Journal
of the
PHILIPPINE MEDICAL ASSOCIATION

PMA-ABBOTT RESEARCH AWARD PAPERS
BASIC SCIENCE
IN THIS ISSUE

VOL. 52, NOS. 9-10 SEPTEMBER-OCTOBER, 1976

duratex

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the antithrombotic

prevents the formation of arterial thrombi

Availability:

ampoule 10 mg/2 ml.	packs of 25's
25 mg. tablets	packs of 100's
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Effectively improve coronary blood flow in coronary insufficiency

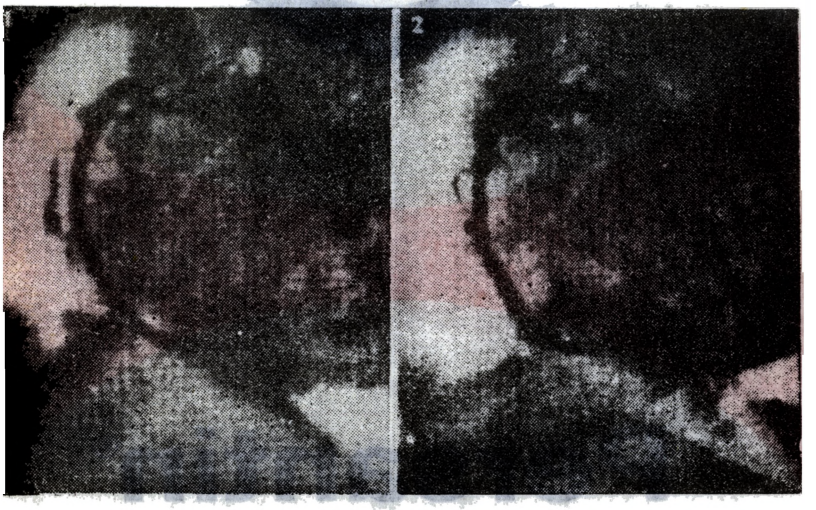

Figure 1 was taken before and Fig. 2 was taken after the administration of 5 mg. ISORDIL sublingually. Significantly, the artery is filled slightly more distally, and its diameter is increased after administration of the drug (Sewell, W.H.: The Medical and Surgical Management of Coronary Insufficiency, a motion picture, on file at Ayerst.)

Current investigations suggest that the symptoms of coronary insufficiency (angina pectoris in particular) result from inadequate oxygen supplies to the heart. The disparity between oxygen required and oxygen available can be resolved by improving coronary artery flow and by reducing myocardial oxygen requirements.

ISORDIL does both.

ISORDIL dilates coronary arteries and collateral blood vessels, improving coronary blood flow, and markedly reduces venous return, resulting in decreased cardiac output and myocardial oxygen requirements.

Presentation:
No. 1100—Sublingual 5 mg., bottles of 100 tablets
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No. 1102—Tembids® L.A. 40 mg., bottles of 100 tablets

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ISORDIL*

isosorbide dinitrate

effective in theory, effective in fact, effective in clinical practice

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AYERST LABORATORIES (PHILIPPINES) INC.

† A Trademark

Dx: Bacterial bronchitis
caused by susceptible strains of *Streptococcus (Diplococcus) pneumoniae*

℞: Rest, fluids, decongestants, and an oral antibiotic

consider **Keflex®**
cephalexin Monohydrate
when oral antibiotic therapy is indicated

Keflex, a member of the cephalosporin family, is available in three convenient oral forms. Four years of clinical use have established Keflex as a useful antibiotic.

When considering oral antibiotic therapy for your next patient with bacterial bronchitis,* think of Keflex.

*Caused by susceptible strains of *Str. pneumoniae.*

Please see back for prescribing information.

Keflex®
cephalexin monohydrate

Description: Keflex is a semisynthetic cephalosporin antibiotic intended for oral administration. It is 7-(D-α-amino-α-phenylacetamido)-3-methyl-3-cephem-4-carboxylic acid, monohydrate.

Actions: *Human Pharmacology*—Keflex is acid stable and may be given without regard to meals. It is rapidly absorbed after oral administration. Following doses of 250 and 500 mg., average peak serum levels of approximately 9 and 18 mcg. per ml. respectively were obtained at one hour. Measurable levels were present six hours after administration. Over 90 percent of the drug is excreted unchanged in the urine within eight hours. Peak urine concentrations are approximately 1,000 mcg. per ml. during this period following a 250-mg. dose.

Microbiology—In-vitro tests demonstrate that the cephalosporins are bactericidal because of their inhibition of cell-wall synthesis. Keflex is active against the following organisms in vitro:

Beta-hemolytic streptococci
Staphylococci, including coagulase-positive, coagulase-negative, and penicillinase-producing strains
Diplococcus pneumoniae
Escherichia coli
Proteus mirabilis
Klebsiella sp.
Hemophilus influenzae
Neisseria catarrhalis

Note—Most strains of enterococci (*Streptococcus faecalis*) and a few strains of staphylococci are resistant to Keflex. It is not active against most strains of *Enterobacter* sp., *Pr. morganii,* and *Pr. vulgaris.* It has no activity against *Pseudomonas* or *Herellea* species. When tested by in-vitro methods, staphylococci exhibit cross-resistance between Keflex and methicillin-type antibiotics.

Indications: Keflex is indicated for the treatment of the following infections when caused by susceptible strains of the designated microorganisms:

Respiratory tract infections caused by *D. pneumoniae* and group A beta-hemolytic streptococci (Penicillin is the usual drug of choice in the treatment and prevention of streptococcal infections, including the prophylaxis of rheumatic fever. Keflex is generally effective in the eradication of streptococci from the nasopharynx; however, substantial data establishing the efficacy of Keflex in the subsequent prevention of rheumatic fever are not available at present.)
Otitis media due to *D. pneumoniae, H. influenzae,* staphylococci, streptococci, and *N. catarrhalis*
Skin and soft-tissue infections caused by staphylococci and/or streptococci
Genitourinary tract infections, including acute prostatitis, caused by *Esch. coli, Pr. mirabilis,* and *Klebsiella* sp.

Note—Culture and susceptibility tests should be initiated prior to and during therapy. Renal function studies should be performed when indicated.

Contraindication: Keflex is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

Warnings: BEFORE CEPHALEXIN THERAPY IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE CONCERNING PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS AND PENICILLIN. CEPHALOSPORIN C DERIVATIVES SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS.

SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

There is some clinical and laboratory evidence of partial cross-allergenicity of the penicillins and the cephalosporins. Patients have been reported to have had severe reactions (including anaphylaxis) to both drugs.

Any patient who has demonstrated some form of allergy, particularly to drugs, should receive antibiotics cautiously. No exception should be made with regard to Keflex.

Usage in Pregnancy—Safety of this product for use during pregnancy has not been established.

Precautions: Patients should be followed carefully so that any side-effects o unusual manifestations of drug idiosyncrasy may be detected. If an allergic re action to Keflex occurs, the drug should be discontinued and the patient treate with the usual agents (e.g., epinephrine or other pressor amines, antihistamines or corticosteroids).

Prolonged use of Keflex may result in the overgrowth of nonsusceptible organ isms. Careful observation of the patient is essential. If superinfection occur during therapy, appropriate measures should be taken.

Positive direct Coombs tests have been reported during treatment with th cephalosporin antibiotics. In hematologic studies or in transfusion cross-matchin procedures when antiglobulin tests are performed on the minor side or in Coomb testing of newborns whose mothers have received cephalosporin antibiotics befor parturition, it should be recognized that a positive Coombs test may be due t the drug.

Keflex should be administered with caution in the presence of markedly im paired renal function. Under such conditions, careful clinical observation an laboratory studies should be made because safe dosage may be lower than tha usually recommended.

Indicated surgical procedures should be performed in conjunction with antibioti therapy.

As a result of administration of Keflex, a false-positive reaction for glucose i the urine may occur. This has been observed with Benedict's and Fehling's solu tions and also with Clinitest® tablets but not with Tes-Tape® (urine sugar analysi paper, Lilly).

Adverse Reactions: *Gastrointestinal*—The most frequent side-effect ha been diarrhea. It was very rarely severe enough to warrant cessation of therapy Nausea, vomiting, dyspepsia, and abdominal pain have also occurred.

Hypersensitivity—Allergies (in the form of rash, urticaria, and angioedema have been observed. These reactions usually subsided upon discontinuation o the drug. Anaphylaxis has also been reported.

Other reactions have included genital and anal pruritus, genital moniliasi vaginitis and vaginal discharge, dizziness, fatigue, and headache. Eosinophilia neutropenia, and slight elevations in SGOT and SGPT have been reported.

Administration and Dosage: Keflex is administered orally.

Adults—The adult dosage ranges from 1 to 4 Gm. daily in divided doses. Th usual adult dose is 250 mg. every six hours. For more severe infections or thos caused by less susceptible organisms, larger doses may be needed. If daily dose of Keflex greater than 4 Gm. are required, parenteral cephalosporins, in appropriat doses, should be considered.

Children—The usual recommended daily dosage for children is 25 to 50 mg per Kg. divided into four doses.

	Keflex Suspension	
Child's Weight	125 mg./5 ml.	250 mg./5 ml.
10 Kg. (22 lb.)	½ to 1 tsp. q.i.d.	¼ to ½ tsp. q.i.d.
20 Kg. (44 lb.)	1 to 2 tsp. q.i.d.	½ to 1 tsp. q.i.d.
40 Kg. (88 lb.)	2 to 4 tsp. q.i.d.	1 to 2 tsp. q.i.d.

In severe infections, the dosage may be doubled.

In the therapy of otitis media, clinical studies have shown that a dosage o 75 to 100 mg. per Kg. per day in four divided doses is required.

