolic gallop rhythm and electrocardiographic changes. The patient was taken off acetylsalicylic acid 3 days before treatment with ACTH was begun. All the known adrenal cortical secretions appeared to be increased by ACTH, although the relative proportion by which the individual factors were augmented cannot be ascertained by current analytical methods. The posterior pituitary-like effect of Armour ACTH and the consequent retention of water lead to a rapid weight gain in most subjects being given ACTH. In a patient with incipient heart failure such a possibility is very undesirable. However, in the limited number

of patients treated and with the dose of ACTH employed, it was found that the improvement in cardiac efficiency, with its beneficial effect on renal circulation, led to an increased urinary volume, rather than to water retention during a period of a week. The over-all benefits were identical with those obtained with Compound E acetate.

Effect of ACTH Administration on Disseminated Lupus Erythematosus. Three patients with acute disseminated lupus erythematosus showed marked clinical improvement, with rapid disappearance of the typical butterfly rash, when given 10 mg. of ACTH intramuscularly every 6 hours. A low initial eosinophil count as seen in one case and also found in another case, is a consequence of bone-marrow hypoplasia with normal adrenal cortical function, rather than a sign of greatly increased adrenal cortical activity as in Cushing's syndrome, in which a marked eosinopenia is diagnostic. It should be noted that the gamma globulins, normally from 12 to 14 percent of the total protein, did not fall below 20 percent during the course of ACTH therapy, and yet the sedimentation rate was decreased and the patient was clinically improved. It is also of interest that the initial, striking clinical improvement was obtained before there was any change in the circulating gamma globulins. Again, all major adrenal cortical functions appeared activated. Forty milligrams of ACTH were given daily for 13 days, followed by 20 mg. daily for 4 days. Five days after discontinuation of ACTH therapy, the characteristic leukopenia, elevated sedimentation rate and enlarged, tender spleen returned. In spite of this, the patient was still feeling well, and the rash had not reappeared. The treatment had thus led to striking temporary improvement, which left the patient in a better clinical state but did not lead to a cure. Two subsequent ACTH courses following partial regression in this patient showed beneficial effects lasting up to 6 weeks.

Effect of ACTH Administration on Gouty Arthritis. In a study of the effect of ACTH on patients with gouty arthritis, it was found that treatment with the hormone caused a large increase in urinary uric acid excretion, with a concomitant fall in serum uric acid levels. The clinical improvement was striking and rapid. This improvement was characterized by increased joint mobility, decreased pain and softening of tophi. Although the rise in uric acid excretion was no greater than that achieved by the administration of 5 Gm. of acetyl salicylic acid per day, the over-all clinical improvement was much more marked with ACTH administration. Upon withdrawal of ACTH, a mild gouty attack occurred after 2 days. This phenomenon has been reported by Hellman.

Discussion. Rheumatic fever, disseminated lupus erythematosus and rheumatoid arthritis may be viewed as related mesenchymal diseases, characterized by a nonspecific inflammatory reaction, presumably brought on by a peculiar susceptibility of the host to certain bacterial or tissue products. Such pathologic states are apparently favorably altered by a sudden increase in the

titer of circulating 11,17-oxysteroids or related compounds of adrenal origin. With a sudden increase in the level of these steroids, the progress of the inflammatory reaction in heart, vessels and synovia is temporarily arrested. The majority of patients with these diseases seem to possess normal adrenal cortical reserve function, but appear incapable of increasing the activity of their adrenal cortex spontaneously. Is such an activation an essential part of the normal defense mechanism? If so, is it absent in those afflicted with mesenchymal disease? Or is the massive activation of adrenal cortical hormone production by ACTH merely a therapeutic implement acting favorably upon the patient's reaction pattern to the disease directly or by neutralizing some biologic antagonist? Evidence in support of this concept is the fact that 100 mg. of Compound E is needed to alter significantly the course of rheumatic diseases, whereas patients with complete adrenal insufficiency may be maintained with from 10 to 20 mg. daily. Effective therapy is only attained when the level of hormone is increased, to supernormal levels.

Obviously, ACTH therapy will only be effective in patients in whom a normal adrenal cortical response is obtained. Á marked decrease in circulating eosinophils following ACTH therapy is a valuable indication of increased secretion of 11,17-oxysteroids, which appear specific in their ability to depress circulating eosinophils and lyse lymphoid tissue and which, to date, are the only type of steroid that has been shown to exert a beneficial effect in rheumatic disease. Because they are synthesized from bile acids, the supply of these steroids will always be limited; therefore, a search for 17-oxysteroids derived from cholesterol or plant sterols and their trial in the rheumatic state is of great practical importance. ACTH, too, is limited by the number of pituitary glands available at any one time; thus, the search for effective nonspecific pituitary-adrenal stimulants must be continued.

