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Surgeons General of the Past

(The twenty-fourth in a series of brief biographies)

Clifford Anders Swanson was born in Marquette, Michigan, 8 June 1901, graduated from Northern State Teachers College in 1921, received his M.D. degree from the Medical School of the University of Michigan in 1925, and was appointed Assistant Surgeon in the Navy 15 June 1925. He served in varied Medical Department assignments throughout the United States, abroad and aboard ships. He circumnavigated the globe in 1935, "414 years," as he said, "after Magellan." He observed diseases of the eye in the Orient, and while Instructor at the Naval Medical School did research on night and color vision, and the effect of pressure and oxygen consumption on the eye, which was of great value in both aviation and submarine medicine. Doctor Swanson served as physician to two Secretaries of the Navy, Claude A. Swanson and Frank Knox. During World War II he was Senior Medical Officer on the battleship Iowa and also served on the staff of Commander, Battleships, Atlantic Fleet. In 1944 at the Bethesda Naval Hospital as operating surgeon, he was especially known for performing the delicate and highly specialized fenestration operation for the relief of certain types of otosclerosis. He accompanied President Roosevelt to the Teheran Conference, represented the United States at the Pan American Eye Conference, and was designated the medical officer to accompany the Congressional Committee which inspected the Pacific War area. He became Surgeon General 1 December 1946, serving in the office until 27 January 1951. Rear Admiral Swanson sponsored legislative actions which made the Nurse Corps a permanent staff Corps, established the Medical Service Corps, and gave doctors added inducements to pursue careers in the Navy. Admiral Swanson was retired from the Navy in July 1955.

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Policy

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The issuance of this publication approved by the Secretary of the Navy on 4 May 1964.

THE PATCH TEST

Walter B. Shelley MD, JAMA 200(10):170–174, June 5, 1967.

Patch testing consists of the application of substances to the skin for the purpose of detecting specific hypersensitivity. It serves as an admirable diagnostic tool in the clinical study of patients who have inflammatory dermatitic reactions of an allergic nature. It allows a rapid and relatively safe review of the tolerance of the skin to a large number of materials known to cause reactions in the sensitized person. Although disarmingly simple in principle, it does require skill in execution and interpretation. It is only one cog on the diagnostic wheel! Furthermore, one must recognize that patch testing involves the deliberate reproduction of disease and as such must be employed with discretion. Admittedly the disease is miniaturized down to a patch, but nonetheless it is iatrogenic. Hence, the responsible physician will generally limit patch testing to those circumstances where the history, the localization, and a thoughtful review of the patient's contactants allow no clear perception of the causal allergen. It may, however, be necessary in convincing a disbelieving employer or insurance carrier that a normally innocuous compound is indeed responsible for a worker's disabling dermatitis. One should add that, for over 70 years, the patch test has provided a direct experimental approach in man to a very common and significant skin disease. As a result, more is known concerning allergic contact dermatitis than about the many diseases which cannot be reproduced at will.

What is the nature of this disease which can be regularly reproduced by appropriate patch testing? Allergic contact dermatitis is a specific acquired hypersensitivity of the delayed type. It is not necessarily associated with circulating immune globulins such as are found in the immediate urticarial type hypersensitivity. Rather it is mediated through a lymphocyte-borne antibody system. Once acquired, such sensitivity persists for years. Although no portion of the skin is exempt, clinically one sees the classic inflammatory reaction *only* at sites where the antigen (allergen) comes in contact with the epidermis and traverses it in adequate (yet trace) amounts. Hence, the art of patch testing depends on the intimate contact of suspect allergen and normal skin, with maximal opportunity for epidermal penetration. The specific reaction developes within 24 to 48 hours and consists of redness, and with increasing sensitivity, swelling, papules, vesicles, pustules, or bullae. Itching is often a prominent symptom, reflecting the intraepidermal inflammatory change. Histologically the changes are largely nonspecific and consist of perivascular lymphocytic infiltrates, vasodilation, and epidermal intracellular and extracellular edema. Recently, smears of the base of allergic vesicles have been shown to have a diagnostic increase in the number of basophils present. Aside from this basophil response, the changes seen clinically and histologically are relatively nonspecific and appear to a degree, also, as a result of primary chemical irritation. Hence, all testing must be done with materials which have been demonstrated to be nonirritating for normal human skin.

Patch testing is thus a procedure designed to aid in the determination of specific chemicals or materials which might induce allergic contact dermatitis in a given patient. It is not of value in directly assessing the many other inflammatory processes in the skin as, for example, psoriasis, urticaria, lupus erythematosus, or seborrheic dermatitis. Nonetheless, in these latter conditions, intolerance to topical medication may ensue and thus at times call for patch testing.

Methodology

The test material is applied directly to normal healthy skin on a small square (0.5 sq cm) of white cotton cloth. This in turn is covered by a larger piece of cellophane and both kept in place by a piece of adhesive tape. Commercial patches may be used, but in any event the material is kept

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TABLE 1.—Representative Causes of Allergic Contact Dermatitis

Source	*Allergen*
Cosmetics, etc.	Flowers (chrysanthemum, primula)
	Hair dyes (paraphenylenediamine)
	Insecticides (chlorophenothane [DDT], pyrethrum)
	Nail preparations
	Rubber
	Soaps (tetrachlorsalicylanilide)
	Sunscreens
Medication	Adhesive tape
	Nitrofurazone (Furacin)
	Lanolin
	Mercury
	Neomycin sulfate
	Dibucaine (Nupercaine)
	Tars
Occupational	Chromates
	Food (citrus fruit, carrots, tomatoes)
	Formaldehyde
	Rubber gloves
	Turpentine
	Weeds (crab grass, poison ivy, ragweed)
Wearing Apparel	Dyes—furs, stockings, leather
	Formaldehyde in fabrics
	Nickel in jewelry clasps
	Shoes—rubber, adhesive, dyes

in a closed covered system for 48 hours to promote penetration and allow time for the delayed reaction to develop. The area must not be bathed. In every instance the patient is instructed to remove (or have removed) the test tape from any site of pain or burning, no matter what the time interval. Some delayed type reactions are relatively rapid and severe.

A great number of variations of technique have been proposed including the use of pressure dressings, cover glasses, chambers, special tapes, and duplicate paired comparisons, but none achieve total uniformity or standardization. For example, reactions in summer regularly exceed those of winter. In all patients with adhesive-tape sensitivity, screening studies should be done with hypoallergenic tapes to find the least reactive covering. It is generally unwise to test without covering since penetration then is minimal, and the allergen may be spread over wide areas raising the possibility of an extensive reaction.

Since as many as 15 to 20 tests are applied at a time, the back, arms, or thighs prove to be suitable areas, but any site may be employed since the skin is universally sensitized. The palms and soles are not satisfactory, however, due to their very low permeability. Also, areas of cosmetic significance, exposed sites, and hairy areas are generally to be avoided.

The materials which may be tested are legion. Indeed, nearly every item of which has come in contact with the specific areas of clinical dermatitis is under suspicion. Nonetheless, certain items are statistically "good bets" and others such as aluminum compounds, histamine, glucose, or hydrocortisone simply are not antigenic and need never be tested.

What to Test.—A review of a list of common sensitizers such as Table 1 may help, or a search of the experience of others may be necessary. Often the clinical patterning allows one to discern the offending agent; eg, hat-band dermatitis, but in the less obvious case, study of distinctive contact patterns may greatly aid. The history may point up suspects from the standpoint of recurrences correlated with the seasons, weekends, social events, hobbies, or occupation. Diligence here is the hallmark of a good dermatologic sleuth. The list of "criminal" suspects is astounding. An allergic contact dermatitis of the eyelids may call for patch tests to one or all of the following reported causes: primula, nickel or plastic glass frames, nail lacquer, rubber eyelash curlers, hair dyes, setting lotions, eyebrow dye, eyelid shadow, eyelash dye, eye drops, soap powders, household polishes, insecticide spray, fruit peel, newsprint, carbon paper, dyed fur, and assorted cosmetics! Even such a list is incomplete as a recent patient of ours proved

TABLE 2.—A 1966 Scout Tray for Patch Testing

*Common Allergens**	*Amount and Form*
Benzocaine	10% in petrolatum
Epoxy resin	10% in petrolatum
Formaldehyde	5% aqueous
Lanolin	As is
Mercaptobenzothiazole†	1% in petrolatum
Mercuric bichloride	0.1% aqueous
Neomycin sulfate	20% in petrolatum
Nickel sulfate (hydrate)	5% aqueous
Paraphenylenediamine	2% in petrolatum
Poison ivy oleoresin‡	2% in acetone (commercial)
Potassium dichromate	0.25% aqueous
Pyrethrum	As is
Ragweed, short	10% in acetone (commercial)
Thiram†	5% in petrolatum
Turpentine	25% in olive oil

*Consider also topical medicaments, and cosmetics specifically used by patient.
†Significant allergen in rubber. ‡Avoid if known reactor.

by showing an eyelid reaction to the mohair upholstery in her antique car.

Given a suspect material, one should consult the extensive published lists of the proper concentration and vehicle for testing. These have been established by studying normal, nonsensitized persons. In the event the material is not listed, the directions for a similar compound may be employed. If the substance is normally used on the skin, it may often be tested "as is." For example, clothing, leather, topical medication and cosmetics may be so handled. Metals or plastic may also be scraped off and applied directly, as a very fine smooth powder. Exceptions are nail polish and any such material in an organic solvent. Here one applies the solution to the cloth, allows it to dry for many hours, and then applies it to the skin. With totally new substances, control studies may have to be done on ten normal volunteers. Always the effort is to find a concentration which will produce no irritation in even the most sensitive (but nonallergic) skin. A thorough assessment must also be made of the potential systemic or toxic effects of any compound absorbed. The indiscriminate application of poisons, such as insecticide sprays, cannot be justified. In case of doubt in these areas, it is mandatory that such skin testing not be done.

TABLE 3.—Selected Examples of the Significance of the Positive Patch Test

Positive Patch Test (Table 2)	*Advise Avoiding*
Chromium (Potassium dichromate)	Antirust solutions, blue prints, cement, chrome-treated leather (shoes, hat bands, camera cases, wallets, belts), electroplating, lithographing, fur dyes, matches, wood stains, chrome glue, zinc chromate paint and varnishes
Formaldehyde	Antiseptic, explosives, fungicide, leathers, nail hardeners, pharmaceuticals, preservative, resins, soap, waterproofing material
Mercury	Batteries, chemicals, dental materials, electroplating, embalming fluid, engraving, fur processing, hats, insecticides, metal work, paints, photography
Nickel	Bracelet, bobby pins, clasps, curlers, dental instruments, door handles, earrings, eyelash curler, eyelets of shoes, garter clasp, hair pins, metal arch support, metal handbag handles, needles, nickel coin, pen, safety pin, scissors, thimbles, watch band, zipper
Poison ivy	Cashew nuts, Japanese laquer, mango, poison oak, poison sumac
Pyrethrum	Chrysanthemum, ragweed
Turpentine	Cleaning fluid, insecticide, medicinals (eg, Sloan's Liniment), oil paints, resins, shoes, store furniture polish, wax solvent

TABLE 3.—Selected Examples of the Significance of the Positive Patch Test—Continued

	Systemic Drug-Therapy to Avoid (Cross-sensitization)
Ethylenediamine	Aminophylline, antazoline (Antistine), thonzylamine (Neo-hetramine), promethazine (Phenergan), tripelennamine (Pyribenzamine), halopyramine (Synopen [Britain])
Formaldehyde	Methenamine mandelate (Mandelamine), methylene blue (Urised), methenamine (Urotropin)
Iodine	Iodides, iodinated compounds
Mercury	Mercurial diuretics, protoiodide of mercury
Neomycin	Kanamycin sulfate (Kantrex), streptomycin
Para-aminobenzoic acid	Carbutamine, chlorothiazide (Diuril), hydrochlorothiazide (Hydrodiuril), local anesthetics, tolbutamide (Orinase), para-aminobenzoic acid, para-aminosalicylic acid, sulfonamides
Thiram	Disulfiram (Antabuse)
	Related Compounds to Avoid (Cross-sensitization)
Para-phenylenediamine	Aniline dyes, azo dyes (yellow) for stockings, benzocaine, artificially colored food and medicine, para-aminobenzoic acid (sunscreen), para-aminosalicylic acid, picric acid, procaine, sulfanilamide
Iodochlorhydroxyquin (Vioform)	Diiodohydroxyquin (Diodoquin), chlorhydroxyquinoline (Quinolor), chlorquinadol (Sterosan)

At times the physician may discern no proper clues. In these instances, patch testing with a scout tray is indicated (Table 2). Using common known allergens, one may successfully screen for significant contact sensitivity. This is a sound statistical approach which assumes the allergen not to be a rare one. Such scout tray materials, as well as other standardized allergens, are commercially available.

Special Methods of Patch Testing

Open Patch Test.—This technique is employed for testing sensitivity to the oleoresins of plants and vegetation. A drop of commercially available acetone extracts of weeds, plants, or trees is ap-

plied. Twenty-five to 50 screening tests may be done at a time using an aperture marking cover. Readings are made at 48 hours. The patient must not bathe the area during the test period.