In the treatment of beta-hemolytic streptococcal infections, a therapeutic dosag of Keflex should be administered for at least ten days.

How Supplied: Pulvules® Keflex® (cephalexin monohydrate, Lilly), equivalent t 250 or 500 mg. cephalexin, in bottles of 24 and Keflex, for Oral Suspension, equi valent to 125 mg. cephalexin per 5-ml. teaspoonful, in 60 ml.-size packages.

ELI LILLY (PHILIPPINES) INCORPORATED
MAKATI, RIZAL, PHILIPPINES


a new perspective
in steroid-responsive
dermatoses...
NEW
FROM SCHERING RESEARCH
Diprosone
(betamethasone dipropionate 0.05%)
CREAM/OINTMENT

from the skin's point of view... a new perspective in topical steroid therapy

new Diprosone*

(betamethasone dipropionate 0.05%)

CREAM/OINTMENT

dramatic clinical results confirm

■ new high in patient responsiveness without occlusive dressings

Results from a major, continuing program of clinical trials initiated in 1968 ...conducted on a world-wide basis by leading clinical investigators in both double-blind controlled and open studies...involving thousands of patients with a variety of allergic and inflammatory dermatoses... confirm the unique dermotropic activity of new DIPROSONE.

95.8% patient response

**1309 patients with psoriasis and other allergic, inflammatory dermatoses were treated B.I.D. without occlusion. Treatment was continued until clinical "cure" was achieved or, in the majority of studies for a period of three weeks.†

■ clinical "cure" rate unsurpassed by other steroids

The following results are from a program of double-blind controlled studies comparing new DIPROSONE with nine leading topical steroids...treatment B.I.D. was evaluated in 1528 patients with psoriasis and other allergic, inflammatory dermatoses.†

	moderate improvement	slight improvement	no improvement	clinical "cure" or marked improvement	
DIPROSONE..... (371 patients)	**4.0%** (15 patients)	**17.2%** (64 patients)	**8.3%** (31 patients)	**70.3%** (261 patients)	in psoriasis
Other topical steroids..... (365 patients)	**6.0%** (22 patients)	**40.8%** (149 patients)	**26.6%** (97 patients)	**26.6%** (97 patients)	
DIPROSONE..... (406 patients)	**2.7%** (11 patients)	**7.4%** (30 patients)	**3.4%** (14 patients)	**86.4%** (351 patients)	in other steroid-responsive dermatoses
Other topical steroids..... (386 patients)	**4.7%** (18 patients)	**17.3%** (67 patients)	**10.9%** (42 patients)	**67.1%** (259 patients)	

PACKAGING: DIPROSONE Cream, 10 gm. tube
DIPROSONE Ointment, 10 gm. tube

† Medical Research Files, Schering Corporation, U.S.A.

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JOURNAL
OF THE
PHILIPPINE MEDICAL ASSOCIATION

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Volume 52 Nos. 9-10
September-October 1976

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TREASURER'S REPORT

RE-ENTERED AS SECOND CLASS MAIL MATTER AT THE MANILA CENTRAL POST OFFICE ON OCTOBER 29, 1974.

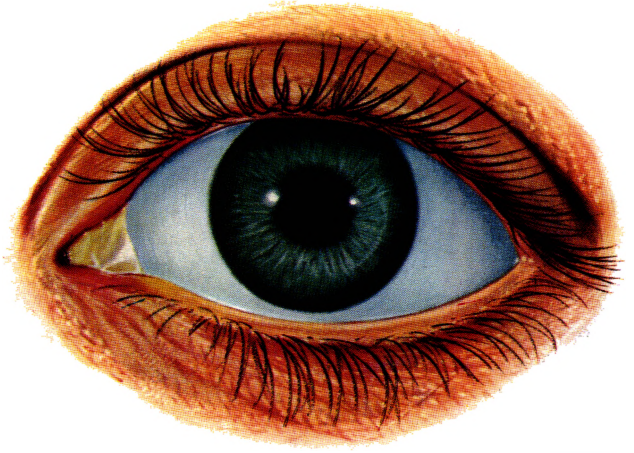
JOURNAL

OF THE

PHILIPPINE MEDICAL ASSOCIATION

Introducing...

The new eye opener...



GARAMYCIN*

EYE DROPS

CLEARS UP

external
eye infections
caused by a wide
range of ocular pathogens

The eye opener... in bacterial conjunctivitis

WIDE GRAM-NEGATIVE SPECTRUM AND GRAM-POSITIVE ACTIVITY

GARAMYCIN*

EYE DROPS

Clears up conjunctivitis and other infections of the external eye and adnexa due to susceptible strains of gram-negative *H. influenzae, E. coli, K. pneumoniae, M. lacunata, Enterobacter aerogenes* (formerly *Aerobacter*), *H. aegyptius* and *Neisseria* sp., including *N. gonorrhoeae.*

Clears up conjunctivitis and other infections of the external eye and adnexa due to susceptible strains of gram-positive staphylococci and streptococci, including *D. pneumoniae.*

Clears up infections of the external eye and adnexa due to problem organisms: *P. aeruginosa* (certain strains) and *Proteus* sp. (sensitive strains—both indole-positive and -negative).

Clears up infections**of the external eye and adnexa generally without sensitivity reactions and irritation.

No significant organism resistance to date.†

Garamycin Eye Drops available in 5 ml. plastic bottle;
also available in ointment form, 3 gm. tube.

**due to susceptible organisms.

†This may occur in the future. Resistance to gentamicin has been produced (with difficulty) *in vitro* by repeated exposures.

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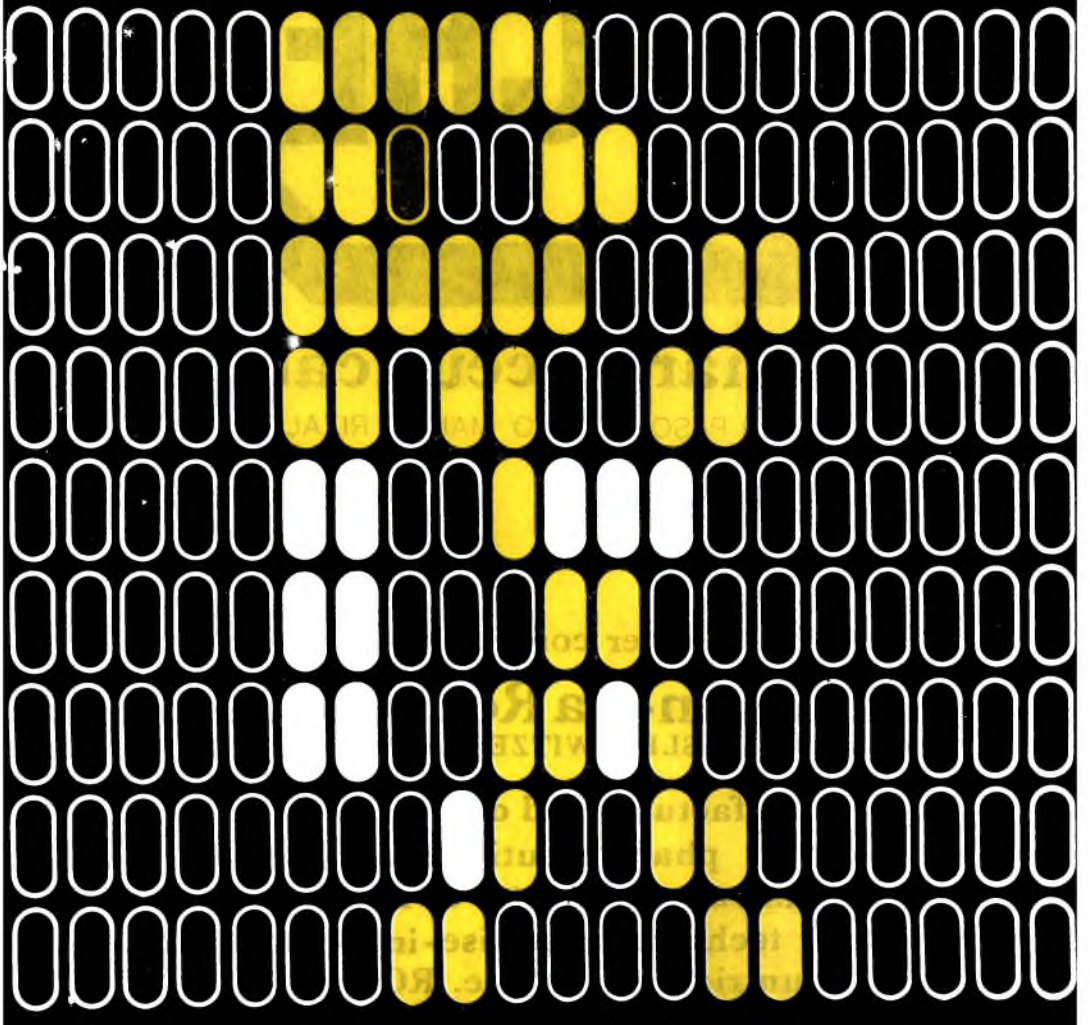

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THE ULTIMATE IN CONVENIENCE AND THERAPEUTIC BENEFITS

Celestone Repetabs

(betamethasone repeat-action tablets)

when a long-acting oral corticosteroid is desired

Today's most active systemic corticosteroid...
in a specially designed long-acting form

Celestone* Repetabs*

(betamethasone repeat-action tablets)

higher degree of safety

☐ possesses a greater margin of safety in both short-term and long-term administration.[6,7,8]

comprehensive therapeutic benefits

☐ rapid and sustained symptomatic relief in allergic or inflammatory conditions[1-5]

☐ enhanced gastric tolerance due to delayed absorption of follow-up dose[1,5]

☐ prolonged activity makes middle-of-the-night doses unnecessary, allows patients the benefit of uninterrupted sleep

matchless treatment convenience

☐ simplifies prescribing regimens. Repeat-dose, prolonged action tablet ensures adequate daily medication

☐ ideal for patients who find multi-dose regimens difficult or inconvenient

☐ ideally suited for hospital use. Dosage convenience simplifies administration of medication

References:

(1) Juarez, L.: Méd. Práct. *245*:4, 1965.
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When it comes to skin...
Nerisona
new
Cream
Ointment
Fatty Ointment

Nerisona

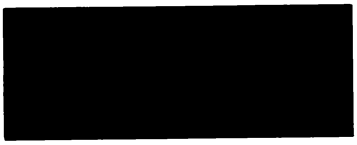
outstanding among today's leading topicals

the superior, new dermocorticoid from Schering AG Berlin/Bergkamen

rapid onset of action

excellent efficacy in psoriasis

available in 3 bases for the 3 types of skin conditions



Nerisona Cream
Nerisona Ointment
Nerisona Fatty Ointment
corticoid preparations for the topical treatment of inflammatory and allergic skin conditions

Composition
1 g of the respective Nerisona preparation contains 1 mg (0.1%) diflucortolone valerate.