The mode of action of 11,17-oxysteroids in these diseases is unknown. Improvement is observed in most patients within from 4 to 6 hours. The blood sedimentation rate usually falls within 48 hours after treatment is begun, but the maximal change may not occur for from 10 to 14 days. The initial changes that occur, such as loss of stiffness and increased capacity to move joints without pain, suggest a decrease in some stiffness factor and an immediate reduction in the chronic inflammatory reaction. A possible cause of these changes is the effect of the hormone on tissue permeability. The singular specificity of adrenal steroids in their action on rheumatic diseases is suggested by the prompt response to Compound E and the ineffectiveness of desoxycorticosterone and dehydrocorticosterone acetate. Excessive DCA treatment in patients with Addison's disease is often associated with increased stiffness of the joints or arthralgia, or both. It is of interest that Selye has been able to accumulate a large amount of experimental evidence suggesting that arthritis is induced in rats by the administration of excessive amounts of desoxycorticosterone, a finding recently confirmed in man.

The improvement in gout brought on by ACTH is apparently not due to increased renal uric acid clearance alone, but must also involve some direct effect on the joint tissue. Even though the effect of salicylates on the uric acid excretion is greater, the clinical improvement noted is far less than that with ACTH.

The dangers of continued ACTH or Compound E acetate treatment are principally the undesirable side-effects associated with a long-continued, high level of adrenal steroids. With chronic ACTH administration, one must be concerned with the possibility of persistent adrenal hyperplasia. Cushing's syndrome has been reported during the prolonged administration of Compound E. On 40 mg. of ACTH per day this danger is minimal, and yet adequate adrenal cortical activation is achieved. With higher doses, Cushing's syndrome is occasionally produced by ACTH as well. In all cases studied thus far on ACTH therapy there has been a rapid return of adrenal function to normal or subnormal levels. The pituitary ACTH mechanism is suppressed by exogenous ACTH and the adrenal cortex is stimulated, whereas with Compound E both the adrenal cortex and the anterior pituitary gland may become atrophic. Thus, withdrawal of Compound E therapy leads to a more acute, temporary adrenal cortical deficiency than the withdrawal of ACTH therapy. To minimize this sudden reduction in adrenal cortical activity, it appears desirable to administer ACTH for from 24 to 48 hours after the withdrawal of therapy with Compound E.

The beneficial effect of 11,17-oxysteroid therapy in the rheumatic diseases marks a great advance in therapy. Adrenal cortical hormone therapy does not, however, appear to affect the fundamental cause of the inflammatory changes that characterize these diseases. The use of adrenal cortical steroids or adrenal cortical stimulants will do much to further fundamental research in the field of rheumatic diseases. Their exact value as therapeutic agents remains to be worked out by long-continued therapy. (New England J. Med., 6 Oct. '49, G. W. Thorn et al.)

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Predisposing Action of Anesthetic Agents on the Vascular Responses in Hemorrhagic Shock: Recent work on experimental shock has clearly established the existence of a variety of initiating and sustaining mechanisms which lead to peripheral circulatory collapse. Among the mechanisms reported to participate in the syndrome are a reduced blood volume via extravascular fluid loss, compensatory and decompensatory changes in the peripheral blood vessels via humoral principles, neurogenic vasoconstrictor influences, and endothelial toxins of tissue and bacterial origin. These different mechanisms do not consistently appear in the same sequence relative to one another, nor do they participate to the same degree in different subjects or in different types of shock. The precise experimental conditions under which the shock is produced

appear to determine which of the several possible factors will predominate and which of them will be excluded. One of the major determinants of the character of the shock syndrome has been shown to be the type of anesthetic agent employed. The influence of the anesthetic agent on the course of the syndrome was found to be exerted in a specific, predictable manner. The specific vascular effects of different anesthetic drugs were such as to make it possible to produce a different sequence in the peripheral circulatory reactions under otherwise identical experimental procedures. Certain anesthetics, such as cyclopropane and morphine, accentuated the compensatory vasoconstrictor aspects of the syndrome virtually to the exclusion of other factors. Other agents, such as sodium pentobarbital and pentothal, aggravated the reduced, circulating volume by depressing the compensatory responses of the peripheral blood vessels. Finally, agents such as ether produced sufficient vascular dilation and endothelial damage to limit severely the compensatory vascular phenomena and to lead to a disruption and stasis of the peripheral circulation early in the syndrome. In the present study, use was made of the predisposing actions of 3 different anesthetic agents, cyclopropane as an agent favoring a predominantly compensatory response to hemorrhage, ether to demonstrate an extreme decompensatory pattern, and sodium pentobarbital to provide an intermediate pattern. The specific properties of these 3 anesthetic agents made it possible to study selectively several of the basic mechanisms participating in the syndrome.