Quantitative Patch Test.—Known dilutions of the compound dissolved in acetone are serially applied in a given volume to determine the threshold dilution. This is of limited value in view of the fact that patch test results are not regularly reproducible to an exact degree. Nevertheless, it is used in research and in separating primary irritant reactions which are notably erratic and appear at higher concentrations.

Provocative Patch Test.—Many times clinically the contact sensitizer is eliciting a reaction in an area already dermatitic. Testing it on normal impermeable skin produces no response since none reaches the reactive subepidermal area. This is particularly true for such sensitizers as neomycin, benzocaine, and penicillin. In these instances, a provocative test may be performed by first treating the normal test site with 10 percent sodium lauryl sulfate (SLS) for one hour. This greatly enhances penetration so that subsequent application of the standard patch test is followed by an appreciably amplified number of significant reactions.

Photo-patch Test.—Far from standardized, nevertheless this technique is of real value to the detection of contact photosensitization. Here both the contact allergen, eg, sulfonamide, phenothiazine, or tetrachlorsalicylanide, and ultraviolet light are necessary to elicit the eczematous response. Neither alone is effective. In operation, the standard patch test is applied for 48 hours. Following this and a negative reading, the site and appropriate control is irradiated with artificial short and long ultraviolet light (calibrated lamp, use measured time and distance), or sunlight in quantity sufficient to produce an erythema. Another 48 hours later the sites are inspected for eczematous dermatitic change exceeding the reaction in normal skin.

Vapor Test.—Rarely this is used to detect hypersensitivity to a volatile material. Usually the gas or vapor in appropriate dilution is kept in a small glass cup taped to the skin for 48 hours. Data on control subjects are necessary.

Mucosal Patch Testing.—Mucosal reactions due to contact allergens is rare since the salivary flow usually prevents adequate contact. Usually specific hypersensitivity can be detected by classical patch testing of the skin, but in some instances the impermeability of the epidermis prevents the demonstration. In these rare examples, intimate contact of the mucosa (which is highly permeable) with the material by means of a tiny suction cup for one hour will suffice. Control data are necessary. Readings are of the delayed type and consist of rather nonspecific inflammatory changes leading to erosions.

Readings

These are to be made and recorded by the physician, not the patient. In any litigations, a careful summary of the exact technique will also prove invaluable.

The adhesive plasters are removed at 48 hours, noting that the allergen cloth is still in situ. Each site is encircled and numbered with a skin pencil to permit possible later identification. Usually the tape reactive erythema is gone in 30 to 60 minutes and at this time one will see a reaction at the site of a positive test, ranging from 1+ to 4+. The same is true for the specialized versions described above. The 1+ reaction is merely erythema and is of doubtful significance. The 2+ reaction is erythema plus palpable infiltrates in the form of papules or edema. The 3+ is largely papules and vesicles, whereas the most severe 4+ is vesicobullous. If truly allergic in nature the reactions persist, and unlike primary irritant responses may enlarge beyond exact site of material. Biopsy is not ordinarily helpful, although a smear of the infiltrate at the base of the vesicles will generally reveal an increased number of basophils if the response is allergic. On occasion rereading at 72 hours is necessary to spot an unusually delayed allergic reaction. Rarely the patient may complain of an itchy spot developing two weeks after testing. This is the result of active sensitization of the patient by the patch test. Repeat testing will thus elicit the same eczematous reaction, but within 48 hours.

In some instances a strongly positive patch test may be associated with a detectable flare in the primary clinical problem. In the case of severe local patch test responses, the subsequent healing may require many weeks. This is especially true when the allergen is not easily destroyed or removed by the body. In the dark-skinned person, the complication of prolonged

hypopigmentation or even hyperpigmentation is a problem. The melanocyte is damaged by any allergic dermatitis. Such damage reflects itself in a decreased or increased capacity to synthesize melanin. Scars and keloids are also possible complications, especially if a primary irritant has been inadvertently employed. Death has never been reported as associated with patch testing.

Significance

The reading of a positive test gives the clinician a surge of confidence that he has found the cause but always the proper interpretation requires review: (1) Was the test performed *lege artis*—avoiding primary irritancy? (2) Was the reaction due to the test material and not the tape? (3) Was contamination by inadvertent transfer avoided? (4) Was the reaction truly eczematous and not merely maceration, miliaria, folliculitis, dye discoloration, pustules (as from nickel), or nonspecific pressure damage as from solid particles? (5) Was the reaction a primary one and not simply an extension of an adjacent markedly positive test? (6) Was the patient's dermatitis relatively mild and restricted at the time of testing so that nonspecific hyperirritability could be ruled out? (7) Could impurities present in the sample have been misleading? (8) Finally, was the test substance a reasonable suspect on the basis of the contact history and localization? Remember the patch test gives objective evidence, but it must fit with the presumptive clinical diagnosis or be possibly irrelevant.

The reading of a negative test likewise gives the clinician a surge of confidence that the patch test material is completely innocuous but again proper interpretation requires review: (1) Was the test performed *lege artis*—providing every change for transepidermal absorption? Are you certain the allergen remained in place for 48 hours? (2) Was the concentration too low, or the amount of material too small? (3) If the material was a solid (eg, clothing), should retesting be done with an extract to achieve greater absorption? (4) Could the patient's sensitivity have been temporarily depressed—a very rare occurrence? (5) Could light exposure be a necessary concomitant? Should a photo-patch test be done? (6) Are special factors of heat, friction, maceration, or trauma operative in the area of clinical dermatitis? In such instances, should not the SLS provocative patch test be done to enhance absorption?

The significance of an unequivocably positive patch test usually extends well beyond the specific chemical tested (Table 3). Modern technology spreads the hazard into highly diverse areas, yet the body discerns the allergen, no matter what the matrix. It is imperative to warn the patient about such possible occult exposures. This demands a comprehensive knowledge of applied chemistry, but lists such as those in Table 3 are helpful. Significantly, in exquisitely sensitive patients, even internal administration of the same or a related medication may initiate a "contact type" dermatitis medicamentosa. Thus the significance of a positive patch test extends to warning the patient against certain internal agents. Finally, the patient should be made aware of the hazard of cross-sensitization. Sensitivity to one compound may extend to numerous other chemically similar compounds. These secondary agents must be as studiously avoided as the primary allergen.

Summary

The patch test is an appealing simple method of deriving considerable information concerning a patient's reaction to his contact environment. Yet, it is apparent that the value of the patch test must ever reflect the skill, knowledge, and ingenuity of the physician employing it. Truly, the patch test is a vibrant living procedure which serves best those who know it best.

This investigation was supported in part by a grant from the John A. Hartford Foundation.

(The figures and references may be seen in the original article.)

ATHEROSCLEROSIS: THE FACTS AND THE MYSTERIES*

William Dock, Chief, Medical Service Veterans Administration Hospital, Brooklyn, N.Y., *Bull NY Acad Med 43(9):792–797, September 1967.*

"In the worry and strain of modern life arterial degeneration is not only very common, but develops often at a relatively early age. For this I believe that the high pressure at which men live and the habit of working the machine to its maximum capacity are responsible. Angiosclerosis is the Nemesis through which Nature exacts retributive justice for the transgression of her laws."**

When Virchow's pupils studied the arterial lesions of men, they revised Lobstein's endarteritis nodosa to arteriosclerosis nodosa, and finally Felix J. Marchand suggested that they stop talking about atheromalike arteriosclerotic lesions and simply say atherosclerosis. Atheroma was the medical term for wen or sebaceous cyst, and is still defined as such in our medical dictionaries. While the material in wens and in arterial atheromas is grossly similar, we now know that the histologic and chemical structure of arterial atheromas is much closer to xanthomas of skin and tendons than it is to sebaceous cysts, which contain sebum secreted by epithelial cells. Xanthomas and atherosclerotic plaques contain material chemically close to beta-lipoprotein of plasma and quite different from the lipid in wens, in platelets, or red cells, and significantly different from the alpha-lipoprotein of plasma (T. D. V. Lawrie, cited in Dock[1]). As Wilens has shown, such lipid accumulates in arterial walls when plasma is allowed to percolate through the wall under pressure in excised vessels.[2] It has also been shown that when animals develop these lesions in consequence of dietary change, with or without hypothyroidism, lesions grow faster in hypertensive than in normotensive rabbits, chickens, or dogs.

In man the pulmonary arteries usually are free of lesions when systemic arteries are severely involved. However, severe atherosclerosis is seen in persons who experience the early onset of pulmonary hypertension, as in congenital left-right shunts and mitral stenosis. The pulmonary arteries have blood containing slightly more platelets and lipid than systemic blood, they have similar velocity and volume flow, and they have the same hemodynamic shear force and turbulence at bends and bifurcations. But as long as pulmonary arterial pressure is normal, i.e., below 60 mm. Hg even during exercise, no atheromas form even in familial hyperlipemia, with xanthomas and severe systemic atherosclerosis. The facts of human pathology, obvious even in Virchow's day, thus indicate that percolation pressure is critical for the development of atherosclerosis. Neither platelet stickiness, hyperlipemia, thrombocytosis, nor the stresses produced by the rapid flow of blood around the curving walls cause these lesions where pressure is below 60 mm. Hg.

Once pressure is at that level, rapid flow does accelerate atherogenesis, as we see in the femoral artery leading to an arteriovenous fistula. Similar lesions never occur in veins, even in portal hypertension, even in thick-walled varicose veins. It is a fact that the deposition of plasma lipids percolating through the intima fits the facts of human and experimental pathology, while the mural thrombosis theory is in conflict with these facts. The theory of formation in situ is supported only by the fact that isotopic precursors of cholesterol can be detected in cholesterol formed by bits of arterial intima growing in cultures. But since all body cells can synthesize cholesterol and all intimal tissue contains living cells, this does not prove anything. It certainly fails to explain the absence of atheromas in pulmonary arteries and in veins.

The localization of atheromas in the systemic vessels is related to the pulse pressure and to innate intimal thickness, or that developed as a re-

*Presented at a meeting of the Rudolf Virchow Medical Society in the City of New York, held at The New York Academy of Medicine, January 9, 1967.

**Osler, W. *N.Y. Med.* J. 64:797–806, 1896.

sult of arteritis or, in experiments, of intimal regeneration after injury. Also the rate of atherogenesis, at any given level of plasma lipid or arterial pressure, is faster in young or fast-growing succulent intima than in the aged relatively static tissue. Thus lipid droplets can be seen accumulating in the intima of the aorta and coronary arteries in suckling humans and suckling rabbits. Here arterial pressure is relatively low, and lipid, though high compared to that at birth or after weaning, is much lower than in dietary atherosclerosis of rabbits or the plasma of most adults in the United States. In the rabbits the lipid droplets reabsorb on weaning. Humans who received no dairy products after being taken off the breast also quickly lose the *"Säuglings-Cholesterolosis,"* as Virchow's pupils named this infantile atherosclerosis.

It is not known whether the composition of the intimal ground substance is an important factor in lipid decomposition. G. Manley (cited in Dock[1]) has given data on the relative amount of chondroitin sulphate, heparatin, and hyalouronate, from fetal life to the senium in aorta, pulmonary artery, iliac, and radial arteries. Hyalouronate is more abundant, chondroitin less, in the pulmonary artery. The chondroitin percentage also falls from aorta to radials, rises in aging vessels, and is higher in severely atherosclerotic than in normal iliacs. But this difference may be a result, not a cause, of the atheroma formation. Ground substance and inner elastic lamellae have been given, even in Virchow's writing, as "the cause" of arteriosclerosis, and this conjecture is still urged by Moon and by Holman. The mystery is why degeneration occurs in certain sites and on certain diets.

It now seems well established that the beta-lipoprotein levels in plasma are higher in animals or men with atheromas than in controls of same age and sex, and that they are higher in young men than young women. But by the time thrombosis and clinical disease occur, cholesterol or beta-lipoprotein levels in many populations are relatively less elevated in coronary cases than are the plasma triglyceride levels. The latter affect platelet stickiness, fibrinolysin, and plasma clotting times more than do the beta-lipoproteins. Another mystery is that the sex difference in lipids, coronary disease, and thromboembolic disease, which is so striking in white people, is absent or, at early ages, reversed in the United States Negroes. Thus sex hormones, genetic background, and diet all play important roles in determining plasma content of the lipids that are deposited in atherosclerosis and that accelerate thrombosis. In white people, the diet of young men and women is very different just at the time when adolescent boys are rapidly developing plaques in the aorta and the coronary arteries but we have no reports on diet, hormone levels, or paths of hormone degradation in Negro women as compared with whites.[3]

So far as relation of diet to plasma lipids is concerned, we have plenty of facts. Individuals and species vary enormously in sensitivity to cholesterol, to saturated fats, to sucrose,[4] and even to high calorie intake of unsaturated fat and starch. In people with xanthomas and high lipids, alcohol and saturated fats raise levels, while diets low in calories, but with a high ratio of polyunsaturated fat to calories may strikingly reduce triglycerides and beta-lipoprotein, as well as cholesterol in plasma. The diets that raise lipids and cause atherosclerosis in birds and animals, the diets consumed by populations with high rates of coronary disease and thromboembolism, are also diets that raise lipid levels in patients with coronary disease when such diets are resumed after they have been on therapeutic trials of diets normal for primates—fruit, vegetables, grain, fish, lean meat, and oils pressed from seeds. Caffeine and nicotine, which raise lipid levels of coronary patients, apparently act like catecholamines, emotional stress, or hypothalamic stimulation of rabbits, all of which raise lipid levels in those on atherogenic diets.