Indications
All skin conditions responsive to topical corticoid treatment, such as contact dermatitis, contact eczema; occupational eczema; vulgar, nummular, degenerative and seborrhoeic eczema; dyshidrotic eczema; eczema in varicose syndrome (but not directly onto ulcers); anal eczema; eczema in children; neurodermatitis; psoriasis; lichen ruber planus et verrucosus; lupus erythematosus discoides; first-degree burns, sunburn; insect bites.

In these indications, the choice of the appropriate preparation (cream, ointment, fatty ointment) is determined by the characteristic appearance respectively the stage of the skin condition:

Nerisona cream, with its base of high water and low fat content, in weeping skin conditions and for application on moist, exposed or hairy skin areas.

Nerisona ointment, with its base of balanced fat/water content, for nearly all stages of inflammatory and allergic skin conditions.

Nerisona fatty ointment, with its anhydrous base, for dry skin conditions or chronic stages.

Contra-indications and risks
Tuberculous and syphilitic processes in the area to be treated; virus diseases (vaccinia, smallpox, chicken-pox).

Topical steroids should not be used extensively during the first trimester of pregnancy, i.e. in large amounts or for prolonged periods.

Possible side-effects
As with other corticoids, the following reactions may occur when Nerisona is applied to large skin areas (about 10% of the body-surface or more) and/or for prolonged periods (more than 4 weeks), particularly when the fatty ointment or occlusive dressings are used: local concomitant symptoms such as skin atrophy, telangiectasias, striae and acneiform skin conditions as well as systemic effects of the corticoid due to absorption.

Please note
In bacterially infected dermatoses and/or mycosis, an additional specific therapy is necessary.
When Nerisona is applied to the face, it should not come into contact with the eyes.

Dosage and administration
Generally, the appropriate Nerisona preparation is applied twice, if necessary 3 times daily, initially, in a thin layer. After clinical improvement, one daily application is often sufficient.
In infants and children up to 4 years of age, duration of treatment should not exceed 3 weeks, particularly when Nerisona is applied to skin areas covered with napkins.
If the skin dries out too much under prolonged use of Nerisona cream, a transfer to a preparation with a higher fat content (Nerisona ointment or Nerisona fatty ointment) is recommended.
For detailed information on Nerisona please consult our scientific literature.

Presentation
Nerisona cream, Nerisona ointment and Nerisona fatty ointment: Tubes of 5, 10 and 30 g

Schering AG Berlin/Bergkamen

Schering

Berlimed Philippine Corp.

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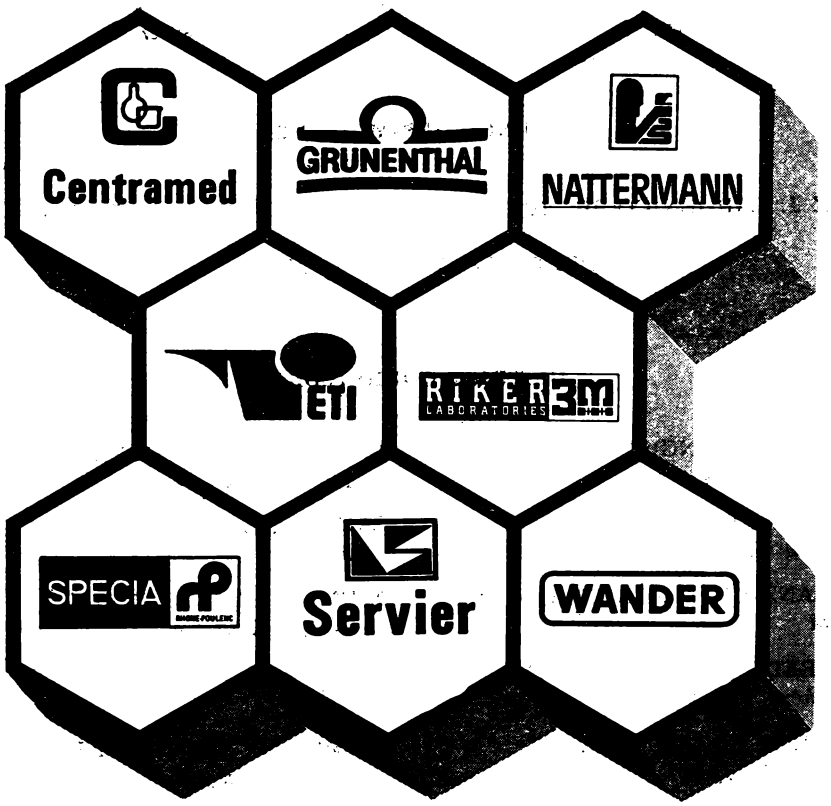

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Help your vitamin-deficient patients get nutritional support for the many stresses of today

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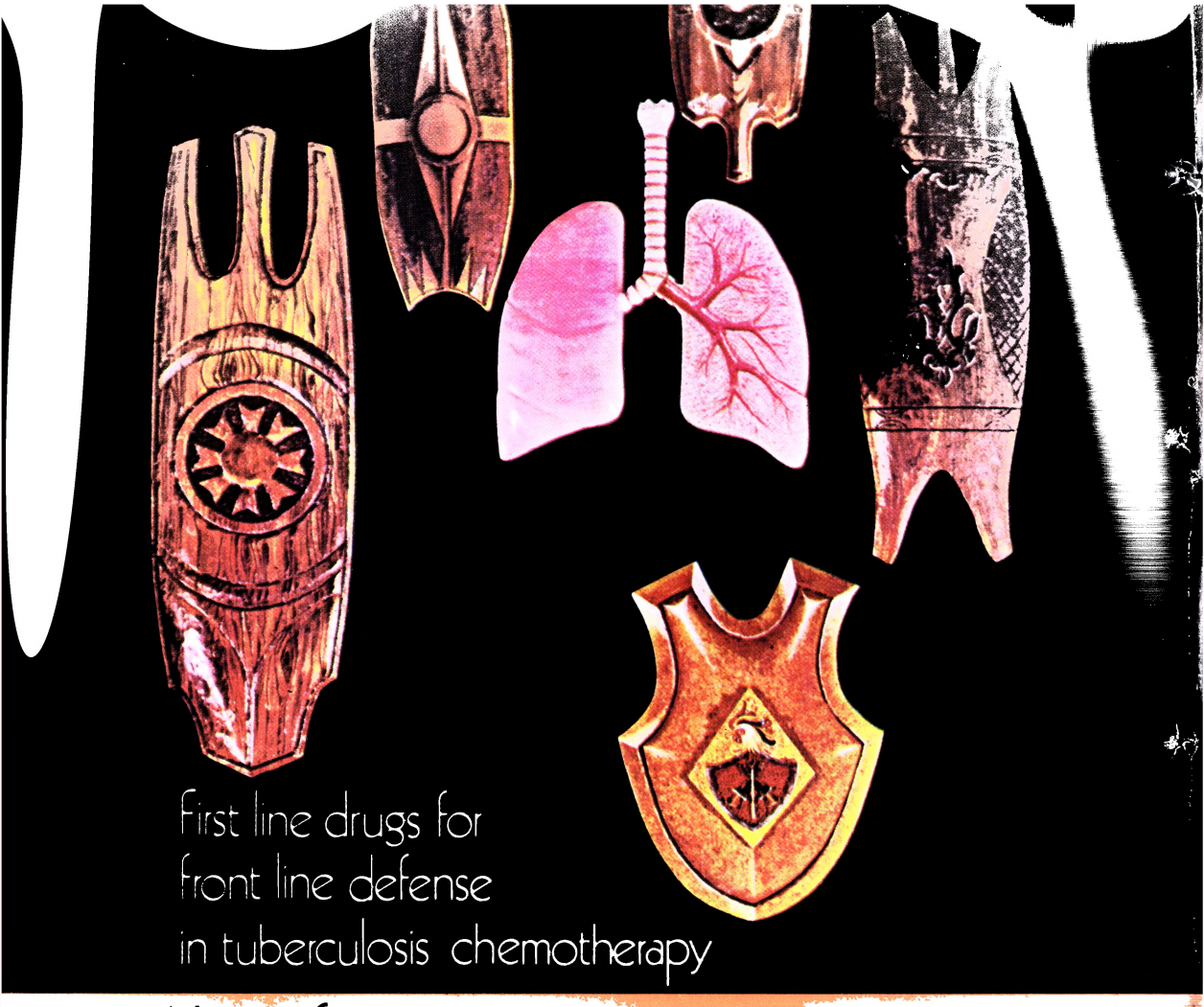
developed thru research by winthrop



New from winthrop

DINACRIN

deploys the two first line drugs considered the primary or major agents for tuberculosis infections.