Chambers, Zweifach, and associates were able by direct visualization of the small blood vessels to follow the progression of shock following hemorrhage on the basis of characteristic alterations in the functional response of the capillary bed. Two patterns of response were noted, (a) an initial period of compensatory activity in which the peripheral vascular apparatus accommodates its capacity and vasomotor activity to the reduced blood volume, and (b) a subsequent decompensatory period in which the capillary bed loses its ability to restrict effectively the circulation in a manner compatible with tissue needs, as a result of which adequate venous return into the general circulation is no longer possible. The decompensatory phase was associated with the development of the so-called irreversible stage of shock. Both the compensatory and decompensatory phases were shown to be related to blood-borne factors (vasoexcitor factor, VEM, and vasodepressor factor, VDM). Although in these studies no direct evaluation was made of the role of the nervous system in the reactions of the peripheral blood vessels to blood loss, it was clear from subsequent experiments on animals subjected to postganglionic sympathectomy that vasoconstriction of the larger vessels during the compensatory stage could, in large part, be ascribed to increased neurogenic stimuli. Increased reactivity of the terminal arterioles and precapillaries, on the other hand, was related to a blood-borne vasoconstrictor factor, VEM, of renal origin. The decompensatory stage did not appear to be related to a failure of neurogenic vasoconstrictor influences but to an interference with the response of the peripheral blood vessels to these stimuli by the progressive accumulation in the blood stream of a vasodepressor factor, VDM, chiefly of hepatic origin.

The effectiveness and widespread use of blood replacement therapy has tended to over-emphasize the fluid-loss aspect of the syndrome and has led to the clinical neglect of other mechanisms which exert a deleterious influence on the blood vessels themselves. Further clarification of the mechanisms leading to the decompensatory phase could be of considerable value in counteracting the progressive refractoriness to corrective therapy which develops during this stage of shock. The present report is therefore concerned particularly with the changes in the peripheral blood vessels, observed by direct microscopic study, as they reflect the influence of anesthetic drugs on the decompensatory, hypo-reactive phase of the shock syndrome.

Following a single massive, fatal blood loss the resulting vasoconstriction of the larger blood vessels is carried to an extreme. The effect is to curtail excessively the circulation in the tissues to an extent that appreciable quantities of blood are trapped on the capillaries and collecting venules. This might be termed an overcompensation productive of an unfavorable situation. With a graded type of bleeding, in which fatal amounts of blood are withdrawn over a period of from 30 to 90 minutes, there is sufficient time for a compensatory hyperreactivity of the capillary bed to develop and thereby to assist in emptying the capillary bed. This compensatory ischemia was most pronounced in unanesthetized dogs subjected to hemorrhage.

An evaluation of the circulatory data from the viewpoint of anesthesia has demonstrated striking differences not only between the reactions of dogs subjected to hemorrhagic hypotension with and without anesthesia, but between dogs bled while under the influence of different anesthetic agents. The predisposing action of anesthetics was readily apparent on the basis of the vascular changes observed through the microscope in the omentum of the dog.

In general, 3 categories of vascular response were observed with hemorrhage as the initiating factor. The first is the purely compensatory type obtained in unanesthetized animals and most closely approximated in the anesthetized group by those animals bled during cyclopropane administration. Under such conditions the capillary bed as an organic unit shows no essential dysfunction. Circulatory collapse, when it occurs, is essentially a mechanical failure of blood to be returned from the tissues as the result of excessive vasoconstriction of the larger blood vessels.

The second or intermediate type of vascular response was obtained with animals subjected to graded hemorrhage in which the hypotension is maintained for an extended period usually from 3 to 4 hours with blood pressures below from 40 to 50 millimeters of mercury. In these animals, although vasoconstriction of the larger blood vessels is relatively unimpaired, there develops progressively a physiologic derangement of the peripheral circulation. Capillary ischemia is no longer complete and a trapping of blood is evident on the venous

side of the bed especially in the collecting venules. This type of response is seen most frequently in animals bled during sodium pentobarbital or morphine anesthesia. The circulatory collapse is not solely a mechanical one because biochemical changes occur in the tissues and result in the appearance in the blood of decompensatory vasotropic factors.

The third or more toxic type of vascular change was obtained when ether was used as the anesthetic agent. In these animals not only were the compensatory responses of the capillary vessels severely curtailed but the vasoconstriction of the larger arteries and veins was not as pronounced as in animals anesthetized with other agents. In addition, this was the only anesthetic agent in which many animals showed signs of increased capillary permeability, with considerable capillary stasis, extravasation, and visible evidence of hemoconcentration in the collecting venules.