Last, let us turn to the theories on mural thrombosis, intimal hemorrhage, and the ulceration of atheromas that so often triggers thrombotic occlusion. Carl von Rokitansky and other early observers thought the plaques might be organized mural thrombi, and this thesis has been espoused recently by J. B. Duguid in Britain. It ignores the absence of similar lesions in veins and pulmonary arteries, and the mural injury that might initiate thrombosis and become "the" original cause. The opposite view was given in detail in 1938 by Milton C. Winternitz.[5] His monograph gives an excellent review of earlier studies of the arterial vasa vasorum and of intimal hemorrhages. To Winternitz purpura from the rare normal vasa entering the intima could initiate the formation of plaque, or by damaging or rupturing the surface could cause mural thrombosis, leading to further

vascularization and larger hemorrhages or occlusive thrombosis.

Lately Friedman[6] has urged the "paucity" of intimal vessels, even when plaques have been formed due to lipid infiltrate from the plasma. He feels that mural hemorrhages are extremely rare, while J. C. Patterson in Canada, and Milton Helpern in New York regard them as frequent and occasionally large enough to cause stenosis and myocardial infarction without luminal rupture and thrombosis. Like M. Friedman, S. Wilens (cited in Dock[1]) is impressed by rarity of vascularization of the plaques and considers this the main reason they become necrotic. Winternitz' beautiful illustrations of vessels in early lesions, both in the aorta, and in coronary arteries, seem to have been overlooked by Friedman. On the other hand, we do not know how rare or common such lesions are when sought by the injection and clearing technique used by the Yale group. We can accept as facts that plaques ulcerate and cause thrombosis, that undermining at sites of ulceration can stimulate mural hemorrhage, but just how ulceration occurs and whether hemorrhage into plaques is very rare, occasional, or frequent remains a mystery.

From the standpoint of Virchow, who thought of morbid anatomy only as a small part of the picture of disease and of the far greater spectacle of human suffering, the most important fact is that arteriosclerosis flourishes best on our curious diet, a product of wealth and our industrial production of eggs, dairy products, and stall-fed swine and cattle, as well as of sucrose, nicotine and caffeine. These latter items were exotic or unknown to Western Europe before the 16th century. The foods were daily items of diet only for the most prosperous people until the 20th century. Frustration, hostility, anger, all raise blood lipid levels, but in animals or men on physiologic diets the effects on the vessels are minimal.

The next most important fact is that patients and doctors would rather risk shortening their lives than give up customary pleasures. Most men and women will reject the notion that diet can cause disease, although they will usually attribute the pain at onset of coronary disease to some item in the last meal they ate. In 1916 William Ophüls, professor of pathology at Stanford University, began to teach medical students that diet was an important and perhaps the only controllable factor in atherosclerosis. T. Leary at Boston University followed in 1934. But none of their students believed a word of it. Today only a minority of physicians accept this in principle, fewer still in practice or in their own way of life. Man not only fails to burn up cholesterol and saturated fat as do the carnivores, but fails to face the facts of life, in pathogenesis as in politics. Machiavelli remarked that "a man would sooner forgive the murder of his father than the theft of his patrimony." As long as men will sooner forgive the loss of their lives than the loss of new-found foods and drugs inhaled or ingested all day long, there will always be a high death rate from atherosclerosis and from bronchial cancer.

References

1. Dock, W. Confusion in coronary lesions compounded, *Amer J. Cardiol.* 18:150, 1966 (13 references).
2. Wilens, S. T. and McClusky, R. T. Permeability of excised arteries and of other tissues to serum lipids, *Cir. Res.* 2:175–82, 1954.
3. Dock, W. Why are men's coronary arteries so sclerotic? *J.A.M.A.* 170:152, 1959 (17 references).
4. MacDonald, I. and Braithwaite, D. M. Influence of dietary carbohydrate on the lipid pattern in serum and in adipose tissue, *Clin. Sci.* 27:23, 1964.
5. Winternitz, M. C., Thomas, R. M. and LeCompte, P. M. *Biology of Arteriosclerosis*, Springfield, Ill., Thomas, 1938.
6. Friedman, M. and van den Bovenkamp, G. The pathogenesis of coronary intramural haemorrhages, *Brit. J. Exper. Path.* 47:347, 1966.

ROLE OF EMOTIONAL STRESS IN THE ETIOLOGY OF CLINICAL CORONARY HEART DISEASE*

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The concept of any disease arising from a single cause is obsolete and misleading. Even if one accepts the view that the plasma B-lipoproteins constitute the etiologic agent in atherosclerosis, there are constellations of interacting factors which may influence not only the concentration of serum

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lipids, but also the susceptibility of the arterial intima to lipid deposition, and the vulnerability of the myocardium to diminished coronary flow. It has been clearly shown in organ cultures that apparently normal intimal cells from patients with atherosclerotic changes have increased susceptibility as a specific characteristic. Thus with similar elevation of blood cholesterol there are considerable variations in the observed severity of aortic and coronary lesions. It is significant that a large proportion of patients with clinical coronary heart disease (as many as 50 percent or more, depending on one's criteria) show no demonstrable abnormality of the lipid constituents of the blood. Consequently, the susceptibility of arterial intimal cells to lipid incorporation, rather than the dose of the agent, may be the determining factor for disease causation in many patients. In similar manner the vulnerability of the myocardium to diminution in coronary flow rather than the extent of the vascular lesion may be crucial in some cases. Particularly on the abundant diet of Western society, the B-lipoprotein concentration may be a less important variable in causing overt disease in many individuals than such factors as stressful and sedentary existence, hypertension, tortuousity of vessels or hereditary predisposition to the degeneration of vascular connective tissue.

Since atherosclerosis is something more than a nonspecific response to hyperlipemia and is often associated with a vascular metabolic abnormality in the handling of serum lipids, the numerous host and environmental factors which influence not only serum lipid concentration, but also vascular reactivity must be carefully considered in any study of its pathogenesis. Olson has presented this broad concept in the following epidemiologic triangle from which it is readily apparent that multiple interacting factors contribute in varying degree to the initiation and progression of this widespread disease.

The Coronary Prone Personality

Seventy years ago, Osler listed heredity, rich diet and, above all, the "worry and strain of modern life" as the causes of arteriosclerosis and especially of coronary diseases. Although there is almost universal agreement that both heredity and a high fat diet are implicated in the pathogenesis of atherosclerosis in man, continued skepticism exists in many quarters concerning the role of the emotions in the causation of this disease. Osler's views were based on an intimate knowledge of the life situation, personality and behavior of patients who develop coronary disability before the age of 60. He described the typical patient with coronary disease as "a keen and ambitious man, the indicator of whose engines is always set at 'full speed ahead.'" Arlow observed, "a compulsive striving for achievement and mastery which never seems to end." Kemple characterized the coronary patient as an aggressive, ambitious individual with an intense physical and emotional drive, unable to delegate authority or responsibility with ease, possessing no hobbies and concentrating all his thoughts and energy in the narrow groove of his career. Wolf has compared the "coronary-prone individual" with the mythologic Sisyphus, "who passed the time in Hades pushing a large rock up a steep hill and never quite getting it there." The candidate for coronary disease, he asserts, is a person who not only meets a challenge by putting out extra effort, but who takes little satisfaction from his accomplishments. An identical behavior pattern, delineated by Friedman and Rosenman, has emphasized the prevalence of intense ambition, competitive drive, sense of urgency, and preoccupation with deadlines among persons predisposed to clinical coronary disease. More than 80 percent of these subjects, they found, exhibited a behavior pattern characterized by "excessively rapid body movement, tense facial and bodily musculature, explosive conversational intonations, hand or teeth clenching, excessive unconscious gesturing and a general air of impatience.

While a significant proportion of our young coronary patients did manifest some or all of these characteristics, we consider this description to be a caricature rather than a portrait of the average coronary patient under the age of 40 in our series. The majority did not exhibit such easily recognized outward behavior characteristics. In fact, most of the young patients under observation have shown a striking degree of self control, dignified reserve, and outward complacency during interrogation. In most of these, psychologic factors would have remained unrecognized had a special inquiry not been made regarding their presence. The most characteristic trait of the young coronary patient was his restlessness during leisure hours and his sense of guilt during periods of "relaxation." As a consequence, he rarely took vacations, and such leisure time as he did possess was frequently regimented by obligatory participation in

TABLE 1.—Incidence of Various Factors in Patients who had Coronary Attacks and in Control Groups

	No.	Heredity (Positive)	High-fat Diet	Stress and Strain (Occupational)	Obesity	Tobacco (30 Cigarettes, Plus)	Exercise
Coronary group	100	67%	53%	91%	26%	70%	58%
Control group	100	40%	20%	20%	20%	35%	60%
Ratio		1.7:1	2.7:1	4.6:1	1.3:1	2:1	1:1

an assortment of social, civic or educational activities. Impressive as these observations all appear to be, they suffer from a common weakness arising from retrospective analysis of values which can only be qualitatively estimated. Strong support for their validity, however, can be found in the careful prospective studies of Rosenman and associates. These authors have shown that possession of the specific behavior pattern, which they have so clearly described, appears to accelerate the advent of manifest coronary heart disease. Moreover, the exhibition of this behavior pattern furnished the most important single predictive entity of all suspected pathogenetic factors. The mechanisms by which behavior may be associated with a higher prevalence of coronary heart disease have not been clearly identified. Any assessment of the etiologic role of a specific personality type presents the same problems as are currently encountered in the evaluation of the pathogenetic significance of tobacco smoking. Both factors may be "causative" or merely associated with an underlying genetic predisposition to the disease. Nevertheless, since emotional stress is, on the one hand, an inevitable by-product of compulsive behavior and, on the other, a major determinant of excessive indulgence in tobacco, this common denominator must continue to be held suspect in coronary disease etiology.

Emotional Stress

Much evidence now suggests that most of the lethalness of a high fat diet in Western society may actually be dependent on the "catalytic" influence of stressful living. While behavior patterns may generate "stress" independently of the demands of the job, there is good evidence to indicate that occupational responsibilities may be directly related to coronary heart disease prevalence rates. In a study of 100 young coronary patients, 25 percent had been holding down two jobs and an additional 46 percent had worked 60 hours or more per week for long periods immediately preceding the onset of symptoms. Although prolonged emotional strain associated with job responsibility had preceded the attack in 91 percent of these 100 cases, similar stress was observed in only 20 percent of the controls. Thus, psychic stress of occupational origin appeared to be far more significant in the etiologic picture of coronary disease than did a positive heredity, a prodigiously high fat diet, obesity, body build, tobacco consumption or exercise (Table 1). Buell and Breslow have confirmed a greater mortality risk from arteriosclerotic-coronary heart disease among occupational groups working more than 48 hours per week. Similarly, a survey of 12,000 professional men in 14 occupational categories showed that the marked gradient in distribution of the disease appeared to be unassociated with heredity or diet, but strikingly related to the relative stressfulness of occupational activity.

It has been argued that racial groups in various geographic areas (Korea, China, Japan and Yemen) who subsist on relatively low fat diets have appeared to exhibit a distinct immunity to coronary disease despite obvious emotional stress in their patterns of life. Since this immunity seems to be lost when high fat diets are ingested, the role of the emotions has been relegated to a position of secondary significance by some observers. It cannot be denied that the lethalness of emotional stress is strongly mitigated, if not nullified, by subsistence on a diet low in fat. Snapper, in studying the Chinese population under the severe

stress of Japanese invasion, long ago concluded that stress has little or no effect if the diet is poor in animal fat. Nevertheless, there is good evidence to indicate that the atherogenicity and lethalness of a high fat diet in Western society is greatly compounded by the influence of stressful living.