INH & PAS
buttressed with **B-COMPLEX VITAMINS**

e management of tuberculous pa-
ts usually consists of the use of
ndard or conventional drugs—iso-
zid (INH), sodium-p-amino sali-
ate (PAS) and streptomycin, or the
ver compounds such as prothio-
nide, ethionamide and ethambutol.
ile the new compounds have their
advantages, they also have their
set of disadvantages. They are
only expensive but are also re-
vely toxic.

ly administration of INH and
S provide the most effective com-
ation in the chemotherapy of tu-
culosis. **Dinacrin** combines them into a formula and in optimum concentration that will insure speed in the reversal of infectiousness.

The formula of **Dinacrin** provides marked benefits for tuberculous patients.

Greater antimicrobial activity of INH is assured which is the fundamental element in the chemotherapy of tuberculosis.

There is considerable speed in the reversal of infectiousness. **Dinacrin** reaches the tubercle bacilli in the deepest tissues and organs.

Even if resistance has already developed towards INH, the clinical status of the patients can still be maintained or even improved throughout the entire period of administration.

Each caplet contains:

Isonicotinic acid hydrazide	50 mg.
Sodium-p-amino salicylate	500 mg.
B1 (Thiamine mononitrate)	10 mg.
B6 (Pyridoxine hydrochloride)	12.5 mg.
B12 (Cyanocobalamin)	10 mcg.

Dinacrin is indicated for intensive oral chemotherapy of pulmonary and extra-pulmonary tuberculosis including:

1. Pulmonary tuberculosis, all forms, from minimal tuberculosis to uncomplicated cavitary disease.
2. Miliary (disseminated) tuberculosis, tuberculous meningitis, and genito-urinary tuberculosis (preferably with concomitant streptomycin regimen).
3. Tuberculosis of the skin, oral cavity and lymph nodes.
4. Tuberculosis of the bones and joints (possibly with surgical intervention in advanced cases).
5. Chemoprophylaxis of tuberculosis in selected cases, e.g., children 4 years of age or less and high-risk adults (physicians, nurses, attendants) with positive tuberculin test.

DOSAGE:
Adults: 2-3 caplets four times a day
Children: Adjusted according to body weight

HOW SUPPLIED:
Box of 100 caplets

NEW HOPE THROUGH SUPERIOR TUBERCULOSIS CHEMOTHERAPY

THE FEW AGAINST THE MANY

For Mild to Moderate Pain

DOLOXENE COMPOUND (propoxyphene, acetylsalicylic acid, phenacetin, and caffeine, Lilly)

Each Pulvule contains 50 mg. of propoxyphene napsylate (equivalent to 32 mg. of propoxyphene hydrochloride), 227 mg. of acetylsalicylic acid, 162 mg. of phenacetin, and 32.4 mg. of caffeine.

USUAL ADULT DOSAGE: 2 Pulvules every four hours as needed for pain.

Joint Pain

For Significant Analgesia

DOLOXENE COMPOUND-65

Each Pulvule contains 100 mg. of propoxyphene napsylate (equivalent to 65 mg. of propoxyphene hydrochloride), 227 mg. of acetylsalicylic acid, 162 mg. of phenacetin, and 32.4 mg. of caffeine.

USUAL ADULT DOSAGE: 1 Pulvule every four hours as needed for pain.

Head Pain

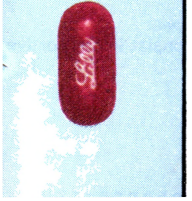
For Pain Relief Only

DOLOXENE (propoxyphene napsylate, Lilly)

Each Pulvule contains 50 mg. of propoxyphene napsylate.

USUAL ADULT DOSAGE: 2 Pulvules every four hours as needed for pain.

Visceral Pain



For Fever and Pain

DOLOGESIC-32 (propoxyphene napsylate and paracetamol, Lilly)

Each tablet contains 50 mg. of propoxyphene napsylate (equivalent to 32 mg. of propoxyphene hydrochloride) and 325 mg. of paracetamol.

USUAL ADULT DOSAGE: 2 tablets every four hours as needed for pain.

Muscular Pain

ILOSONE (erythromycin estolate, Lilly)

DESCRIPTION:

Erythromycin is produced by a strain of *Streptomyces erythraeus* and belongs to the macrolide group of antibiotics. It is basic and readily forms salts with acids. The base, the stearate salt, and the esters are poorly soluble in water and are suitable for oral administration.

ILOSONE is the lauryl sulfate salt of the propionyl ester of erythromycin.

ACTIONS:

Erythromycin inhibits protein synthesis without affecting nucleic acid synthesis. Some strains of *Hemophilus influenzae* and staphylococci have demonstrated resistance to erythromycin. Culture and susceptibility testing should be done. If the Bauer-Kirby method of disc susceptibility testing is used, a 15-mcg. erythromycin disc should give a zone diameter of at least 18 mm. when tested against an erythromycin-susceptible organism.

Orally administered erythromycin estolate is readily and reliably absorbed. Because of acid stability, serum levels are comparable whether the estolate is taken in the fasting state or after food. After a single 250-mg. dose, blood concentrations average 0.29, 1.2, and 1.2 mcg. per ml., respectively, at two, four, and six hours. Following a 500-mg. dose, blood concentrations average 3, 1.9, and 0.7 mcg. per ml., respectively, at two, six, and twelve hours.

After oral administration, serum antibiotic levels consist of erythromycin base and propionyl erythromycin ester. The propionyl ester continuously hydrolyzes to the base form of erythromycin to maintain an equilibrium ratio of approximately 20% base and 80% ester in the serum. Further, the propionyl ester contributes to the activity of the drug through additional hydrolysis to the base at the bacterial cellular level.

After absorption, erythromycin diffuses readily into most body fluids. Only low concentrations are normally achieved in the spinal fluid, but passage of the drug across the blood-brain barrier increases during meningeal inflammation. In the presence of normal hepatic function, erythromycin is concentrated in the liver and excreted in the bile; the effect of hepatic dysfunction on excretion of erythromycin by the liver into the bile is not known. Less than 5% of the orally administered dose is excreted in active form in the urine.

Erythromycin crosses the placental barrier, but fetal plasma levels are low.

INDICATIONS:

STREPTOCOCCUS PYOGENES (Group A Beta-Hemolytic)— Upper and lower-respiratory-tract, skin, and soft-tissue infections of mild to moderate severity.

ALPHA-HEMOLYTIC STREPTOCOCCI (Viridans Group)— Short-term prophylaxis against bacterial endocarditis prior to dental or other operative procedures in patients with a history of rheumatic fever or congenital heart disease who are hypersensitive to penicillin.

STAPHYLOCOCCUS AUREUS— Acute infections of skin and soft-tissue which are mild to moderately severe. Resistance may develop during treatment.

DIPLOCOCCUS PNEUMONIAE— Upper and lower-respiratory-tract infections of mild to moderate severity.

MYCOPLASMA PNEUMONIAE (Eaton Agent, PPLO)— In the treatment of primary atypical pneumonia when due to this organism.

TREPONEMA PALLIDUM— Erythromycin is an alternate choice of treatment of primary syphilis in penicillin-allergic patients. In primary syphilis, spinal-fluid examinations should be done before treatment and as part of follow-up after therapy.

CORYNEBACTERIUM DIPHTHERIAE— As an adjunct to antitoxin, to prevent establishment of carriers, and to eradicate the organism in carriers.

CORYNEBACTERIUM MINUTISSIMUM— In the treatment of erythrasma.

ENTAMOEBA HISTOLYTICA— In the treatment of intestinal amebiasis only. Extraenteric amebiasis requires treatment with other agents.

LISTERIA MONOCYTOGENES— Infections due to this organism.

CONTRAINDICATION:

ILOSONE is contraindicated in patients with known allergy to erythromycin estolate.

WARNINGS:

The administration of erythromycin estolate has been associated with the infrequent occurrence of intrahepatic cholestasis. Hepatic dysfunction, with or without jaundice, has occurred, chiefly in adults. It may be accompanied by malaise, nausea, vomiting, abdominal colic, and fever. In some instances, severe abdominal pain may simulate the pain of biliary colic, pancreatitis, perforated ulcer, or an acute abdominal surgical problem. In other instances, clinical symptoms and results of liver function tests have resembled findings in extrahepatic obstructive jaundice.

Laboratory findings have been characterized by abnormal hepatic function test values, peripheral eosinophilia, and leukocytosis. If the above findings occur, discontinue ILOSONE promptly.

Initial symptoms have developed in some cases after a few days of treatment but generally have followed one or two weeks of continuous therapy. Symptoms reappear promptly, usually within forty-eight hours after the drug is readministered to sensitive patients. The syndrome seems to result from a form of sensitization, occurs chiefly in adults, and has been reversible when medication is discontinued.

Safety of this drug for use during pregnancy has not been established.

PRECAUTIONS:

Because erythromycin is excreted principally by the liver, caution should be exercised in administering the antibiotic to patients with impaired hepatic function.

SIDE-EFFECTS (also see WARNINGS):

The most frequent side-effects of erythromycin preparations are gastrointestinal (e.g., abdominal cramping and discomfort) and are dose-related. Nausea, vomiting, and diarrhea occur infrequently with usual oral doses.

During prolonged or repeated therapy, there is a possibility of overgrowth of nonsusceptible bacteria or fungi. If such infections arise, the drug should be discontinued and appropriate therapy instituted.