It is interesting to note that the 3 types of vascular response to hemorrhage are correlated with the prognosis for the effectiveness of therapy in each group. Animals showing no functional derangement of the peripheral blood vessels readily recover after fluid replacement therapy. The second or intermediate type of vascular response is associated with a progressive refractiveness to blood replacement therapy. The third type of vascular response is associated with an extremely poor response to similar therapy. It is also noteworthy that there is a comparable correlation in these 3 types of vascular response with regard to the ability to tolerate blood loss.

Under normal conditions there exists a precisely controlled relationship between the volume of circulating blood and the capacity of the vascular bed in which it is contained. Two fundamentally different mechanisms can disrupt this normal hemodynamic equilibrium. Peripheral circulatory collapse may be induced either by decreasing the volume of blood through hemorrhage or by increasing the capacity of the vascular bed through peripheral insufficiency. Both of these factors contribute to some extent to all types of shock. Under ordinary circumstances, it is difficult to predict the extent to which each of these 2 mechanisms participate. The observation that following uncomplicated hemorrhage, different anesthetic drugs, of themselves serve to emphasize the pattern of the vascular disturbance by shifting it to one or the other extreme, would seem to offer further evidence that both mechanisms operate to some degree in all types of shock. (Surg. Gynec. and Obstet., Oct. '49, B. W. Zweifach and S. G. Hershey)

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Aureomycin in Experimental Polyarthritis with Preliminary Trials in Clinical Arthritis: A polyarthritis of rats can readily be reproduced by intraperitoneal or intravenous injection of broth cultures of the L4 strain of the

pleuropneumonia-like organism. This experimental polyarthritis has been used as a means of making chemotherapeutic trials. In man pleuropneumonia-like organisms have repeatedly been isolated from the genitourinary tract and may be related etiologically to an acute infectious type of arthritis and to Reiter's syndrome. Dienes has isolated L type cultures from many Gram-negative bacilli and several large Gram-positive bacilli, although thus far no one has reported isolation of such forms from streptococci. Unfortunately these micro-organisms are species specific as far as their pathogenicity is concerned so that human strains do not produce infections in animals. Although the polyarthritis of rats is not the same disease as rheumatoid arthritis in man, the course of both is favorably altered by the use of gold salts. In the rat the arthritis may be prevented by the intramuscular injection of gold at the time of infection, or after the arthritis has developed, healing will occur more rapidly in those treated with gold than in those not receiving it. The authors' effort in the chemotherapy of this rat arthritis has been directed toward finding agents which might be as effective as gold, but less toxic, for possible trials in rheumatoid arthritis of man. The new antibiotic, aureomycin, has proved to be successful in this experimental polyarthritis.

When 0.1 percent or 0.3 percent aureomycin was mixed with the ground Purina dog chow complete protection of all animals occurred. When aureomycin was administered by stomach tube to fasting animals in single daily doses of 50 mg. per kg. for 2 days, there was an incidence of 20 percent arthritis with an average arthrogram score of 0.4, although the incidence among the controls was 77.4 percent, and the average arthrogram score was 2.41, the survival rate being 96 percent. A single dose of aureomycin, 100 mg. per kg., given subcutaneously on the day of infection gave an incidence of 20 percent and an average arthrogram score of 0.3, compared to a much higher value (2.41) for the controls.

The curative effect was evaluated by giving 100 mg. per kg. of aureomycin subcutaneously on the seventh and eighth days after the infection was begun and at a time when there was a 55 percent incidence of arthritis. Because crude aureomycin is quite acid and caused local necrosis, further injections were not given. In 4 days the incidence of arthritis had fallen from 55 to 5 percent in the treated group although it had increased from 66 to 73 percent in the controls. At the same time the average arthrogram score for the treated animals had decreased in 4 days from 1.6 to 0.15, although in the controls it had increased from 1.3 to 1.35. At the outset there was a less severe degree of arthritis in the controls, the drug being tested against a more severe arthritis, yet the outcome was more favorable.

In vitro, a concentration of 2 ug. aureomycin per cc. of the broth permitted questionable growth of the microbes in 24 hours and definite growth in 48 hours as estimated by the turbidity of serial dilutions. Using 3 ug. of aureomycin per cc. of broth, no growth was observed.

Preliminary clinical trials were made in 4 advanced cases of rheumatoid arthritis in which there had been an unsatisfactory response to several therapeutic agents, and in one early case, using 2 Gm. aureomycin daily by mouth for one month. Two patients noted an improvement in appetite, and one patient had to discontinue the medication on the third day because of a marked gastro-intestinal upset. In none of these patients was there any improvement in range of motion of affected joints and 3 of them developed increased pain and swelling while under treatment. One patient with Reiter's syndrome responded dramatically, gaining 6 lb. during the first week of treatment and losing all joint pain. At the end of one month he showed no more joint swelling. His blood sedimentation rate (Wintrobe Method) decreased from 40 mm. to 12 mm. per hour in 2 weeks. (Proc. Soc. Exper. Biol. & Med., Aug. '49, W. C. Kuzell et al.)