Pathogenetic Interrelationship Between Emotional Stress and Dietary Fat

Groen and associates' findings in a study of Benedictine and Trappist monks provide insight into the role of fat as related to stress in the genesis of coronary disease. Both groups live in rural areas removed from the stresses of urban life and, in the monastic environment, are free from economic and family problems. The Benedictines have a diet substantially the same as other Europeans, while the Trappists do not eat fish, meat, eggs or butter. Although there is a much higher average level of blood cholesterol among the Benedictine monks, no striking differences were observed in coronary heart disease prevalence and not a single instance of significant disease was encountered under the age of 65 in either group. Moreover, both groups showed a far smaller incidence of coronary disease than the general population. It appears significant, therefore, that although the "unstressed" Benedictine monk eats as much fat as the greatly harassed general practitioner of medicine, he suffers only about one-fifth as frequently from clinical coronary disease. Of the many variables which undoubtedly participate, none appears more decisive than psychic stress. Similarly, it is noteworthy that Somali camel herdsmen appear to be relatively free from clinical symptoms suggestive of atherosclerosis although they subsist on a high fat diet derived from approximately 5 liters of camel's milk per day. While many theories may be advanced to explain this paradoxic immunity, a major factor in these persons, whose pastoral and patriarchal way of life has remained unchanged for centuries, could be their relative freedom from serious psychologic stress. Although physical fitness as a result of vigorous activity has been reported to protect the Masai despite a diet rich in animal products and dairy fat, freedom from clinical disease in this East African pastoral people could also be, in the main, an outcome of the simplicity of their way of life. In like manner, the unusually low incidence of death from myocardial infarction reported for the Italian-American community of Roseto, Pennsylvania similarly suggests that the way of life may be an important determinant of the atherogenicity of a high fat diet. Consequently, while habitual diet and stressful living both appear implicated in the pathogenesis of clinical coronary disease, there is mounting evidence to suggest that *each is dependent upon the other for pathologic significance.*

Influence of Stressful Living in Animals

Inasmuch as dietary habits among various population groups reflect profound differences in patterns of living, "diet cannot be readily isolated from the matrix of man's total transaction with his environment." In the animal kingdom, however, major environmental factors have been identified and controlled far more readily and completely than is possible with the corresponding factors in human society. For example, in mammals and birds at the Philadelphia Zoo on a constant diet, there has been a ten-fold increase in arteriosclerosis of the coronary arteries during the last decade. This increased susceptibility to vascular degenerative lesions has been ascribed to psychologic disturbances evoked by social interactions attending increased population densities in the zoo. Man's response to population density appears to correspond closely to that of other animals. This is reflected in the significantly higher death rate from clinical coronary heart disease that has been found in metropolitan communities as compared with rural areas.

Stress and Atherosclerosis in The Experimental Animal

Experimentally, the profound but dependent role of "stress" in atherogenesis has been clearly confirmed. Thus, it has been shown that hypercholesterolemia and aortic atherosclerosis in cholesterol-fed rabbits may be either augmented or reduced by drugs which stimulate or depress the central nervous system. Similarly, greater degrees of hypercholesterolemia and coronary atherosclerosis have been evoked in rats fed an atherogenic diet and exposed to a particular form of stress than in their unstressed controls. Additional experiments were needed, however, to determine whether such stresses alone are capable of initiating atherosclerosis when the diet is low in fat. Clear answers were provided by the care-

ful studies of Gunn and associates in rabbits. These authors found that on a cholesterol-rich diet, hypothalmic stimulation, like other forms of stress, increased the atherogenicity of diet alone. More important was the observation that hypothalamic stimulation in controls on a low cholesterol diet left the vascular system unimpaired. These experimental studies appear to correlate with epidemiologic data obtained in man. Thus, like "stressed" animals in the laboratory, "stressed" humans have manifested no increased susceptibility to atherosclerosis unless the composition of the diet had been relatively high in animal fat.

At present, there is no clear understanding of the manner in which emotional stress may hasten the advent of clinical coronary artery disease. Elevation in blood cholesterol level, metabolic changes in the vascular wall leading to an increase in its lipid receptiveness, augmentation of myocardial oxygen requirements, and increase in the coagulability and viscosity of the blood all appear to be implicated. Thus, prolonged emotional stress acting through the cerebral cortex and hypothalamus via neurohormonal and hormonal mechanisms may contribute not only to the initiation and progression of atheromatosis but also to its clinical complications.

Influence of Emotional Stress on Homeostasis

Numerous investigators have shown that stressful life experiences are capable of evoking hypercholesterolemia despite constant diet and exercise. Bogdonoff and associates have also shown that emotional episodes cause rapid mobilization of nonesterified fatty acids from the body tissues into the circulation and have obtained similar results with infusions of epinephrine and arterenol. Steinberg and Shafrir and others have demonstrated in animals that it is cortisone which enhances the ability of epinephrine to trigger sharp blood lipid increases under the influence of psychic stress. They observed a marked and almost immediate rise in the nonesterified fatty acids followed by a slower but definite rise in serum cholesterol. According to Sabin, free fatty acids are irritating and, in excess, may cause subendothelial hemorrhage and small mural thrombi. Whatever the exact mechanisms underlying such responses may be, hyperlipemia so evoked is believed to "provide metabolic substrate for the aroused organism."

As a result of stress, sympathetic adrenergic effects on vascular tissue metabolism, by primarily damaging the intima, may prepare the soil for subsequent lipid depositions. Prolonged vasoconstriction could reduce blood flow in the vasa vasorum and produce vascular wall ischemia leading to increased permeability and intramural edema. Raab and Humphreys have shown that catecholamines also diminish myocardial efficiency by wasting oxygen in a disproportionate fashion. Through this action, the hormones are capable not only of increasing myocardial vulnerability in the presence of coronary atherosclerosis, but also of inducing severe, potentially necrotizing myocardial hypoxia in animals with perfectly normal coronary vessels. Indeed, Raab and associates have recently produced myocardial necroses in rats solely by subjecting these animals to sensory and emotional stresses. Groover and others have also reported myocardial infarction without demonstrable atherosclerosis in baboons subjected to the emotional storm induced by trapping and caging. It seems probable, therefore, that occult disease in man may surface to clinical view solely or prematurely as a result of stressful life experiences.

The blood clotting elements have also been found to be susceptible to emotional stresses. Dreyfuss and Czaczkes measured the clotting time and found it to be accelerated in 36 medical students the morning of a final examination in medicine. Still and Heiffer demonstrated sharp increases in viscosity mediated through action of the sympathetic nervous system as the result of emotional stimuli in animals. More significantly, stress-induced platelet elevation with reduction in blood clotting time has been reported in human subjects. Such changes appear to be part of an adaptive response to combat, designed to prevent blood loss. When this mechanism reacts excessively over a prolonged period of time, blood with increased coagulability and decreased fluidity may slow sufficiently in passing through narrowed coronary or cerebral arteries to produce thrombosis.

Atherosclerosis as a Maladaptation Syndrome

Wolff has stated that, "Man, feeling threatened, may use for long-term purposes devices designed for short-term needs. They are not designed to be used as lifelong patterns and when so utilized may damage structures they were designed to protect." In many instances, therefore, atherosclerosis and coronary heart disease may represent a maladaptation syndrome in which the organism already

oversupplied with metabolic substrate remains in a chronic state of mobilization for "fight or flight" as a result of stressful life situations. While mechanisms so evoked appear innocuous in "immune" groups subsisting on a low fat diet, these adaptive devices may greatly augment the atherogenicity and lethalness of excessive ingestion of fat and hypercholesterolemia.

The American Heart Association has recently listed the chief risk factors in coronary heart disease as hypercholesterolemia, overweight, high blood pressure, lack of exercise, cigarette smoking and diabetes. It is well recognized that emotional tension may result in compulsive eating, drinking, and smoking in many persons as compensation for anxiety. Moreover, it does frequently contribute to the failure to achieve daily exercise by promoting fatigue, creating a sense of time urgency, and decreasing motivation. Nervous strain of occupational, cultural, social or domestic origin is known to elevate blood pressure, to increase the tendency to obesity, to contribute to excessive smoking and lack of exercise, to participate in hypercholesterolemia, and to aggravate diabetes, through psychic influences and alteration of the functional characteristics of the mode of life. *Consequently, even such indirect effects of emotional stress, barring all others, must elevate this factor to a position of considerable significance in the etiological picture of coronary heart disease.*

Summary

The concept of any disease arising from a single cause is obsolete and misleading. Much evidence now suggests that most of the lethalness of a high fat diet in Western society may actually be dependent on the "catalytic" influence of stressful living. Indeed, while habitual diet and psychic stress both appear implicated in the pathogenesis of clinical coronary disease, there is mounting evidence to suggest that *each of these factors is dependent upon the other for pathologic significance.* Observations in the animal kingdom, in the experimental laboratory, and in epidemiologic surveys all attest to the validity of this pathogenetic interrelationship. Like "stressed" animals in the laboratory, "stressed" humans have manifested no increased susceptibility to atherosclerosis unless the composition of the diet had been high in animal fat. Contrariwise, numerous examples are now at hand to indicate the low atherogenicity of a high fat diet when there is relative freedom from serious psychologic stress.

Despite the profound effect of "stress on homeostatic mechanisms this factor has been largely ignored by most authorities in the field of coronary artery disease. Major emphasis has been placed on hypercholesterolemia, overweight, high blood pressure, lack of exercise, cigarette smoking and diabetes. Nevertheless, nervous strain is known to elevate blood pressure, to increase the tendency to obesity, to contribute to excessive smoking and lack of exercise, to participate in hypercholesterolemia, and to aggravate diabetes, through psychic influence and alteration of the functional characteristics of the mode of life. Consequently, even such indirect effects of emotional stress, barring all others, must elevate this factor to a position of considerable significance in the etiologic picture of coronary heart disease.

(The omitted figures and references may be seen in the original article.)

PORPHYRIA PRECIPITATED BY FASTING*

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A variety of chemotherapeutic drugs, such as barbiturates, sulfonamides, estrogens and griseofulvin, may precipitate the acute onset of symptoms in patients with acute intermittent porphyria. Toxic porphyria in human beings and experimental porphyrinuria in animals have been induced by exposure to several different chemicals.

Caloric reduction may have a profound influence on both experimental porphyrinuria and spon-

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taneous acute intermittent porphyria in human beings. The incidence of allylisopropylacetamide-induced porphyria in rats was increased by a reduction of the carbohydrate and protein content of the diet, with a high percentage of porphyrinuria occurring during starvation. Welland et al. described increased excretion of δ-aminolevulinic acid and porphobilinogen in patients with latent acute intermittent porphyria by caloric restriction, particularly reduction of carbohydrate and protein, although total caloric deprivation was not undertaken.

Recently, the first attack of porphyria developed in an obese patient while he was undergoing fasting for weight reduction.

Case Report

K. C., an 18-year-old Negro male food-service worker, was admitted to the Metabolic Unit of Wilford Hall USAF Hospital on November 30, 1965, for the study of total caloric deprivation. He had been obese for his entire life, but otherwise was in good health. Specifically, he denied rashes, sensitivity to light, dark urine, abdominal pain or neurologic symptoms. There was no family history of porphyria. Physical examination revealed an obese Negro who weighed 90.7 kg. (200 pounds) and was 173 cm. tall. The remainder of the examination was noncontributory, without abdominal or neurologic abnormalities.

He was given only distilled water, with no vitamin supplementation. On the 8th day of fasting he suddenly became nauseated and vomited, but had no abdominal pain. Jaundice was not present, and an abdominal examination was negative. Transient oliguria developed, with the passage of only 250 ml. of mahogany-colored urine in 24 hours. Several qualitative tests for porphobilinogen using chloroform, butanol and ether extraction were positive. On the following day diffuse cramping abdominal pain began, gradually increasing in intensity. The abdomen remained soft, with active bowel sounds, but moderate left-lower-quadrant tenderness to deep palpation and localized rebound tenderness occurred. The patient complained of difficulty in swallowing and inability to control tongue movements. Fluids containing glucose, 150 gm. per 24 hours, were infused intravenously, and the fast discontinued. The symptoms gradually abated over the next several days. The qualitative test for porphobilinogen remained positive for 3 days after the onset of symptoms, with adequate flow of urine, but became negative after 36 hours of fluids given intravenously. Treatment included chlorpromazine, prochlorperazine, meperidine, trimethobenzamide and diphenhydramine, without barbiturates or sulfonamides.

There had been no further attacks of porphyria as of March, 1967.

Discussion

Acute intermittent porphyria is a unique metabolic disease, being the first inborn error of metabolism associated with an increase, rather than a decrease, of a specific enzyme; δ-aminolevulinic acid synthetase (ALA synthetase) is the rate-controlling enzyme of porphyrin biosynthesis. An excess of this enzyme, and subsequently of porphobilinogen, is due to the induction of the synthetase in liver mitochondria. Chemical substances precipitating acute porphyria or producing experimental porphyria have been shown to induce a marked increase in the synthetase. Its induction is inhibited by carbohydrate administration, producing an explanation for the reciprocal relation between the carbohydrate intake and the ability to reproduce experimental porphyrinuria or to increase the excretion of δ-aminolevulinic acid and porphobilinogen in patients with latent porphyria. Fasting produces an increase in several hepatic enzymes and an increase in δ-aminolevulinic acid synthetase may also occur during fasting, resulting in an attack in a susceptible patient with latent acute intermittent porphyria.

Conclusions

Fasting, as well as certain chemotherapeutic agents, may be capable of precipitating symptoms in latent acute intermittent porphyria. Experimental evidence indicates that the mechanism probably is the induction of δ-aminolevulinic acid synthetase by caloric deprivation.

(The references may be seen in the original article.)

EFFECTIVE ANTIFUNGAL DRUGS AND INDICATIONS FOR THEIR USE

Harry M. Robinson, Jr., MD, Med Clin N Amer 51(5):1181–1188, September 1967.*

During the past 10 years many chemotherapeutic agents have been developed for the management of superficial and deep fungus infections. Some of these, such as amphotericin, nystatin, and griseofulvin, are antibiotics; others, like tolnaftate and hydroxystilbamidine, are complex chemical compounds. Most of these drugs have selective specific action against certain individual superficial or deep fungus infections. Prior to the introduction of griseofulvin for the systemic treatment of superficial mycotic infections, physicians were dependent on relatively ineffective topical preparations containing keratolytic agents (benzoic acid, salicylic acid, or the salts of undecylenic acid and propionic acid) as the active ingredients.