Mild allergic reactions, such as urticaria and other skin rashes, have occurred. Serious allergic reactions, including anaphylaxis, have been reported.

DOSAGE AND ADMINISTRATION:

ADULTS— The usual dosage is 250 mg. every six hours. This may be increased up to 4 Gm. or more per day according to the severity of the infection.

CHILDREN— Age, weight, and severity of the infection are important factors in determining the proper dosage. The usual regimen is 30 to 50 mg. per Kg. per day in divided doses. For more severe infections, this dosage may be doubled.

If administration is desired on a twice-a-day schedule in either adults or children, one-half of the total daily dose may be given every twelve hours.

STREPTOCOCCAL INFECTIONS— In the treatment of group A beta-hemolytic streptococcal infections, a therapeutic dosage of erythromycin should be administered for at least ten days. In continuous prophylaxis of streptococcal infections in persons with a history of rheumatic heart disease, the dosage is 250 mg. twice a day.

When ILOSONE is used prior to surgery to prevent endocarditis caused by alpha-hemolytic streptococci (viridans group), a recommended schedule for adults is 500 mg. before the procedure and 250 mg. every eight hours for four doses afterward; for children, 30 to 50 mg. per Kg. per day divided into three or four evenly spaced doses.

PRIMARY SYPHILIS— A regimen of 20 Gm. of erythromycin estolate in divided doses over a period of ten days has been shown to be effective in the treatment of primary syphilis.

AMEBIC DYSENTERY— Dosage for adults is 250 mg. four times daily for ten to fourteen days; for children, 30 to 50 mg. per Kg. per day in divided doses for ten to fourteen days.

OVERDOSAGE:

SYMPTOMS— Nausea, vomiting, and diarrhoea.

TREATMENT— General management may consist in supportive therapy.

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EDITORIAL

THE RESPONSIBILITY OF MEDICAL SCHOOLS

If Medical Schools are to pursue their commitment and assume their important role in the progress of medicine in our country, their responsibility to strive for and maintain quality basic medical education is of paramount concern. The maximum of efforts must be exerted continuously to provide Medical Schools with a competent faculty, adequate facilities for laboratories and research, and a well organized training hospital. An academic environment must exist and be preserved. It is probably because of these existing factors that medical students become more motivated, eventually successful graduates and grateful as well as loyal alumni. These alumni as a potent body may in turn contribute voluntarily and generously to support and further improve the Medical Schools. It is a well known fact, that institutions of higher learning such as Medical Schools abroad particularly in the advanced countries, are fortunate recipients of substantial funding and aid from their alumni, philantrophists, and foundations who are truly and fully convinced of the schools' excellence and undoubted role in the progress and leadership of their country. Their own governments also contribute generously in this partnership.

The future professional career of medical students is to a great extent dependent on the quality of basic medical education he had undergone. Inadequate basic education simply leads to mediocrity. It is not the few who become successful, but, the greatest number who are.

The faculty must be well chosen and encouraged, for the quality of medical education is dependent on the quality of its faculty. This is a critical and serious problem in our country. It cannot be overemphasized that the backbone of any institution of learning is its faculty. A medical school or any institution for that matter is only as good as its faculty. There is no substitute for a competent, responsive, and progressive faculty.

In the not distant future, the standard of medical service and health care delivery will reflect the effects of what basic medical education our present undergraduates had. Whatever it maybe, our Medical Schools must provide the answer.

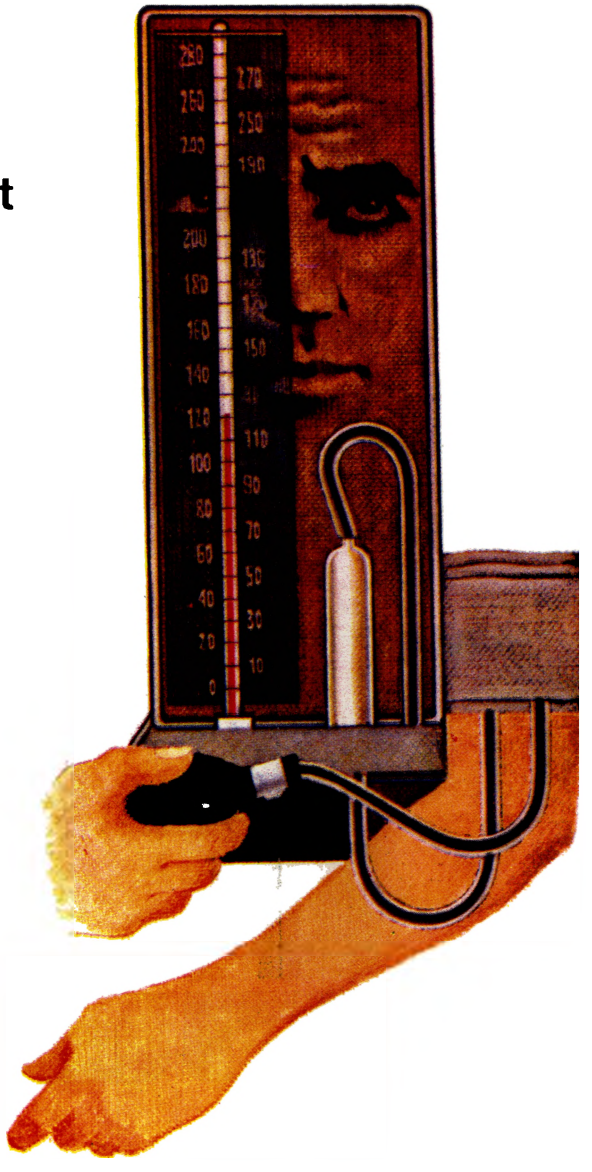
A. J. RAMOS, M.D.

For patients under pressure
from anxiety

Ativan* ½ & 1 mg.

(lorazepam, Wyeth)

now truly your key to successful management of anxiety



- helps regulate blood pressure in stress-induced hypertension[1]
- completely compatible with standard antihypertensive therapies: reserpine, hydralazine, methyldopa, furosemide[2]
- no effects on antihypertensive or cardiotherapeutic regimens were observed, nor was there any evidence of changes in orthostatic circulation, as occasionally reported with some benzodiazepines[3]

1. Carballo, R. *et al.* "Clinical Investigation With a New Anxiolytic, WY-4036, Lorazepam," *La Prensa Médica Argentina* 59:28 (1972) 1076-80.

2. Khorana, A. B. "Lorazepam, a New Benzodiazepine, in Psychosomatic Disorders," *Journal of the Association of Physicians of India* 22:2 (February 1974) 173-8.

3. Höffkes, H. "Effect of Lorazepam on Standard Therapies," *Arztliche Praxis* 24 (1972) 2871-4.

Ativan ½ & 1 mg.

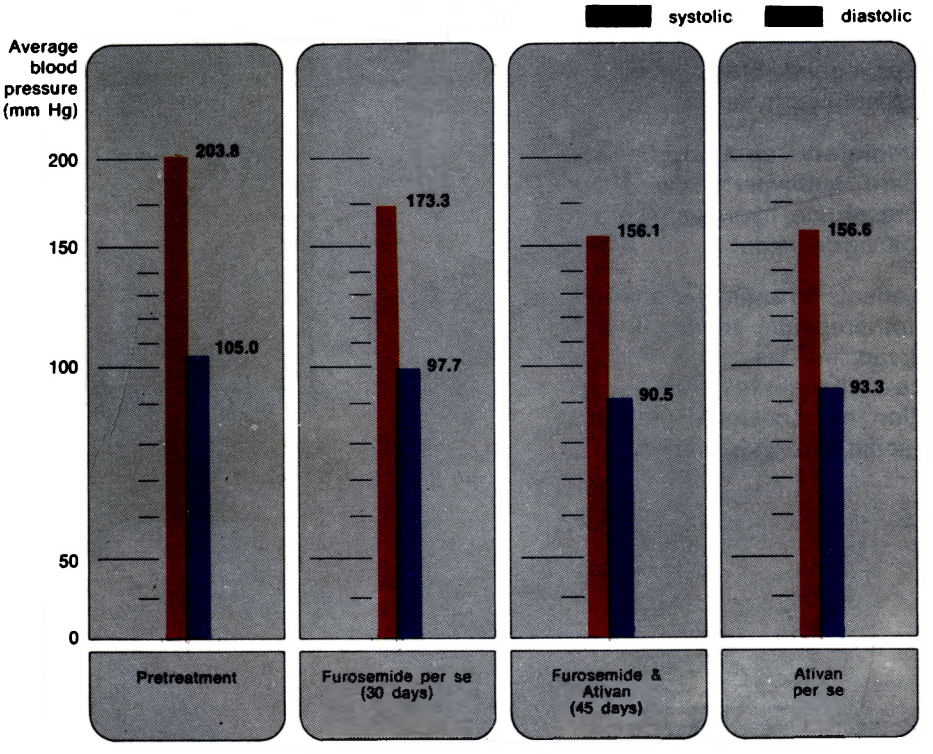
(lorazepam, Wyeth)

for a wider range of anxiety states

effective in improving patient's physical and emotional condition

helps regulate blood pressure in stress-induced hypertension

clinical trials[1] show:



Wyeth

ORIGINAL ARTICLES

The Coconut Water Egg Malachite Green Medium (CEM) for the Isolation of Mycobacterium Tuberculosis*

V. BASACA-SEVILLA, M.D., M.P.A.,**
JOSUE S. SEVILLA, D.D.M.,***
POTENCIANA C. FARAON, D.D.M.,**
CELESTE L. FERNANDO, A.B.** and
JOSEFINA A. UVERO, B.S. Pharm.**

TUBERCULOSIS in all forms is the second leading cause of deaths in this country, fourth in causing disease and the number one disease killer of our children. On its early diagnosis depends its cure and control and an assured healthy people. Toward this end, government and private agencies have joined efforts in the detection and treatment of infectious cases as well as the institution of preventive measures. The most utilized tools of detection are sputum microscopy and x-ray. While sputum microscopy has been the least expensive and most efficient tool in mass case detection, there is **still need for other laboratory tools in the more scientific study of detected cases.** The isolation of **Mycobacterium tuberculosis is one of the more reliable aids in the diagnosis of symptomatic cases with negative sputum for acid fast bacilli.** For those cases under therapy with apparently no clinical or bacteriological improvement, a bacteriological work-up is necessary to determine sensitivity or resistance to the drug being used, or where a possible change of drug is contemplated. For those where actual identification of the infecting organisms is necessary, a bacteriological work-up is the only tool.