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List of Recent Reports Issued by Naval Medical Research Activities:

Naval Medical Research Institute, NNMC, Bethesda, Maryland

Project	Report No.	Date	Title
NM 000 002	4	29 Jul '49	An Electromagnetic Focusing Device for the Electron Microscope
NM 000 006	1	7 Sep '49	Use of the Polarograph for Concentration Measurements in Protein Solutions. I. Analysis of the Albumin-Zinc and Albumin-Mercury Complexes
NM 005 007	9	22 Aug '49	The Transmission of Japanese Encephalitis by Mosquitoes after Experimental Hibernation
NM 007 039	23	6 Jul '49	The Sequence of Cellular Response to Injury in Mice Exposed to 1100 r Total Body X-Radiation
NM 007 039	24	25 Jul '49	The Effect of Total Body X-Radiation, Antistine, and Pyribenzamine on the Phagocytic Function of the Reticulo-Endothelial System in Rabbits Injected Intravenously with Radioactive Colloidal Gold
NM 007 047	6	6 Jul '49	Augmentation of the Thermogenic Effects of Pyrogens by Homologous Plasma in Rabbits

Naval Medical Research Institute, NNMC, Bethesda, Maryland and Enteric Bacteriology Laboratory, USPHS, Communicable Disease Center, Chamblee, Ga.

Project	Report No.	Date	Title
NM 005 010 (X-756)	9	7 Sep '49	The Natural Occurrence of Phase 2 of Salmonella paratyphi A
			(Summaries of Research 1 January - 30 June 1949)

Naval Medical Field Research Laboratory, Camp Lejeune, N. C.

NM 004 004	1	19 Aug '49	Human Protection from Ultraviolet Radiation
NM 011 021	14	15 Jul '49	Sterilizer, Pressure Cooker Type, Testing of
NM 011 021	16	19 Sep '49	Performance Evaluation of the Taykit Gasoline Burner as Compared with the Coleman Military Burner Model No. 527 Currently Used with the Field Instrument Sterilizer
NM 011 021	17	15 Sep '49	Field Testing of Seamless Die-Drawn Aluminum First-Aid Kits
NM 011 021	18	9 Sep '49	Evaluation of (Kore) Disinfectant and Germicide
NM 011 021	23	13 Sep '49	Testing of Presto, A Commercial Beverage Powder as a Possible Substitute for the Beverages Contained in the Wartime Luncheon "K" Ration

Medical Research Laboratory, U. S. Naval Submarine Base, New London, Conn.

NM 003 008	2 MRL 146	5 Aug '49	The Effect of Low Color Temperature Illumination and Red Illumination Upon Subsequent Dark Adaptation
NM 003 020	4 MRL 145	1 Aug '49	The Effect of Sensation Level on Intensity Discrimination for White Noise

School of Aviation Medicine and Research, NAS, Pensacola, Florida and Tulane University of Louisiana

NR 140 455 NM 001 037	Joint No. 7	10 Sep '49	The Perception of the Vertical IV. The Visual Vertical as a Function of Centrifugal and Gravitational Forces

School of Aviation Medicine and Research, NAS, Pensacola, Florida and Kenyon College of Gambier, Ohio

Project	Report No.	Date	Title
NR 872 004 NM 001 053	Joint No. 2	9 Sep '49	Loudness of Speaking I. The Effect of Heard Stimuli on Spoken Responses
NR 872 004 NM 001 053	Joint No. 3 1	23 Sep '49	Rate of Speaking (Responses to Heard Stimuli) II. Repetitions of Phrases Containing Logical and Illogical Pauses
NR 872 004 NM 001 053	Joint No. 3 2	23 Sep '49	Rate of Speaking (Responses to Heard Stimuli) III. Relationship Between Original and Repeated Phrases for Speakers with Various Normal Rates

School of Aviation Medicine and Research, NAS, Pensacola, Florida

NM 001 055	1	13 Sep '49	Automatic Regulation of the Oxygen Saturation of Arterial Blood in Man

Note: Those interested in seeing copies of the complete reports should address their request to the research activity from which the report originates.