It must be emphasized that these antifungal drugs are specifically intended for the management of mycotic infections and are of no value in the treatment of other conditions. The failure of other dermatoses to respond to administration of these compounds has been repeatedly demonstrated. The similarity in clinical appearance of cutaneous fungus infections and other dermatoses makes the laboratory diagnosis essential. The presence of fungi must be established by direct microscopic examination before therapy is initiated with these new remedies. The causative organism must be demonstrated by culture.

Although specific agents have been developed for the treatment of many of the deep fungus infections, the saturated solution of potassium iodide is still the drug of choice in the treatment of sporotrichosis. Penicillin is the most effective agent in the treatment of actinomycosis and the sulfonamides are preferred in the treatment of nocardiosis.

Topical Therapy

The preparations described in the following paragraphs are the only effective topical fungistatic or fungicidal drugs commercially available for human use. Preparations containing the salts of undecylenic acid or propionic acid depend on keratolytic activity for therapeutic value and are inferior to tolnaftate, nystatin, and amphotericin B in producing satisfactory subjective and objective improvement.

Tolnaftate

Tolnaftate (O-2-naphthyl m, N-dimethylthiocarbanilate), synthesized in 1960, is the first chemical compound to have specific fungicidal activity on topical application. It is a colorless, odorless compound that is soluble in most organic solvents and insoluble in water. In vitro studies indicate that tolnaftate has the ability to distort hyphae and stunt the mycelial growth of susceptible species.[1] Quantitative studies using the agar dilution test method showed that tolnaftate in a concentration of 0.075 μg./ml. is fungistatic against Trichophyton mentagrophytes and at 0.0075 μg./ml. by the tube dilution method. The fungicidal level was 0.75 μg./ml. by the agar dilution method and 0.075 μg./ml. by the tube dilution method. In vitro studies also proved that tolnaftate is ineffective against Candida albicans and gram positive and gram negative bacteria.

Oral and parenteral administrations of tolnaftate were ineffective in the treatment of guinea pigs inoculated with mycotic infections. However, when these same pigs were treated with the drug applied topically, involution of lesions and negative cultures developed within 7 to 9 days. In vitro studies indicate that tolnaftate has antifungal activity against infections produced by Microsporum gypseum, Trichophyton rubrum, Microsporum canis, Epidermophyton floccosum, Trichophyton tonsurans, Microsporum audouini, and Trichophyton mentagrophytes. Clinical trials proved it to be effective in the treatment of tinea versicolor. Cutaneous monilial infections were not benefited.

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Clinical Indications. One percent solution of tolnaftate in polyethylene glycol or a vanishing cream base proved to be an effective agent for the treatment of superficial mycotic infections due to Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum, Microsporum canis, Trichophyton tonsurans, and Microsporum audouini. Lesions on the trunk and in the groins involuted in 10 to 14 days. Lesions on the scalp due to Trichophyton tonsurans and Microsporum audouini did not respond to this topical medication. Lesions due to Candida albicans did not respond. Satisfactory results were not obtained in the treatment of onychomycosis. In all conditions in which itching was a prominent symptom, there was relief in 24 to 72 hours regardless of the duration of the eruption. Involution of interdigital lesions due to the previously mentioned susceptible fungi was complete in 7 to 21 days. This result could not be accomplished by the use of systemically administered griseofulvin or topically applied keratolytic agents. Tolnaftate solution is effective in the treatment of tinea versicolor.

One percent solution of tolnaftate in polyethylene glycol or in a vanishing cream base is to be applied topically to the involved areas twice daily. It is usually necessary to use 10 percent salicylic acid ointment or Whitfield's ointment alternately with the tolnaftate preparation in the treatment of hyperkeratotic palmar or plantar infections.

Toxic Effect. Adverse reactions to the topical application of tolnaftate were not encountered. In massive doses, administered to dogs, the drug did not produce toxic effects. Doses of 0.5 gm./kg. daily for 30 consecutive days did not produce abnormalities in external appearance or body weight and there were no gross or microscopic pathologic changes observed at autopsy.

Evaluation of Results. Tolnaftate in one percent solution or cream applied topically proved to be an effective antifungal agent in the treatment of eruptions due to Trichophyton rubrum, Trichophyton mentagrophytes, Trichophyton tonsurans, Epidermophyton floccosum, Microsporum canis, Microsporum audouini, Microsporum gypseum, and Malassezia furfur. Evidence of primary irritation or acquired contact sensitivity was not encountered in a series of 323 patients. The preparation has proved to be ineffective in the treatment of eruptions due to Candida albicans or lesions in the scalp or nails due to the dermatophytes. The relapse rate in patients treated with tolnaftate approximates the rate obtained with those treated with griseofulvin. Evidence of resistance did not occur and patients responded to retreatment with the topical compound. Establishment of the diagnosis by laboratory methods is essential.

Acrisorcin (Akrinol)

Acrisorcin (9-aminoacridine salt with 4-hexylresorcinol; 9-aminoacridinium 4-hexylresorcinolate) is an antifungal agent whose sole value is in the treatment of tinea versicolor. It is a colorless, odorless compound dispensed for clinical use in 0.2 percent concentration in a vanishing cream base. The effectiveness of this substance in the treatment of tinea versicolor was determined by clinical experimentation alone because suitable laboratory methods for its evaluation have not been developed.[2] The use of Akrinol should be restricted to the treatment of tinea versicolor because it is not effective in the treatment of any other cutaneous infection.

Dosage. The 0.2 percent acrisorcin cream is applied to the involved areas twice each day. Patients should be instructed to take a shower with copious amounts of soap and water each morning and evening, rinse thoroughly, pat the skin dry, and then apply the medication. Treatment should be continued for at least 4 weeks after direct microscopic examinations from the lesions are negative for Malassezia furfur.

Evaluation of Results. The difficulties of performing an adequately controlled study in the treatment of tinea versicolor are apparent. The condition itself is chronic and prone to relapse. Experience has indicated that relapses do respond to re-treatment with acrisorcin. The drug is not as effective as tolnaftate solution or cream.

Nystatin (Mycostatin)

Nystatin, $C_{46}H_{77}NO_{19}$, is a pale yellow, water-insoluble, almost odorless substance. It is an antibiotic extracted from Streptomyces noursei and has specific action against Candida albicans. The drug is of no value in the treatment of any other type of infection. It is poorly absorbed from the gastrointestinal tract and even after administration of exceptionally large doses the blood level is insignificant.

Clinical Indication. Nystatin is effective in the treatment of localized candida infections in the vagina, on the skin, and in the mouth. It may be

used in conjunction with broad spectrum antibiotics to prevent intestinal monilial infection. The superficial monilial infections that commonly occur in the groin, vagina, and mouth, at the angles of the mouth, between the fingers, and in the nail folds respond to topical therapy with Mycostatin when dispensed in a suitable medium. Nail involvement due to Candida albicans is not benefited.

Dosage. A combination of Mycostatin with neomycin and a steroid prepared in a vanishing cream or ointment base is effective in the treatment of pérleche (angular cheilitis) and Candida albicans infections of the groins or anal area.

Monilial infection of the vagina will respond to the insertion of vaginal tablets (100,000 units) twice daily for a minimum period of 2 weeks. It may be necessary to repeat this treatment for relapses. Evidence of resistance to the drug has not been encountered. In the treatment of thrush (monilial oral infection), Mycostatin powder is an aqueous suspension containing 100,000 units of nystatin per cubic centimeter, is administered orally. Patients are instructed to take approximately 2 cc. in the mouth and hold it for a prolonged period before swallowing. This same procedure is to be repeated three or four times daily. Treatment should be continued for a prolonged period after all clinical lesions have subsided.

The coated tablets of nystatin, each of which contains 500,000 units, are effective in the treatment of intestinal monilial infection. The patient should be given four 500,000 unit tablets daily in divided doses. If given concurrently with a bacterial antibiotic, the Mycostatin must be administered over the same period of time as the other drug.

Monilial infection of the lungs, liver, and other organs responds poorly to systemic nystatin primarily because of poor absorption from the gastrointestinal tract.

Selenium Sulfide

Selenium sulfide detergent suspension (2.5 percent) and the 0.5 percent ointment have been recommended as a topical treatment for seborrheic dermatitis. Robinson and Yaffe[3] found that selenium sulfide is of value in the treatment of tinea versicolor. Their original study was conducted using the 0.5 percent selenium sulfide ointment but more recently the suspension has also been found effective.

Clinical Indication. The clinical appearance of tinea versicolor is characteristic. It is simple to prove the diagnosis by direct microscopic examination. Cultural methods are not uniformly satisfactory.

The patient should take a shower with warm water and soap, rinse thoroughly, and pat the skin dry. The ointment is applied without rubbing twice each day. When the selenium sulfide suspension is used, it is applied to the wet skin immediately after the shower and the skin is gently massaged until a lather forms. This is allowed to dry. Treatment should be performed daily for at least one week after all lesions have become quiescent and the direct microscopic examinations are negative.

Adverse Reactions. Selenium sulfide has a low index of sensitization. The preparation should not be used on any area where there is any evidence of acute inflammation. Patients should be instructed to wash the hands thoroughly and clean beneath fingernails to remove all traces of the drug after each application. If ingested, selenium sulfide is a very toxic substance.

This drug has proved to be effective in the treatment of tinea versicolor. Evidence of resistance has not developed and relapses have responded to re-treatment with the same preparation.

Amphotericin B Lotion

This is an antifungal antibiotic derived from a strain of Streptomyces nodosus. The amphotericin B lotion (Fungizone) has great activity against Candida albicans and is a superior method of treatment of cutaneous and mucocutaneous monilial infections. This includes inframammary, groin, interdigital, and oral lesions. It is especially effective in the treatment of monilial infections of the diaper area. Fungizone is not active against lesions produced by the superficial dermatophytes.

Amphotericin B lotion contains 3 percent of the active ingredient in an aqueous lotion vehicle. When used in the treatment of lesions under the breasts, in the axillae or groins, about the anus, in the interdigital spaces, and about the fingernails, the lotion is to be applied two or three times daily. Response to treatment is usually prompt. Lesions subside completely in a week to 10 days. Applications should be continued for at least one week after all signs and symptoms have disappeared. The lesions between the fingers may require more prolonged therapy. Treatment of toenail lesions has been unsatisfactory.

Toxic Effect. There has been no evidence of systemic toxicity from topical application of this material. The sensitizing potential is very low.

Systemic Antifungal Therapy

Griseofulvin, amphotericin B, and hydroxystilbamidine isethionate are effective on systemic administration in the treatment of most of the superficial dermatophytes and deep fungi, the exceptions being sporotrichosis, actinomycosis, and nocardiosis.

Saturated solution of potassium iodide administered orally is the drug of choice in the treatment of sporotrichosis. Therapy is initiated with a dose of 10 drops three times daily in one fourth glass of water. This dose is increased by one drop per dose per day until the patient is receiving 60 drops of saturated solution of potassium iodide three times each day. This large dose may cause nausea and vomiting. Long-continued administration of potassium iodide frequently causes severe folliculitis or cutaneous granuloma formation.

Penicillin is by far the most effective drug used for the treatment of actinomycosis. The antibiotic should be given by injection, using one of the long-acting preparations so that the patient may receive the large quantity in each daily dose necessary for satisfactory result. A minimum dose of 1.2 million units should be given each 24 hours and continued for at least 3 weeks after all signs and symptoms of the condition have disappeared.

Sulfonamides are the drugs of choice in the treatment of nocardiosis. Sulfadiazine in a dose of 6 to 8 gm. daily should be given until all objective signs of the disease have disappeared. Administration of the drug should be continued for at least 2 weeks after healing is complete. Some of the nocardia species are susceptible to the broad spectrum antibiotics. It may be desirable to use a combination of a broad spectrum antibiotic with the sulfonamide of choice.

Griseofulvin

Griseofulvin (7 - chloro - 2′,4,6 - trimethoxy - 6′ - methylspiro - (benzofuran - 2(3H), 1′ - (2) - cyclo - hexene)-3,4′-dione) is an antifungal antibiotic isolated from Penicillium griseofulvum. This is the first chemical compound proved to be effective on oral administration in the treatment of infections due to the superficial dermatophytes.[4] It is an odorless, white, thermostable substance that has some cytotoxic properties similar to those of colchicine. It is relatively insoluble in water and olive oil but is soluble in ethyl alcohol, Carbowax 300, chloroform, acetone, and butylacetate. In vitro studies proved this drug to be fungistatic against Trichophyton rubrum, T. tonsurans, T. mentagrophytes, T. verrucosum, T. sulfureum, T. schoenleini, Microsporum audouini, M. canis, M. gypseum, and Epidermophyton flocossum. It is not effective against bacteria, Candida albicans, or any of the deep fungi.