Today less than 10 clinical laboratories all over the country can afford to continuously and regularly do the routine bacteriological isolation of **Mycobacte-**

*The Process and Product is covered by Philippine Patent No. 9768 awarded first prize (Pharmaceuticals and Chemical Category) Invention Contest on the 10th National Philippine Inventor's Week, April 9, 1976.

**Division of Laboratories, Bureau of Research and Laboratories, Department of Health, Manila.

***Philippine Atomic Energy Commission.

● **First Prize PMA-Abbott Research Award on Basic Science 1976.**

rium tuberculosis. Currently these laboratories are utilizing a medium principally composed of eggs or other protein sources, mineral salts and a dye. With the exception of eggs and the distilled water, the reagents and chemicals that make up the formulas have to be procured from abroad entailing difficulties like irregular supply, increased cost, and because too few laboratories are using the special medium, there is very little interest to make the purchase from abroad.

The formula of the medium currently in use for the isolation of **M. tuberculosis** may be one of the following:

1. Lowenstein-Jensen medium, modified

KH_2PO_4	2.4 gm.
$MgSO_4.H_2O$	0.24
Magnesium citrate	0.60
Aspargine	3.6
Glycerol	12 ml.
Malachite green 2% aq. solution	20 ml.
Potato flour	30 gm.
Distilled water	600 ml.
Eggs (fresh, whole)	1000 ml.

2. Lowenstein-Jensen medium, modified

Mineral salt solution

KH_2PO_4	4.0 gm.
$MgSO_4$	0.4
Magnesium citrate	1.0
Aspargine	6.0
Glycerol	20.0 ml.
Distilled water	1000.0 ml.

Complete formula

Mineral salt	300.0 ml.
2% malachite green	10.0 ml.
10 beaten eggs, approx.	500.0 gm.

3. American Trudeau Society (ATS medium, modified)

Potato peeled and diced	140 gm.
Glycerol, reagent grade 2%	335 gm.
Egg yolk (fresh) with) 3 white	400 ml.
2% malachite green	10 ml.

4. Petragnani medium

a. Pasteurized, homogenized whole milk	275.0 ml.
Potato starch (Fisher)	20.0 gm.
Aspargine (Difco)	1.9 gm.
b. Fresh whole eggs	10
Fresh egg yolk	3
Glycerine	30 ml.
c. 2% aq. sol. malachite green	

5. Middle-brook-Cohn 7H-10 agar

Solution [1]

Monopotassium phosphate, ACS	15 gm.
Disodium phosphate, ACS	15 gm.
Distilled water	250 ml.

Solution 2

Ammonium sulfite, ACS	5.0 gm.
Monosodium gllutamate	5.0 gm.
Sodium citrate (2 H_2O) USP	4.0 gm.
Ferric ammonium citrate	0.4 gm.
Magnesium sulfate (7 H_2O)	5.0 gm.
Biotin (in 2 ml. 10% ammonium hydroxide)	5.0 gm
Distilled water	250.0 ml.

Solution 3

Calcium chloride (2 H_2O), ACS	50.0 mg.
Zinc sulfate (7 H_2O), ACS	100.0 mg.
Copper sulfate (5 H_2O), ACS	100.0 mg.
Pyrodoxine HCL	100.0 mg.
Calcium panthothenate	100.0 mg.
Distilled water	100.0 ml.

Solution 4

Reagent grade glycerine

Solution 5

Malachite green, 0.01% aq. sol.

Solution 6

Albumin-oleate dextrose solution
50 gm. bovine albumin, fraction V
in 900 ml. sterile saline
Sodium oleate solution
50% aq. solution of dextrose

A glance through the above formulas will reveal their varying complexity, the cost it will entail in their preparation, the time involved in the weighing of each constituent especially those where an analytical balance is required, the physical facilities for the preparation and the need for personnel of higher technical training. The preparation of formula nos. 4 and 5 require more skill. Formula no. 3 or ATS medium is a more simple one, but still it makes use of potatoes which have to be peeled and diced besides eggs.

METHODS

In answer to the need for maximizing the utilization of isolation and culture of **M. tuberculosis** in all laboratories, a new medium, the coconut water egg malachite green medium (CEM) has been devised. It has the following formula:

Coconut water ..... 300 ml.
Whole eggs 10
(approx. 500 gm.)
2% malachite green

Water from young green coconut is sterilized by boiling or autoclaved for 10 min. at 10 lbs. pressure. The eggs are cleansed thoroughly with soap and water; rinsed well and soaked in 70% alcohol, and dried with sterile towel. The eggs are aseptically broken into a sterile conical flask or an Erlenmeyer flask with a pipette or glass rod. The flask is shaken to break up the eggs and the coconut water added with malachite green solution enough to produce a light green color of the mixture. The contents are shaken well to mix, then filtered through sterile gauze. The mixture is

aseptically distributed into screw-capped test tubes and inspissated at 80° to 85°C one hour in a slanting position.

The sputum swab culture method devised by Nassau was followed in the evaluation of this medium for the isolation of **M. tuberculosis** from sputum. The modified Lowenstein-Jensen medium, formula 2, was used as control. One or two sterile swabs are moistened with sterile distilled water and both held in one hand, dipped into the sputum sample and vigorously rotated, mixing well the sample. The swabs are then placed in tubes, two-thirds full with 5% sterile oxalic acid and allowed to stand at room temperature for 35 minutes. Then the swabs are transferred to another tube also two-thirds full with sterile 5% sodium citrate and allowed to stand in the solution for 10 minutes. Two slopes of CEM and of Lowenstein-Jensen media are inoculated with each sample. The swabs are firmly rubbed on each slope while the swab is being rotated.

RESULTS

Laboratory standard strains of **Mycobacterium** like H37Rv, **M. xenopei, M. avium, M. kansasii,** a Scotochromogenic strain, 607 strain, BCG strain and **M. leprae murium** have been cultured and maintained in CEM medium and **M. tuberculosis** have been successfully isolated from sputum samples using CEM. Illustrations of these cultures may be seen in Plates 1—4. It has been noted that the growth of the **Mycobacterium** strains in CEM has been very good.

The standard laboratory human Saranac virulent strain H37Rv has maintained the rough characteristic of its colonies light buff color, somewhat dry in CEM as in the Lowenstein-Jensen medium. A Group II Scotochromogenic strain of the Runyon group of atypical mycobacteria has shown its moist, smooth, confluent colonies with yellow to orange pigments in both CEM and Lowenstein-Jensen media. **Mycobacterium avium,** a virulent avian tubercle bacilli, produced smooth glistening colonies with cream or buff non-photochromogenic confluent colonies in both CEM and Lowenstein-Jensen media. Another atypical mycobacterium **Mycobacterium xenopei** in both CEM and Lowenstein—Jensen media produced smooth, pale yellow non-photochromogenic, moist growth. Another laboratory strain used by the NIST is strain no. 607 of Runyon Group IV which maintains its confluent, finely irregular, light buff colored colonies in CEM as in Lowenstein-Jensen medium. **Mycobacterium kansasii** of Runyon Group I showed yellow pigmented somewhat rough colonies when exposed to light in both media. A-20, a strain of the Scotochromogenic group isolated locally from sputum did not lose its yellow orange pigmented colonies when grown in CEM.

CEM was found as efficient as Lowenstein-Jensen medium in the isolation of Mycobacterium from sputum samples; buff colored rough colonies were produced. At no instance were negative results obtained from CEM when Lowenstein-Jensen medium was positive for isolation.

Using the sputum swab culture technique of Nassau, contamination from other bacteria presented no problem in utilizing CEM or Lowenstein-Jensen medium.

CEM was provided by the authors to another independent worker and he was successful in growing both **M. leprae murium** and BCG strain.

Plate I — Shows the characteristic growth of **M. xenopei, M. avium, M. kansasii, H37Rv, H607** and a Scotochromogen strain in CEM and LJ media.