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Reserve and Regular Navy Correspondence Courses Administered by the Bureau of Medicine and Surgery: The following correspondence courses are now available for distribution and may be obtained from the Bureau of Medicine and Surgery by personnel of the Medical Department of the Naval Reserve and regular Navy as indicated below, 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)
Medical Department Administration	1	12	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)
Functions of Officers of the Medical Department	1	12	MC, DC, MSC, NC, HC (officers only)
Submarine Medicine Practice	2-1/2	32	MC, DC, MSC, NC, HC (officers only)
Aviation Medicine Practice	2-1/2	32	MC, DC, MSC, NC, HC (officers only)
Naval Preventive Medicine	3	36	MC, DC, MSC, NC, HC (officers only)
Special Clinical Services (Dental)	2-1/2	32	MC, DC, MSC, NC, HC (officers only)

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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Dental Department of Long Beach Naval Hospital Approved by ADA: The Dental Department of the Naval Hospital, Long Beach, California, has been approved, as of 20 September 1949, by the Council on Hospital Dental Service of the American Dental Association.

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Atomic Medicine: This is the name of a textbook, the first of its kind to be written, and just published by Thomas Nelson and Sons of Edinburgh, New York, and Toronto. The book is edited by Captain C. F. Behrens, MC, USN, Director of the Atomic Defense Division of BuMed and Medical Officer in Command of the Naval Medical Research Institute at the National Naval Medical Center, Bethesda, Maryland.

It is stated in a part of the preface that an earnest effort has been made to assemble such of this material as is appropriate to the needs of the medical and allied professions, and to present it as clearly as possible, steering a middle course between a presentation suitable only to specialists in the fields of radiation biology and physics and one unduly elementary.

The chapter headings are as follows:

I. Scope and General Background of Atomic Medicine....Clarence J. Brown, M.D.

II. The Atom Family and Associated Physics.....Charles F. Behrens, M.D.

III. Fission, Piles and Bombs .....Charles F. Behrens, M.D.

IV. The Atomic Bomb in Action.....Harry H. Haight, M.D.

V. The Ionizing Radiations.....Charles F. Behrens, M.D.

VI. Fundamental Biology of Ionizing Radiations....Friedrich Ellinger, M.D.

VII. The Pathologic Anatomy of Total Body Irradiation....John L. Tullis, M.D.

VIII. The Hematology of Ionizing Radiation.....Eugene P. Cronkite, M.D.

IX. Cumulative Effects and Permissible Dosage Limits of Ionizing Radiations .....Charles F. Behrens, M.D.

X. Radiation Illness: Its Pathogenesis and Therapy....Eugene P. Cronkite, M.D.

XI. Detection and Measurement of Radiation....F. W. Chambers, Jr., and Maynard Eicher

XII. Radiological Safety.....John C. O'Leary, M.D., and O. Schneider, M.D.

XIII. Atomic Disaster Planning.....O. Schneider, M.D., and E. Richard King, M.D.

XIV. The Acceleration of Electrically Charged Particles and Related High Voltage Apparatus.....Richard H. Lee, Ph.D.

XV. Tracer Methods in the Biologic Application of Radiosotopes..... David Minard, M.D.

XVI. Radioactive Isotopes: General Considerations....Charles F. Geschickter, M.D., and Murray M. Copeland, M.D.

XVII. Radiophosphorus and Radioiodine....Charles F. Geschickter, M.D., and Murray M. Copeland, M.D.

XVIII. Radioisotopes of Medical Interest, Other Than Radiophosphorus and Radioiodine.....Charles F. Geschickter, M.D., and Murray M. Copeland, M.D.

XIX. The Design and Operation of Laboratories Employing Radioisotopes in Medical Research.....Gordon C. Bell and George W. Imrie, Jr.

XX. Radiation Effects of Particular Importance in the Practice of Dentistry .....James A. English, D.D.S.

XXI. Research in Atomic Medicine....Shields Warren, M.D., and Rupert H. Draeger, M.D.

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BUMED CIRCULAR LETTER 49-124 29 September 1949

From: Chief, Bureau of Medicine and Surgery
To: Commandants, Naval Districts and River Commands

Subj: Public Health Bulletin No. 302, "Emergency Health and Sanitation Activities of the Public Health Service During World War II"; Transmittal of.

Encl: (1) Subject Bulletin

1. The Public Health Service of the Federal Security Agency has furnished the Bureau of Medicine and Surgery with copies of subject Bulletin for appropriate distribution.

2. The Bulletin records the services provided by the Public Health Service to state and local health activities as well as the services and co-operation afforded the Armed Forces to meet the health and sanitation problems brought on by the war effort. It is believed that the Bulletin may be of value not only in planning for future emergencies but in current operations involving the principles of preventive medicine.

3. It is requested that subject Bulletin be brought to the attention of appropriate officers and activities of your command. C. A. Swanson

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BUMED CIRCULAR LETTER 49-125 29 September 1949

From: Chief, Bureau of Medicine and Surgery
To: All Ships and Stations

Subj: X-ray Film: Protection of When Mailed

1. Exposed X-ray film, when mailed without proper protection is often crimped or cracked so that the worth of the film is markedly diminished or destroyed.