Clinical Indications. Griseofulvin is effective in the treatment of tinea capitis, tinea corporis, onychomycosis, and tinea cruris. Results are disappointing when the drug is used in the treatment of interdigital infections due to the dermatophytes. It is of no value in the treatment of tinea versicolor or monilial infections.

In the treatment of tinea capitis due to Microsporum audouini, M. canis, or Trichophyton tonsurans, a single massive dose of 3 gm. of the large particle griseofulvin or 1.5 gm. of the micronized griseofulvin will produce a satisfactory result in about 80 percent of the patients. A satisfactory result is not obtained until 4 to 5 weeks after therapy is initiated. The patient should be observed periodically under the Wood light until fluorescence has completely disappeared. A negative culture from the involved area is final evidence of cure. If the continuous form of therapy is used in place of the massive dose technique, the patient is to receive 1 gm. of the large particle griseofulvin or 0.5 gm. of the micronized griseofulvin in divided doses daily for 4 to 5 weeks.

Massive dose therapy of griseofulvin is of no value in the treatment of tinea corporis or tinea cruris. Oral therapy with griseofulvin using the large particle (1 gm. per day) or the micronized form (0.5 gm. per day) must be administered daily in divided doses over a period of 4 to 5 weeks. Treatment of onychomycosis with these drugs is of great value but the daily dose must be administered continuously without a rest period for 4 to 6 months. Fingernail involvement usually has an excellent response to treatment but toenail infections have a poor prognosis.

Adverse Reactions. Epigastric discomfort, nausea, and diarrhea are the most commonly encountered side effects of oral administration of griseofulvin. Photosensitivity reaction and urticaria are occasionally observed. Patients under griseofulvin therapy should avoid unnecessary exposure to sun-

light. Serious adverse reactions have not been encountered.

Evaluation of Results. In vitro and in vivo studies have failed to develop evidence that susceptible species will develop resistance to this antibiotic. Patients who have suffered relapses after successful treatment with griseofulvin have responded to retreatment.

Amphotericin

This is an antifungal antibiotic derived from Streptomyces nodosus. It is a yellowish powder that is relatively insoluble in water. For intravenous use it is prepared as a sterile lyophilized powder and it is dispensed in vials containing 50 mg. of amphotericin B and approximately 41 mg. of sodium desoxycholate with 10 mg. of dibasic sodium phosphate and 0.89 mg. of monobasic sodium phosphate added as buffers and 6.2 mg. sodium chloride. The drug has fungistatic action against Coccidioides immitis, Histoplasma capsulatum, Candida albicans, Cryptococcus neoformans, Blastomyces dermatitidis, and Blastomyces brasiliensis. The antibiotic is not active against bacteria, protozoa, or viruses. The therapeutic effect of this drug is probably due to the fact that it interferes with a critical metabolic pathway in intact yeast cells. It is poorly absorbed from the gastrointestinal tract therefore in order to exert its action it must be injected intravenously.

Clinical Indications. This drug is specifically intended for the treatment of deep mycotic infections including coccidioidomycosis, cryptococcosis, systemic moniliasis, histoplasmosis, South American leishmaniasis, and North and South American blastomycosis. Patients to be treated with this drug should be hospitalized.

The preparation for intravenous administration must be carefully supervised. The recommended concentration is 0.1 mg./cc., which is obtained by first dissolving 50 mg. of amphotericin B powder in 10 cc. of sterile water and agitating this until clear. This is further diluted with 5 percent dextrose solution to provide a concentration of 0.1 mg. of amphotericin B per cubic centimeter.

Therapy should be initiated with a daily dose of 0.25 mg./kg. of body weight and gradually increased until the optimum level is obtained. It may be possible to reach the level of 1 mg./kg. of body weight provided that serious adverse reactions do not develop. For seriously ill patients, not benefited by this amount, it may be possible to increase the daily dose gradually to 1.5 mg./kg. provided there is no evidence of renal failure. After improvement is evident it is usually possible to reduce the drug administration to every other day. The usual course of therapy lasts from 6 to 8 weeks. If treatment is discontinued too soon, there may be a relapse.

Adverse Reactions. Amphotericin B is a nephrotoxic drug and therefore the blood urea nitrogen level and other kidney function tests must be checked regularly during the course of treatment. The chief toxic effects are nausea, vomiting, fever, loss of appetite, hematuria, and albuminuria. If evidence of kidney damage develops, it usually subsides when the medication is discontinued.

This is an effective preparation but it must be remembered that it is fungistatic and not fungicidal; therefore, treatment should be continued until all signs and symptoms of the disease have disappeared.

Hydroxystilbamidine Isethionate

This drug, a yellow crystalline powder, is stable in air but decomposes on exposure to light. This compound has been found effective in the treatment of North American blastomycosis, leishmaniasis and African trypanosomiasis. It is of no value in the treatment of torulosis or histoplasmosis.

Clinical Indication. In the treatment of blastomycosis, for which it is specifically indicated, the dose is 150 mg. daily, diluted with 200 cc. of 5 percent dextrose solution administered as a slow intravenous drip. Treatment must be given daily for a period of 8 to 10 weeks, depending on the extent of the condition and response of the patient. The preparation for injection must be carefully supervised. The solution will decompose and form toxic products when exposed to heat, sunlight, or ultraviolet radiation. Patients who are under treatment with this drug must avoid exposure to direct sunlight during the course of therapy.

Adverse Reactions. Immediately following injection of the drug the patient may experience a fall in blood pressure with tachycardia, flushing of the skin, sweating, nausea, vomiting, dizziness, shortness of breath, and fainting. Trigeminal neuropathy may also develop.

References

1. Robinson, H. M., Jr., and Raskin, J.: Tolnaftate therapy of mycotic infections. J. Invest. Derm. 42:185–187, 1964.
2. Robinson, H. M., Jr.: Treatment of tinea versicolor. South. Med. J. 54:764–765, 1961.
3. Robinson, H. M., Jr., and Yaffe, S. N.: Selenium sulfide in the treatment of pityriasis versicolor. J.A.M.A. 162:113–114, 1956.
4. Blank, H., and Roth, F. J., Jr.: The treatment of dermatomycoses with orally administered griseofulvin. A.M.A. Arch. Dermat. 79:259–266, 1959.

MEDICAL ABSTRACTS

GAUCHER'S DISEASE—REVIEW OF THE LITERATURE AND REPORT OF TWELVE NEW CASES

Mary Chang-Lo MD, Lung T. Yam MD, and Albert I. Rubenstone MD, Amer J Med Sci 254(3):303–315, Sept 1967.

The literature on Gaucher's disease is reviewed. Twelve new adult cases presenting interesting features are reported. In all instances, diagnosis was confirmed by bone marrow aspiration during life. The patients generally had few complaints and the disease was compatible with life. In necropsy cases, pertinent pathologic findings are described in detail. Bone, spleen, liver and, less frequently, lymph nodes were the usual sites of Gaucher cell infiltration. Unusual sites were lungs, kidneys, adrenals, pancreas, stomach, small intestines, and meninges. Gaucher cells were commonly found in the capillaries, sinusoids and lymphatics. Occasionally they were found in the connective tissue. The unusual clinical, hematologic and pathologic findings are discussed.

RESULTS IN THE FIRST 2,500 PATIENTS UNDERGOING OPEN-HEART SURGERY AT THE UNIVERSITY OF MINNESOTA MEDICAL CENTER

C. Walton Lillehei PhD MD, Richard L. Varco PhD MD, Randolph M. Ferlic MD, and Robert D. Sellers PhD MD, Surgery 62(4):819–832, Oct 1967.

Twenty-five hundred open-heart operations using extracorporeal circulation have been carried out at the University of Minnesota Medical Center and Variety Heart Hospital from March 26, 1954 through August 16, 1966. This experience includes 1,773 operations for congenital cardiac diseases and 727 operations for acquired cardiac lesions. In the period from 1963 through 1966, 52 percent of the procedures were carried out for acquired disease.

The operative mortality has fallen steadily in both the congenital and acquired groups in spite of an increase in the difficulty of the cases being accepted for surgical management. This decreased risk has resulted from improved preoperative, operative, and postoperative management, improved perfusion equipment and techniques, and finally the judicious use of various prostheses.

The late mortality has also decreased following surgical treatment for both congenital and acquired cardiovascular lesions to 1 and 5 percent, respectively, for the years of 1963 through 1966. These gratifying improvements have resulted from both improved surgical techniques and knowledge, as well as the development of satisfactory valve prostheses.

Thus, it can be said that many of these procedures are approaching the intended goal of being truly curative rather than merely palliative.

ACUTE RENAL FAILURE DUE TO HEAT INJURY

CAPT Robert M. Vertel MC and LTCOL James P. Knochel MC, Amer J Med 43(3):435–451, Sept 1967.

Acute renal failure is generally considered to be an extremely serious complication of heat injury, carrying a poor prognosis. Ten patients with oliguric acute renal failure associated with various forms of heat injury were treated at the U.S. Army Surgical Research Unit during the period from 1958 through 1965. In contrast to the general impression that this complication of heat stroke is almost invariably fatal, seven of these patients survived, with complete clinical recovery of renal function. Also noteworthy was the high incidence of rhabdomyolysis and myoglobinuria, affecting four of the ten patients. Certain features in these cases, correlated with clinical and experimental findings reported by others, suggest that the development of heat stroke and rhabdomyolysis may possibly be related to a disordered potassium metabolism which appears in many subjects during heat acclimatization.

ACUTE SUBDURAL HEMATOMAS— A REVIEW OF EIGHTY-FOUR CASES, A SIX YEAR EVALUATION

Richard H. Moiel MD and Pedro C. Caram MD, J Trauma 7(5):660–666, Sept 1967.

An analysis of the 84 cases of surgically verified acute subdural hematomas operated on within the first three days of trauma, resulted in the following conclusions:

1. The early recognition and accurate diagnosis of this disease are important. If the neurological state allows, bilateral carotid arteriograms should be performed.

2. Bilateral acute subdural hematomas are commonly associated with intracerebral hematomas.

3. Intracerebral hematomas and significant intracerebral mass lesions, due to contusions and lacerations of the frontal and temporal lobe, are significant components of the acute subdural hematoma, and the presence of these associated injuries is most significant. The early recognition of this component of the disease process is most important; early surgical intervention results in a lower mortality and morbidity rate in patients with acute subdural hematoma.

4. The operative procedure performed should be a large subtemporal craniectomy, or a craniotomy. They believe that a craniotomy should be the procedure of choice, even though the statistics of this retrospective study did not confirm this impression. A craniotomy does not result in increased morbidity or mortality, when compared to the multiple burr hole procedures that have been performed. The craniotomy not only allowed adequate exposure, enabling the surgeon to control sites of common venous bleeding, but also allowed access to the sites of cerebral contusions and hematomas, and visualization of the extent of cranial injury.

DENTAL SECTION

CONSERVATIVE DENTISTRY GOLD IN YOUNG PERMANENT TEETH

Richard E. Bantz and Thomas Biner, Los Angeles, Calif. J S Calif State Dent Assn 33(10):460–461, Oct 1965.

The material of choice for the restoration of inconspicuous Class III lesions in young adults is cohesive gold foil. The temporary silicate placed in cavities in teeth which have long life spans leads to additional replacements. Two contraindications to the use of foil are: (1) pulp exposure and (2) potential damage by extreme dentin compression and trauma to the periodontal ligament. Exposure of the pulp can be avoided by applying the findings of dental anatomists which accurately relate the dimensions and spatial configuration of the pulp chamber to the external morphology of the teeth. Trauma to the dentin and periodontal ligament do result from heavy hand malleting and pneumatic condensing. The introduction of the electronic condenser offers exciting possibilities in minimizing the condensing trauma. The solubility of silicate and the percolation accompanying acrylic make frequent replacements of these materials a necessity. As each new restoration is placed additional tooth structure is lost. Gold, as a permanent restoration, is needed in these young teeth rather than ten years later. Young patients with interproximal caries on anterior teeth indicate marked caries susceptibility. Consequently this group of patients needs not only the best restorative dentistry but also the best advice and counsel to prevent further caries. Since caries in anterior teeth alarm parents and patients this is the opportunity to educate, as advice at this time, will fall on attentive ears. Cohesive foil should be combined with this aggressive program in preventive dentistry.

(Abstracted by: CAPT Nelson W. Rupp, DC USN, From: Oral Res Abs 1(2): 147.)

PERSONNEL AND PROFESSIONAL NOTES

RESEARCH ASSISTANTS GRADUATE AT NDS

"When is the sum of the whole equal to more than the sum of the parts?" was the question posed by CDR William B. Shreve, Jr., DC USN, in his commencement address to the graduates of the

Dental Technician, Research Assistant, School at the Naval Dental School on September 1. The graduates, DT2 Russell C. Clogston and DT2 Timothy E. Mikels knew exactly what CDR Shreve was driving at, for they are the first product of a school that had its conception as far back as 1961, and which consummated a pioneer program of training technicians in depth to become able assistants to researchers.