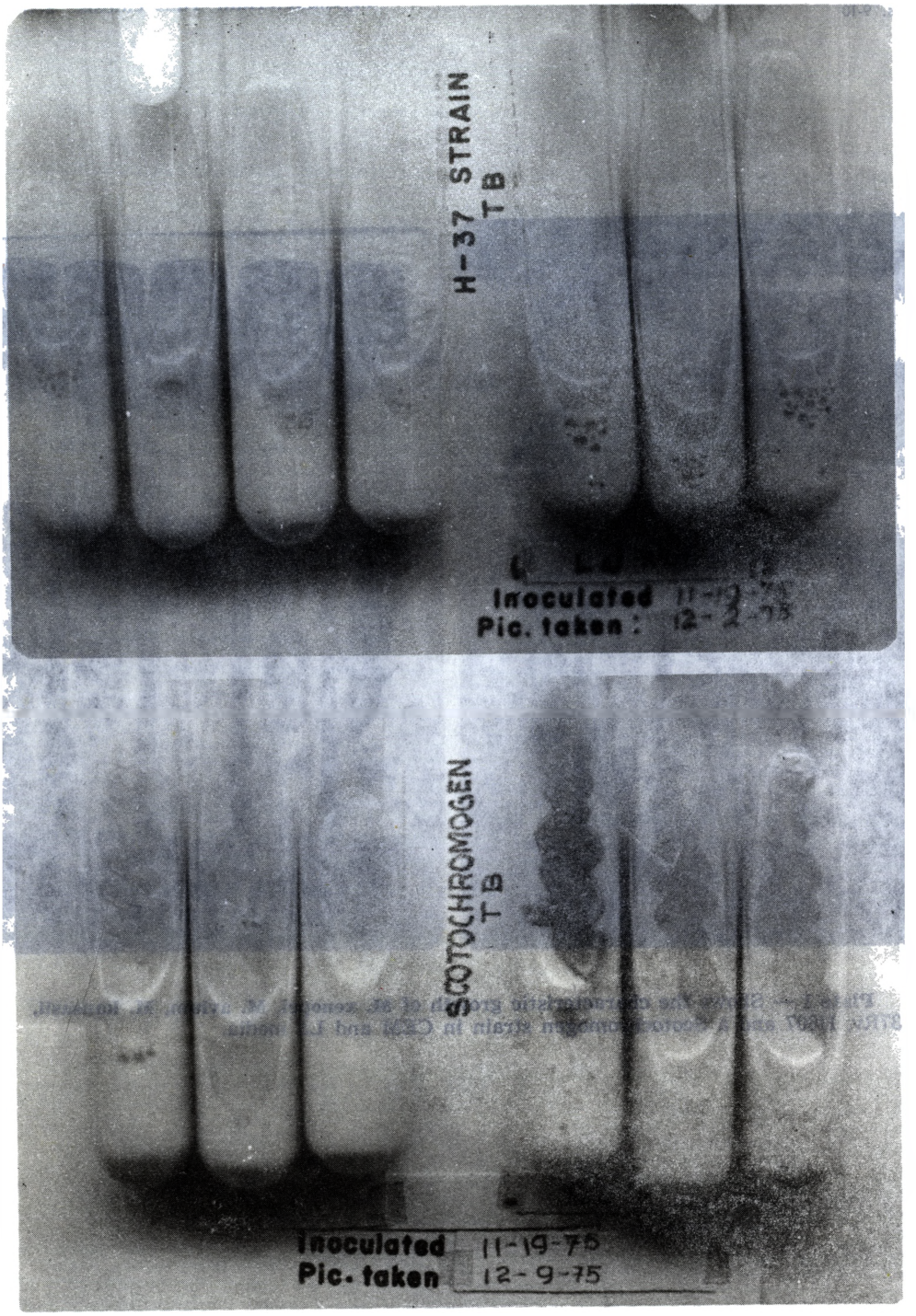


Plate II — Shows a close-up of H37Rv and a Scotochromogen strain in both CEM and LJ media.

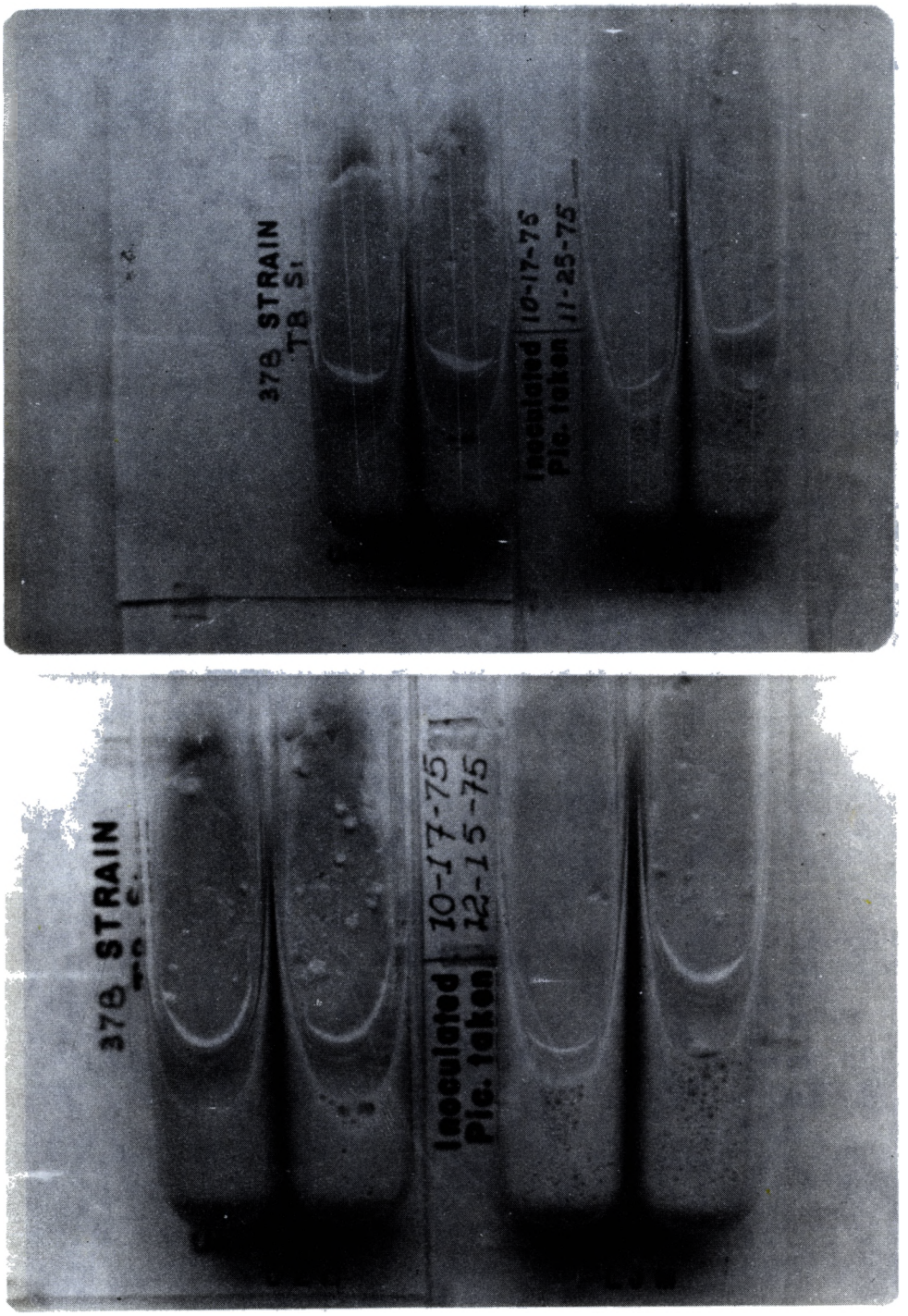


Plate III — Shows the isolates from a sputum sample (378) on different days after inoculation of CEM and LJ media.

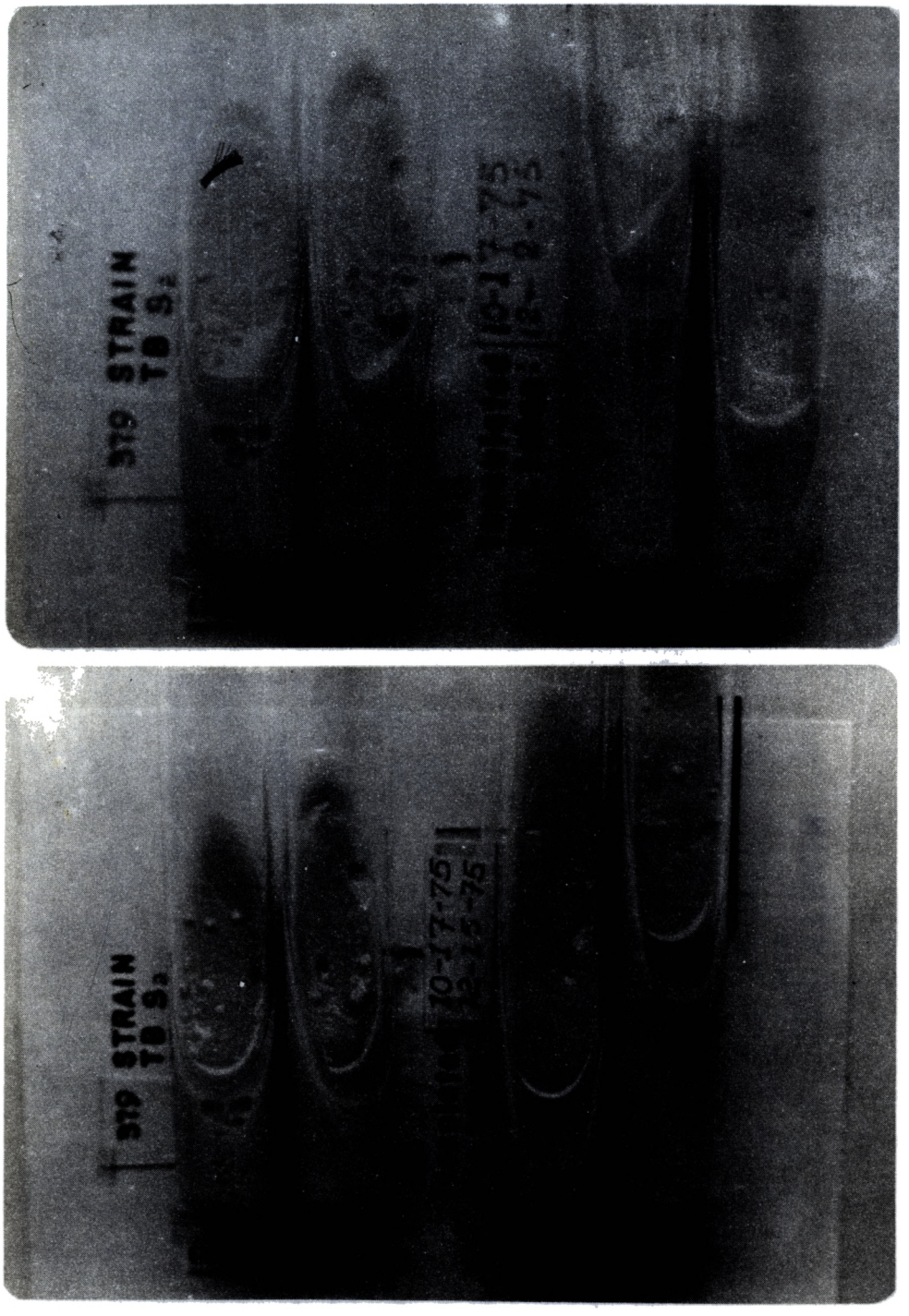


Plate IV — Shows the isolates from a sputum sample (379) on different days after inoculation of CEM and LJ media.