2. In order that this damage be reduced to a minimum, exposed X-ray film forwarded from naval activities should be placed between cardboard leaflets and enclosed in an X-ray mailing envelope. The envelope should be plainly labeled, X-RAY FILMS, DO NOT BEND.

3. X-ray mailing envelopes are under procurement and it is anticipated that these will be available on and after 1 Nov 1949 at the Naval Medical Supply

Depots, Brooklyn, N. Y. and Oakland, California. These will be listed in the Army-Navy Catalogue of Medical Materiel as Envelopes, Mailing, X-ray film, 14x17 inches, Stock Number 6-014-900. C. A. Swanson

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BUMED CIRCULAR LETTER 49-126 30 September 1949

From: Chief, Bureau of Medicine and Surgery
To: BuMed Management Control Activities

Subj: Survey of Field Printing and Reproduction Facilities

Ref: (a) Chairman Management Committee OSD memo of 31 Aug 1949
(b) Chairman Administrative Management Council OSD memo of 12 Sep 1949
(c) AO ND ltr EXOS:AO(Pub)IRP:ps of 21 Sep 1949

Encl: (1) DD Form 255 Part I
(2) DD Form 255 Part II
(3) Instructions for preparing DD Form 255

This letter sets forth certain facts concerning references and requests addressees to furnish BuMed with certain information as provided for on the enclosures not later than 18 October.

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BUMED CIRCULAR LETTER 49-127 30 September 1949

To: All Ships and Stations

Subj: Tetanus Toxoid: Dosage of

Ref: (a) Article 22-24, Manual of the Medical Department, U. S. Navy, 1949 (Par. 35B12, MMD, 1945)

1. The standard dosage of tetanus toxoid alum precipitated utilized in the Navy is established as 0.5 cc. by reference (a).

2. While most of the toxoid now being used calls for 0.5 cc. per dose, certain lots of weaker strength tetanus toxoid are on hand which require 1.0 cc. of material for immunization. This toxoid is so labeled.

3. In all cases in the future, the dosage of tetanus toxoid as specified on the label shall be administered. Courses or partial courses already given will be considered adequate even though doubt may exist as to the strength of tetanus toxoid used. --BuMed. C. A. Swanson

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BUMED CIRCULAR LETTER 49-128 4 October 1949

From: Chief, Bureau of Medicine and Surgery
To: BuMed Management Control Activities

Subj: Change of Designation "Medical Officer in Command" and "Dental Officer in Command" to "Commanding Officer"

1. The Secretary of the Navy has approved a change in designation of "Medical Officer in Command" and "Dental Officer in Command" to "Commanding Officer."

2. The redesignations will become effective upon publication of an official directive by the Chief of Naval Operations. C. A. Swanson

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BUMED CIRCULAR LETTER 49-129 5 October 1949

From: Chief, Bureau of Medicine and Surgery
To: All Ships and Stations

Subj: Fog Fluid Oil as an Insecticide Solvent: Use of

1. Fog fluid oil is repeatedly being used as an insecticide solvent for use in fog generators. Information has been received to the effect that certain smoke chemicals, which might be utilized as solvents, may be dangerous to operators of spray equipment.

2. Smoke producing materials, JAN Specification C-379-Chlorosulfonic acid - sulfur trioxide solution (FS) Bureau of Ordnance Code Number 60100-C and JAN Specification T-357 Titanium tetrachloride (FM) Bureau of Ordnance Code Number 60200-C are unsatisfactory products and shall not be used for spray purposes because of the hazards involved.

3. Fog fluid oil Number 1, Specification 14F3, Standard Stock Number 14-0-881-55 is the only fog material suitable as a solvent for use in insecticidal fog generators. It is roughly similar to a light machine oil and is not a particularly good

solvent for DDT, in most instances being inferior to Diesel or fuel oils of heavier grades. So far as is now known there are no existing surplus stocks of this material available.

4. The following oils should be used in insecticide fog operations unless special reasons exist for substitutions:

a. First choice Numbers 2, 3, or 4, burner fuels (FS VV-0-326, Amend-3) (GSS Catalog Stock Numbers 7-0-163, 164, 165 or 166).

b. Second choice A/Diesel Fuel Grade A (all purpose, Cetane Number 40 min.-GSS Catalog Stock Number not yet assigned).

c. Third choice (First choice if staining is important consideration) Lighter grade fuel or Diesel oils. C. A. Swanson

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BUMED CIRCULAR LETTER 49-130 7 October 1949

From: Chief, Bureau of Medicine and Surgery
To: All Stations, Continental, having Medical and/or Dental Personnel Attached

Subj: BuMed Cognizant Activity-Excess Property: Disposition of

Ref: (a) NPR&D Regulation No. 1 (Revised 15 April 1949)
(b) BuMed CirLtr 48-73, enclosure C
(c) BuMed CirLtr 49-52