Present at the ceremony were RADM Frank M. Kyes, DC USN, Assistant Chief of the Bureau of Medicine and Surgery (Dentistry) and Chief of the Dental Division, and CAPT Herschel C. Sudduth, MC USN, Commanding Officer of the Naval Medical Research Institute, both of whom have given substantial help in inaugurating and supporting the Research Assistant School's activities. CAPT Kenneth L. Urban, Commanding Officer of the Naval Dental School, as well as CAPT Nelson W. Rupp, Officer Education Department, reiterated an underlying principle for establishing new courses, capsuled best in CAPT Urban's remark, "It is the School's responsibility to encourage, develop, and provide opportunity for those with ability and desire to keep pace with demands." CAPT Rupp, formerly Head of the Research and Sciences Division, was actively involved in laying the groundwork for the Research Assistant Program.

The Dental Technician, Research Assistant, School, although new in fact, is not new in theory, for scientists and researchers realized long ago that the rapid advance in knowledge, or as they termed it "the explosion of knowledge," had changed the concept of what a technician should be able to do in assisting the scientist in his special field of study. Upon this base the Naval Dental School developed a 52-week course of instruction designed to make the technician more proficient in areas of administration, experimental pathology, microbiology, biochemistry, microphotography, experimental surgery, and experimental animal care.

Thus it is, that the sum of the whole—a well trained and able research assistant—equals more than the sum of the parts.

DENTAL CORPS STATISTICS

The increased military action in SEASIA has made many additional demands upon personnel of the Dental Corps to provide optimum dental health to all members of the Navy and Marine Corps. At the same time, other programs (Preventive Dentistry and Children's Dental Health) have added other pressures to demands for the time of the dental officer and his auxiliary personnel.

The number of operative procedures accomplished may be considered as a barometer in assessing the effect of the additional demands placed upon the Dental Corps. For example, in comparison of the second quarter of FY 1966 with that of FY 1967, dental officer strength increased by 3.4 percent; at the same time, operative procedures increased by 6.6 percent.

In consideration of the above, all dental officers, dental technicians and auxiliary personnel are deserving of a "well done" for their efforts in providing an increased degree of oral health, as reflected by the above statistics, to all members of the Navy and Marine Corps.

PREVENTIVE DENTISTRY TREATMENT PROVIDED JAPANESE NAVY

In what may be a "first", the Naval Dental Corps' Preventive Dentistry Program was provided to officers and men of a foreign ship. On July 7, 1967, the entire ship's complement of the Japanese destroyer "ISONAMI" received stannous fluoride treatments at the U.S. Naval Dental Clinic, Yokosuka, Japan. Two hundred and thirty individuals participated in the self-preparation prophylaxis method followed by topical application of stannous fluoride.

Based upon information from dental officers of the Japanese Maritime Self-Defense Force, plans are being developed for the construction of a Preventive Dentistry Clinic similar to those utilized by the U.S. Navy. Following completion of the clinic, it is expected that the preventive dentistry treatment will be provided all members of the Maritime Force.

RESERVE SECTION

SATISFACTORY YEAR, ANNIVERSARY YEAR, FISCAL YEAR

As Gertrude Stein might have said "a year is a year is a year" but to a member of the Naval Reserve it is a year of participation which may or may not count toward eventual retirement. A family,

a busy practice and an active community life make the days slip by quickly and suddenly it is gone, but was it a satisfactory year of service in the Naval Reserve?

Effective 30 June 1949, the accumulation of a minimum of 50 retirement points in an anniversary year is considered a "satisfactory year of service" for retirement purposes. This seems clear enough but RORA, NRMC Bainbridge and the Reserve Division in BUMED frequently receives letters from Reserve Officers saying "I earned 50 points last year but I have not been so credited. Please explain."

The records are checked and the answer is found. Points earned were not all earned within the anniversary year as required. The key word here is "anniversary year." Like other anniversaries this one may be forgotten, and once lost the year cannot be retrieved under existing laws and regulations.

For Reservists who entered the Navy *before* 30 June 1949, the anniversary year will be from 1 July to 30 June—the same as the fiscal year. For those members entering *after* 30 June 1949, or whose reserve service was broken after that date, the anniversary year extends from the date of entry or re-entry.

Another reason to remember the importance of the anniversary year and a year of satisfactory service is that effective 1 July 1967 in order to stay in the Ready Reserve if you are now qualified for retirement you must attain 50 retirement points a year. Official word on this subject will be delineated in forthcoming BUPERS directives.

A closing word from your Reserve Sponsor. Satisfactory years have been lost by Reserve Officers who forget that retirement points must be earned within an anniversary year. Don't jeopardize your Reserve status and future retirement by not earning credit for a satisfactory year of service. Participation in the Naval Reserve is the way to assure your points for the future.

OCCUPATIONAL MEDICINE SECTION

BENEFITS AND HAZARDS OF ORGANOPHOSPHORUS INSECTICIDES

H. H. Golz MD and N. J. Wayne, JOM 9(9):435–438, Sept 1967.

Evidence that we are a health-conscious nation is all around us. One reason for our health-consciousness is the fact that there has been no appreciable period during the last decade or two when there has not been some health issue on the front pages of our newspapers, some area described as a threat to our national well-being.

Recent examples of such issues are quite familiar. They include such questions as carcinogenicity of food additives, drug evaluation, automobile safety, and of course, pesticides. The pesticide issue was spawned by the best-seller *Silent Spring*. Its postulates generated an unusual amount of public furor until automobiles and air pollution took over center stage. The epitaph to *Silent Spring* was written by a congressional investigating committee which found that its conclusions were based on speculation and on data that had been carefully chosen to support the author's preconceived conclusions; the chairman of that committee characterized the book as science fiction, written with a magic pen.

No one denies that pesticides are toxic—they wouldn't be of much use if they weren't. Many in common use are highly toxic. However, toxicity is not synonymous with hazard, and it is the hazard of a pesticide, not its toxicity, that is of primary importance in questions relating to the public health.

The elaboration of this argument might be academic for the sophisticated, were it not for the inhibiting effect that such emotional excesses have on the search for answers to some of the most pressing problems that confront society today. One of these is how to produce enough food to meet the minimum nutritional requirements of the burgeoning world population. It is a fact that most of the countries of the world are not meeting even their present requirements and that the population is growing at a rate that exceeds that of

food production. As the number of people increases, more food is needed to feed them. But less is available because land is taken out of agricultural production to provide them with living space. American complacency is ill-founded, for our surpluses are diminishing rapidly and the day is not far distant when we too will have to face up to this problem.

Our present surplus productive capacity is largely attributable to the dramatic progress that we have made in agricultural technology, especially since World War II. A significant part of this advanced technology has been pesticide development. Despite the incalculable increase in our food supply that has been made possible by the development of synthetic organic pesticides in the period since World War II, it is a sad fact that even today pests consume or destroy one-third of all the food that is produced in the world. In some areas crop losses to insects run as high as 80%, it is estimated by WHO that the food lost each year through insect activity would be sufficient to feed 700 million people.

Clearly, pesticides are critically important in food production. Of possibly even greater importance is the life-saving role that they have played in the control of the infectious diseases of man that depend for transmission wholly or in part on insect vectors. Malaria and typhus are but two of the many examples.

What then about the hazards of pesticides? Published data indicate that they are used in the U.S. today at a rate ten times greater than 25 years ago when the first synthetic insecticide, DDT, became available. This increased usage is accounted for entirely by the post-World War II synthetic organic compounds. However, the present death rate from all pesticides is the same as it was when DDT first became commercially available, and it is actually lower than it was 50 years ago. In actual numbers, pesticide deaths in the U.S. have been in the range of 100-150 per year for many years. It is of interest to note that the death rate from common aspirin is four times as high as that from all pesticides combined.

Tabulation of pesticide fatalities by cause shows that even today two-thirds result from the old pre-World War II agents such as the inorganic compounds of arsenic, lead, mercury, phosphorus, and thallium, and the alkaloids nicotine and strychnine. Thus, the synthetic organic compounds that have been the target of so much criticism account for fewer than 50 deaths per year. When these are related to volume of use, it becomes obvious that the safety record of the new synthetic insecticides is far better than that of the older, less efficient materials upon which we depended so complacently for so many years. Furthermore, 80% or more of these deaths result not from the application of the pesticides, but from the accidental or deliberate ingestion of carelessly stored concentrates. As might be imagined, most of them occur in young children. These deaths are in no respect peculiar to insecticides; rather they are but one facet of the much broader problem of accidental poisoning.

Most of the 30 to 40 deaths per year attributable to the post-World War II pesticides are caused by two types of insecticides: the chlorinated hydrocarbons, of which DDT is the prototype, and the organic phosphates, of which parathion is the prototype. Since deaths from the organophosphates outnumber those from the chlorinated hydrocarbons by a ratio of about 4:1, the remainder of this report will be confined to that group.

Hazard

With the exception of ingestion by accident or intent, the risk of poisoning is largely limited to three occupational categories: chemical manufacturing, insecticide formulating, and commercial agricultural operations. Some measure of discipline and control is maintained over these groups, with the consequence that the over-all safety record has been good, despite certain reports to the contrary.

The risk of illness from eating food that has been treated with the organophosphates is virtually nonexistent. This is due to a number of factors, such as the small amounts that are applied, the stringent rules that regulate their use, and the rapid disappearance of residues. In this country there has never been a case of illness from ingestion of food that had been treated in compliance with recommendations and regulations, and there have been only two or three episodes of transient, mild illness from consumption of food that was treated in gross disregard of recommended procedures.

We are not aware of any instance of poisoning from the use of the phosphate esters in amateur gardening. This may be attributed to the fact that most states permit over-the-counter sale of only those organophosphates that have been shown to have a low order of toxicity, such as malathion.

The phosphates may enter the body by any route of exposure, but absorption through the intact skin is by far the most common. The vapor pressure of

most members of this group is so low that inhalation is without hazard even though the odor may have reached an unpleasant level. However, during or immediately after agricultural operations, the concentration of airborne particles of liquid or dust is often sufficient to create an inhalation hazard to those in the immediate vicinity.

Toxicity

With but one or two exceptions, notably malathion, the phosphates are highly toxic once they have entered the body of man or animal. They all exhibit a number of characteristic pharmacological properties and this simplifies the problems of diagnosis and medical management.

The latent interval between exposure and onset of illness is short—rarely as long as 6 hr. and usually less than 1 hr.

They have only one pharmacological action—inhibition of the cholinesterase enzymes. The clinical picture results from the inhibition of acetylcholinesterase, which is the mediator of nerve impulses at the synapses of the autonomic nervous system and at the motor end plates. Upon absorption, enzyme inhibition begins immediately and usually reaches its maximal degree within minutes or hours. Enzyme regeneration goes on continuously. In the absence of continuing absorption of the insecticide, functionally adequate regeneration occurs within 12–24 hr.

The most prominent signs and symptoms are those that result from diffuse stimulation of the parasympathetic nervous system. The fully developed clinical picture is typical and is not seen in any condition other than poisoning by cholinergic drugs or by nonedible mushrooms. It is always an acute illness of short duration. It reaches maximal intensity within a few hours after onset. In nonfatal cases, spontaneous recovery begins about 12–18 hr. and is usually complete at 24–48 hr., depending upon the severity of the poisoning. There are no residua of any kind and chronic poisoning does not occur. Detailed descriptions of the clinical picture are widely available in the published literature. In cases of mild or moderate severity, the diagnosis may be difficult because of the incomplete development of the typical clinical picture. A definite history of recent exposure and a high index of suspicion will help.

Determination of cholinesterase activity in the peripheral blood is a specific diagnostic test. Clinical poisoning is always accompanied by a reduction in the red cell and plasma enzyme activity to less than 50% of normal and it is often below 25% when symptoms appear. Simple screening tests for cholinesterase activity are readily available for office use and there are now many clinical laboratories in all parts of the country that perform reliably the more precise techniques such as the electrometric.

Atropine is a specific antidote for which there is no substitute. Patients poisoned by any of the phosphates not only tolerate but require much larger doses than are given for any other condition. In severe cases the recommended dose is 4–8 mg. intravenously every 10–15 min. until full atropinization is attained. It will be noted that these doses are 6–12 times greater than the amounts usually employed. In milder cases the dose may be reduced to 2–4 mg. by the intramuscular route every 30 min. For children, proportionately smaller amounts are used.

Physicians are often reluctant to give such quantities of atropine. Their anxiety is unfounded, for if the appearance of the usual signs of atropinization is used as the indication to reduce dosage, significant overdosage will not occur. The most conservative position that a physician can take is to start the drug in the full recommended dosage at the earliest possible moment. Over the years many deaths have occurred because atropine was not given in sufficient amount soon enough, but we do not know of a single death or serious injury from atropine overdosage, even when the original diagnosis of poisoning was incorrect.

The critical period of illness is the first 24 hr. After that, spontaneous regeneration of functionally adequate amounts of cholinesterase has usually taken place. The purpose of atropine during this critical period is to block the action of excess accumulations of acetylcholine in the central nervous system until there has been enough spontaneous regeneration of cholinesterase to hydrolyze it. The importance of adequate atropine early is obvious. In the last few years a new class of drugs, known as oximes, has become available. Under some circumstances they can reverse the inhibiting action of the insecticide on the cholinesterase enzyme. To date only one member of the group has been released by the FDA. Called Protopam Chloride, it is commonly referred to as 2-PAM. There has not been enough experience yet with the oximes to know whether they will live up to their early

promise or whether they will be equally effective with all of the organophosphorus insecticides. Until more experience has been gained, it is recommended that they be used only as adjuncts to the standard therapeutic regimen and that they not be employed as substitutes for atropine.

COLD SENSITIVITY—REPORT OF A CASE

Robert N. Armen MD, Monroeville, Pa., JOM 9(9):468–470, Sept 1967.

The body responds to cold by making certain physiological adjustments: Heat production is augmented, and heat loss from skin is diminished as an effort at heat conservation. This is a joint process of compensation which serves adequately at moderate exposures.

Clinical response to cold manifests itself in a variety of forms. Tolerance varies among different individuals and groups and the compensatory effort depends partly on the intensity and the duration of the exposure. Certain disorders with marked intolerance to cold, such as cold urticaria, cold hemoglobinurias, cold erythema, and cryoglobulinemia have been grouped under the term "cold sensitivity." Other investigators, unhappy with this terminology, have suggested the use of the all-inclusive term "cryopathy," which is made to embrace not only those cold-sensitive states with possible immunologic mechanisms but also others lacking evidence of true hypersensitivity, such as Raynaud's disease, physical allergy, ischemic states with tissue injury, ergotism, and others. Strictly speaking, cold sensitivity is meant to imply a response that is allergic in nature, with urticaria, erythema, edema, etc., or the presence of an immunologic mechanism with demonstrable circulating immune bodies or abnormal protein fractions.

However, not all responses to cold can be categorized by such implications. Often, all that can be demonstrated, is a state of decreased tolerance, manifested by vasospasm unusual in degree and unusual in duration. In other words, the cold-sensitive individual responds with an intensity beyond the normal range of physiologic expectation, suggesting an extension or an exaggeration of the normal response. In this context, therefore, cold sensitivity implies diminished tolerance and reflects the extent of the tolerance.

(A case report of a 32-year-old male with sensitivity to cold is presented in the original article.)

The Problem of Industrial Practice

A casual glance at this problem might suggest that cold injury is not a statistically significant hazard in industrial practice. Such an attitude would be quite unfortunate. As practitioners of preventive medicine we are as interested in the prevention of a few isolated cases as we are in hazards of greater abundance.

It should not be inferred either, that cold injury, although important, is an unlikely hazard. As emphasized by Johnstone and Miller, a large number of workmen is daily assigned to duties in artificially cooled environments. The frozen-food industry is a good example. In many other modern industries, one can find segments of the work force exposed to excessive cold, sometime or other during the 8-hr. work day. Examples may easily be found among dry-ice workers, butchers, fishermen, ground crews and snow removers, farmers, aviators, divers, food-locker employees, and others. One other group with whom I have had personal experience is handlers of liquified gases as liquid nitrogen. These workers, daily engaged in the transfer and transport of liquids with temperatures in the range of minus 200–300°F., are potentially exposed to severe cold burns through accidental spillage.

Preventive Medicine

Since protection against cold can be practiced more effectively than against heat, there are greater rewards for the physician who remains alert to protect the potential victim from unnecessary injury.

Among the important reasons for doing a preemployment and a periodic examination is the determination of physical abilities (as well as disabilities) of the employee so that proper placement can be intelligently made. Identification of the cold-sensitive individual and his proper placement, with available protective equipment where indicated, is essential in the prevention of the occurrence or recurrence of symptoms.

We should keep in mind that certain underlying pathological conditions are known to pre-dispose to cold injury; these should be detected and corrected. Among these are malnutrition, metabolic diseases such as diabetes, circulatory diseases, and hypothyroidism, and anemia. A proper diet is of paramount importance as it will provide the cal-

ories necessary for the maintenance of body temperature.

Maxcy points out that in general, proper clothing, proper exercise, and proper environmental heating, are the cornerstones of an effective preventive program, and that clothing should be thick, multilayered, light in weight, and wind-proof. "Thick clothing composed of fibers which are not easily compressed and which allow air to be trapped but which prevent convection currents is the best type for cold exposure." Wet garments and tight garments should be avoided. Feet should be protected from dampness. In cold weather sweating of feet, especially in rubber boots, becomes a problem to be watched. Feet should be dried frequently and loose-fitting, dry socks substituted as often as it becomes necessary.

The use of gloves is a simple measure and will protect most individuals from cold injury as far as the hands and fingers are concerned. Ordinary gloves will do in most cases, and if necessary a double pair may be worn. In unusually sensitive cases, one may resort to especially manufactured thermal-lined gloves. Such items are offered for sale by various safety equipment manufacturers. Usually, these gloves have a plastic outside lining and a long gauntlet that grips firmly at the wrist. The insulation is provided by soft-napped, bulky, waffle-weave-type thermal liners of cotton. The many tiny pores in the weave permit circulation of air and help to prevent perspiration. Thus they combine all the qualities necessary to conserve and prevent the dissipation of heat from the hands.

Summary

The response to cold assumes a variety of forms. Some present themselves in clinical allergy; others depend upon the presence of some immunologic mechanism. Certain responses are in the form of actual tissue injury, while others are ill-defined, demonstrating no more than an unusual degree of vasospasm. However, all are characterized by one common denominator: the precipitating factor, the trigger, is almost always exposure to cold, often coupled with an inherent diminution in tolerance. Prevention is relatively easy and can be made effective by appropriate measures.

METALLIC MERCURY

Henry L. Verhulst, Director, John J. Crotty MD, Associate Director, Washington, D.C., National Clearinghouse for Poison Control Centers, HEW, PHS, pages 5–6, Sept–Oct 1966.

Mr. Arthur Blank of the Connecticut Poison Information Center has forwarded a case report worthy of wider dissemination. A 2-year-old child ingested a large quantity of metallic mercury from a bottle that she had found in her home. The child had been given syrup of ipecac at the emergency room of the hospital one and a half hours later and had vomited, but no mercury was in the emesis. A physician was informed when he inquired of the Connecticut Poison Information Center about the acute toxicity of metallic mercury of the difficulties in removing metallic mercury from the stomach either by lavage or by the induction of emesis. He was then reassured that substantial quantities of mercury were known to have been ingested without causing significant untoward sequelae.

Further investigation revealed that the mercury had been brought into the house by an uncle who was interested in chemistry. Since the markings on the inside of the bottle (probably oxide of mercury) showed the top level of the mercury in the empty container, the physician was asked to add water to the bottle from a graduated cylinder until the top of the water reached the top of the mercury mark. It required 16 cc of water. The mother was unable to find any spilled mercury and it was concluded that 16 cc was ingested which would have weighed slightly over 215 grams. Radiographs were advised to show presence of mercury in the gastrointestinal tract. On follow-up of the case by Mr. Blank, he learned that the radiographs showed the presence of radiopaque substances and that some remained in radiographs taken the following day. According to the mother, the child had no untoward symptoms except she seemed to be a little more irritable than usual. There was evidence that the child was eliminating the mercury during the two days. One week later Mr. Blank again called the child's mother who stated that the child appeared to be all right and wondered if her irritability might have been due to her teething.

A third x-ray taken on the advice of the child's pediatrician showed small amounts of metallic mercury still remaining. Eight days after the ingestion, the child developed an erythematous papular rash over her entire body. Physical examination showed no significant signs, the child did not seem to have symptoms from the rash, and there were no scratch marks. The private physician had inquired as to whether the rash might be related to the ingested

mercury, but since it did not resemble acrodynia, he felt it was of viral origin. The rash disappeared in three days.

Three weeks after the ingestion the private physician had felt that there were no untoward sequelae and the mother stated the child was all right except for irritability at times.

The ingestion of such a large amount of metallic mercury without any definite signs or symptoms lends evidence to the innocuousness of ingestion of thermometer mercury or that which is found in small toys. However, metallic mercury still presents a danger from sublimation, or vaporization when heated.

A MESSAGE TO MEDICAL OFFICERS REGARDING OCCUPATIONAL HEALTH

The Navy has a continuing need for the services of medical officers trained in the specialty of Occupational Health. The occupational health needs of a Navy and Marine Corps of over one million military personnel and 375,000 civilian employees represent a challenge to the Medical Corps and afford an opportunity for an interesting and rewarding career for those medical officers trained in this specialty. Individuals thus trained may look forward to varied assignments at Naval industrial establishments at levels of responsibility commensurate with their training and experience. Board certification requires two years of academic instruction leading to the Master of Public Health degree (or other degree depending on the institution) and a third year of in-plant residency training. Successful applicants may receive their training at any approved university providing such instruction.

Medical officers interested in receiving occupational health training should apply in accordance with BUMEDINST 1520.10C or write for further information to the Chief, Bureau of Medicine and Surgery (Code 73), Navy Department, Washington, D.C. 20390.

EDITOR'S SECTION

MEDICAL EDUCATION FOR NATIONAL DEFENSE (MEND)

The program known as "Medical Education for National Defense" (MEND) was begun in 1952 at the request of the Joint Committee on Medical Education in Time of National Emergency which represented the Association of American Medical Colleges (AAMC) and the American Medical Association (AMA). The program was an outgrowth of the Committee's study of the Medical ROTC Program plus its attempt to explore methods for introducing into the medical school curriculum those special subjects which medical graduates vitally needed if they were to serve competently in the Armed Forces or as civilians in time of national emergency. At that time the Medical ROTC Program, although active in almost 50 medical schools and operating at a cost of approximately 2 million dollars per annum, did not appear to be meeting these needs.

The basic purpose of the Program from its inception was to foster and encourage within the nation's medical colleges an appropriate attitude or an awareness towards the practice of medicine under adverse emergency conditions or within a hostile environment. Specifically, this has reference to the education and training of new physicians in the principles of medicine and surgery as they are applied within a military or civil disaster situation. This approach is felt necessary since undergraduate medical education in the United States is oriented primarily towards the education of physicians for the civilian practice of medicine under ideal professional conditions.

At the request of the Joint Committee, the Department of Defense agreed, during the academic year 1952–53, to support an experimental program in five medical schools: University of Buffalo, University of California (SF), Cornell University, University of Illinois, and Vanderbilt University. Evaluation of the pilot study in 1954 led the Committee to conclude that (1) there was a well defined and recognized need for modification of the medical curriculum to make medical graduates better

able to cope with medical problems encountered in disaster and war; (2) the underlying philosophy of the pilot program was consistent with sound concepts of medical education; (3) acceptance by the faculties and student bodies in the pilot schools had been remarkably good. The committee recommended, therefore, that the program be continued and extended to involve all of the nation's medical schools desiring to participate. Since that time schools have affiliated with the Program at the rate of 10 to 15 each year and thus by 1963 all of the nation's 88 undergraduate medical schools were, and continue to be, MEND participants. As new schools come under development, they too are invited to participate.

Direction of the MEND Program within the Federal government is the responsibility of the Federal Committee on Medical Education for National Defense, membership of which is composed of representatives of the Departments of Defense, Army, Navy, Air Force, and the Public Health Service. The National MEND Coordinator is responsible to the Committee for all aspects of the Program's operation.

Policies of the MEND Program set by the Federal MEND Committee consist only of general guidelines and do not attempt to prescribe a standard MEND curriculum for the participating schools. The activities conducted under MEND auspices tend therefore to differ somewhat from school to school, each faculty being free to implement the concepts of MEND in a way which fits the local conditions and philosophy of medical education. In each medical college a faculty member is appointed to serve as the school's MEND Coordinator. It is his role to coordinate into the established curriculum the integration of materials which relate to the military application of basic scientific and medical principles, health programs in major disasters, and mass casualty care. In addition, he plans or supervises such lectures, demonstrations, symposia, courses, and other activities that would best carry forward MEND objectives at his particular school.

At the national level, MEND conducts a series of teaching symposia each year for the benefit of faculty and students of the medical colleges. During the period, 1965–67, eight such symposia were attended by over 1,500 faculty and students. The Program also sponsors the attendance of faculty and students at various courses conducted by the Armed Forces and the Public Health Service, all dealing with MEND-related subject matter. A total of almost 1,000 individuals participated in such courses in the academic years 1965–66 and 1966–67.

As an additional service, MEND makes available to faculty and students through their school coordinator, speakers, films, texts, reports, and other forms of professional information generated by Federal agencies and falling within the scope of MEND.

EIGHTH ANNUAL AFIP LECTURES 1968—18–22 MARCH 1968

This is a review and compilation of recent information in anatomic pathology (and clinical pathology methods as they apply to pathology) involving all of the various organs and body systems. The review includes common pitfalls in diagnosis, review of unusual cases, statistical data as appropriate, review of articles published or to be published by staff members, new advances in histologic techniques, application of newer histochemical, bacteriological, biochemical, immunological and toxicological methods in the daily practice of pathology. This course provides the busy practicing pathologist with a concise combined period of instruction and review, and also with the latest concepts in pathological anatomy.

Applicants must be members of the Medical Corps either Board certified or Board eligible in pathology. Qualified civilians will be accepted on a space available basis.

To apply, write The Director, Armed Forces Institute of Pathology, ATTN: MEDEM-PAD, Washington, D.C. 20305.

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