This letter states that it is the policy of the Department of the Navy that excess property shall not be retained, idle property shall be returned to productive use, and the needs of the Navy shall be supplied to the maximum extent possible out of materials and supplies on hand; and accordingly directs that addressees take the following actions:

a. Re-evaluate their stock requirements for BuMed materials required for current operating purposes and emergency expansion reserves as set forth in references (b) and (c).

b. Report all quantities of such materials that are in excess of their current operating and emergency expansion reserve requirements to the Materiel Division, BuMed, 84 Sands Street, Brooklyn 1, New York. Report shall be made on Form WAA-1001 in accordance with instructions contained in Sections VI and IX of reference (a). (This applies to all excesses even though previously ordered held.)

Particular attention is to be given to the realistic assignment of condition codes on Form WAA-1001. Material in "N-1" condition shall be reported separately, that is, while diverse items in "N-1" condition may be reported on a single WAA-1001 form, items of lesser condition shall not be included with reports of material in "N-1" condition. All materials in conditions less than "N-1" may be included in a separate single report. Reports are to go to Materiel Division, BuMed, 84 Sands Street, Brooklyn, N. Y., prior to 15 November.

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BUMED CIRCULAR LETTER 49-131 7 October 1949

From: Chief, Bureau of Medicine and Surgery
To: Hospital Ships, Continental Hospitals and Activities having a Dispensary

Subj: Laboratory Examination, NAVMED-HF-27; Return of Excess Stock

This letter states that standard forms in the clinical record series have been developed as part of an interagency program to standardize medical records. Included in this series are standard laboratory forms to replace the Laboratory Examination, NAVMED-HF-27. Activities will be advised at an early date relative to the availability and installation of these new laboratory forms. Instructions are given for returning stocks of NAVMED-HF-27 in excess of 60 days' supply, for district publications and printing offices to cancel all back-orders for the NAVMED-HF-27, and for addressees having back-orders for the NAVMED-HF-27 to review their needs on the basis of a 60 days' supply, and submit new requisitions.

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BUMED CIRCULAR LETTER 49-132 11 October 1949

From: Chief, Bureau of Medicine and Surgery
To: All Activities having Industrial Health Program

Subj: Photodosimetry; Integration into Industrial Health Program

Refs: (a) NCPI 88
(b) C/L 48-10 (Par 11.2 b and 11.2 c)
(c) MMD Par 12D8

This letter (1) states that the photodosimetry program has been integrated into the industrial health organization, (2) requests that industrial

radiological health data be included in the Monthly Industrial Health Reports, (3) states that the Industrial Health Report Data Sheet (NAVMED-576) will be revised, and (4) requests that certain information be furnished BuMed.

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BUMED CIRCULAR LETTER 49-133 12 October 1949

From: Chief, Bureau of Medicine and Surgery
To: Spectacle Dispensing Units, Ophthalmic Service Units, and Ophthalmic Lens Laboratories

Subj: NAVMED-1174 (Rev 8-49), Ophthalmic Report; Submission of

Ref: (a) BuMed C/L 49-63

Encl: (1) Copies of NAVMED-1174 (Rev 8-49), Ophthalmic Report

In order for BuMed to evaluate the effectiveness of the Navy Ophthalmic program, this letter requests addressees to submit reports for months of July, August, and September, and monthly thereafter.

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BUMED CIRCULAR LETTER 49-134 12 October 1949

From: Chief, Bureau of Medicine and Surgery
To: All Ships and Stations

Subj: Procedures for Applying Requisition Priority Indicators to Requisitions for Medical and Dental Materials

Ref: (a) BuMed C/L No. 48-80 dated 26 July 1948; N. D. Bul. of 31 July 1948, 48-550
(b) BuSandA Manual, Vol. II, Paragraph 23004

1. Reference (a) is hereby canceled and superseded by this letter.

2. All requisitions, including dispatch requests, for medical and dental materials submitted by addressee activities shall have priority indicators established in strict accordance with instructions contained in reference (b).

3. Activities coming under the jurisdiction of fleet commanders shall comply with the specific procedures established by the cognizant command regarding screening of priority A and B requisitions.

4. Priority A and B requisitions originating from continental medical or dental activities will not be screened. However, supply activities shall, after processing the requisition, report any apparent misassignment of priority indicators to BuMed for action.

5. Addressees are enjoined to base assignment of priority indicators on a realistic basis in order to derive full benefit from the procedure. Violators will not only harm themselves, but will cause hardship and very possibly physical discomfort for the sick and wounded by misuse. Consequently, it is intended to take necessary corrective measures in cases of violation of the procedures established. H. L. Pugh, Acting

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NAVY DEPARTMENT
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