DISCUSSION

CEM utilizes coconut water as its main and only source of mineral salts in addition to its nutrients like protein and carbohydrates, to mix with whole eggs as a culture medium for a fastidious group of organism like the **mycobacteria.** It was definitely shown in this work that used with eggs it can support the growth of **mycobacteria.**

Blauvett[1] reported that non-cooked, non-sterilized coconut water from "ripe fresh fruit" added to ordinary nutrient agar and broth nearly doubled the culture qualities of the latter in growing **Staphylococcus aureaus, B. faecalis alcalis alcaligenes,** and **B. welchii.** Paguio et al[2] in 1970 utilized coconut water medium for the isolation of **Vibrio cholerae.** Agasan[3] in 1975 has proven the sensitivity of coconut water medium in detecting coliforms in waters and foods and the growth of **Salmonella, Shigella** and **Klebsiella** in the same medium.

Several workers have analyzed the composition of coconut water from young green coconuts. Peters[4] gave the range of concentration of the important components of coconut water per 100 ml. as follows:

Protein	0.23 — 0.43 gm.%
Carbohydrates	3.68 — 5.0 gm.%
Fats	0.64 — 0.8 gm.%
Calcium	0.03 gm.%
Phosphorous	0.01 — 0.22 gm.%

Pradera and his co-workers[5] reported the mineral content of 100 ml. of coconut water as follows:

Calcium	29.0 — 46.0 mg.
Chlorine	105.0 — 160.0 mg.
Phosphorous	5.5 — 9.0 mg.
Potassium	134.0 — 220.0 mg.

Child and Nathaniel[6] reported the constituents to be:

Water	95.50%
Nitrogen	0.50
Phosphoric acid	0.60
Calcium oxide	0.69
Magnesium oxide	0.59
Iron	0.50 mg. in 100 gm.
Total solids	4.71 gm./100 ml.
Red sugar as invert sugar	0.80 gm./100 ml.
Add. sugar as sucrose	1.28 gm./100 ml.
total sugar	2.08 gm./100 ml.
ash	0.62 gm./100 ml.
Unidentified organic solids	2.01 gm./100 ml.
Ascorbic acid (Vit. C)	2.20 — 3.70 mgm./100 ml.
Nicotinic acid	0.640 microgram/100 ml.
Panthotenic acid	0.520 microgram/100 ml.
Folic acid	0.003 microgram/100 ml.

Vanderbelt[7] found the following amount of vitamin B complex as:

Nicotinic acid	0.64 microgram/ml.
Panthotenic acid	0.52 microgram/ml.
Biotin	0.02 microgram/ml.
Riboflavin	0.01 microgram/ml.
Folic acid	0.003 microgram/ml.

Pradera and his co-workers (5) made a thorough study of the amino acid content of the water and found them present as peptones based on dry protein content of the water to be as follows:

Glutamic acid	9.76 — 14.50 gm.%
Arginine-1	12.75 gm.%
Leucine	1.95 — 4.18 gm.%
Lysine	1.95 — 4.57 gm.%
Proline	1.21 — 4.12 gm.%
Aspartic acid	3.60
Tyrosine	2.83 — 3.00
Alanine	2.41
Histidine	1.95 — 2.05
Phenylalanine	1.23
Serine	0.59 — 0.91
Cysteine	0.97 — 1.17

The present work has shown for the first time the full utilization of coconut water to support the growth of a fastidious group of organisms not just the use of its "growth factor". Quite a number of workers have shown this growth factor as capable of stimulating growth of certain bacteria. Ramakrishnan, et al[8] in 1958 has shown that coconut water even at a dilution of 1 in 10,000 when used as a supplement to the ordinary medium for the cultivation of **Mycobacterium tuberculosis** showed maximum growth in 12 days only instead of the usual 20 days. We failed to elicit any change in the growth period of the **Mycobacterium** in CEM compared to Lowenstein-Jensen although in some cases growth has been more luxuriant in CEM especially in isolations from sputum samples. In our particular work the growth factor in coconut water is only an incidental advantage when the water is utilized as a whole.

Green coconuts can be procured anywhere especially in the provinces. The simplicity of the formula and preparation does not require much technical skill nor physical laboratory facilities which suit local conditions.

A laboratory that is going to start a TB bacteriology service would need to invest in the following if it will utilize Lowenstein-Jensen medium:

Materials	Cost
KH_2PO_4	₱ 42.00/lb.
$MgSO_4$	56.70/lb.
Magnesium Citrate	45.00/lb.
Aspargine	150.00/100 gm.
Glycerol	95.00/480 cc.
Distilled water	2.50/liter
Malachite green	50.00/25 gm
10 eggs	4.50

However, if it will utilize CEM, the cost estimate would only be:

Green coconut	₱ 0.30 — 0.70/nut depending on where you procure it
10 eggs	4.50 — if procured in the city
malachite green	50.00/25 gm.

So that it is very apparent that one has to have about ₱445.00 to start with the Lowenstein-Jensen medium and only about ₱56.00 or only 1/8 of the former, for CEM. With CEM, even if malachite green is not available, the medium can still be used. CEM is a medium that can be produced from materials locally available.

Since it is a cheap medium, the preparation of CEM may be done at a central laboratory and tubes of the medium dispensed to peripheral areas. Actual production of the media can even be done in a small laboratory. The tubes can be inoculated in the peripheral area using the sputum swab culture technique of Nassau. The inoculated media are then transported to more developed laboratories where it can be incubated, observed and studied. Instead of screw-capped tubes, ordinary tubes with rubber stopper may be used, thus further lowering the cost of each slope. CEM keeps very well at room temperature for at least 3 months and sterile coconut water for about 6 months. The addition of malachite green improves the gross visibility of the colonies. The green color of the media brings out very well the colonial characteristics.

CEM is an ideal medium for the isolation of **mycobacteria** since it supports early and eugonic growth for small inoculum; enables easy recognition of organisms; is easily prepared and inexpensive; and keeps the growth of contaminating organisms to a minimum. CEM medium is most useful wherever tuberculosis is a problem; wherever there is need for a more scientific work-up of detected cases especially for antimicrobial studies; wherever there is a lack or shortage of technical skills and physical laboratory facilities; wherever there is difficulty in the procurement of chemicals and reagents produced or manufactured in developed countries; wherever there is need to lower the cost of medical care delivery and wherever coconut is grown. CEM answers all these needs, which will not only be in the Philippines but in many developing countries where tuberculosis is a health problem.

SUMMARY

For the first time a coconut water egg malachite green medium (CEM), has been devised for the isolation of **Mycobacterium tuberculosis.**

CEM utilizes all the coconut water as its main and only source of mineral salts in addition to its nutrients like protein and carbohydrates to mix with whole eggs as a culture medium for a fastidious group of organisms like **mycobacteria.** Laboratory standard strains of **mycobacteria** like H37Rv, **M. xenopei, M. avium, M. kansasii,** a Scotochromogenic strain, No. 607 strain, BCG strain and **M. leprae murium** have been cultured and maintained in CEM. **Mycobacterium tuberculosis** has been successfully isolated from sputum samples using CEM.

CEM is simple and inexpensive nor does it require much technical skill and physical laboratory facilities to prepare. It is an ideal medium for the isolation of **Mycobacterium** since it supports early

and encourage growth for small inoculum; enables easy recognition of organism and keeps the growth of contaminating organisms to a minimum. It utilizes materials locally available. CEM will be most useful not only in the Philippines but in other developing countries where tuberculosis is a health problem.

ACKNOWLEDGEMENT

Sincere appreciation is due to Dr. J. S. Sumpaico, Director of the Bureau of Research and Laboratories, for his interest in making this study possible; our sincere thanks to those who in one way or another helped in this study particularly to Mrs. Remedios Fernandez, Mr. Eduardo Fontanos, Mrs. Erlinda Villadelgado, Mr. Bernardo Fotruna and Mr. Sol Dungca; to Mr. Sofronio Tomandao for the photographic illustration in this paper; to Miss Victoria Sanchez for her patience in typing the manuscript of this article; to Dr. Tirso Banzon and Attys. Fermin Galang and Nicolas Tayao for helpful suggestions in the preparation of this article; to Dr. Eulalia Venzon of the NIST and Miss Esperanza Basaca of the NSDB for valuable assistance in the literature research; our special appreciation to Dr. Antonio Jacalne of the Institute of Public Health, U.P., for his interest and actual trial of the medium and encouragement to go through with the study.

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The Effects of Glycopyrrolate on the Motor Functions of the Esophagus *•

HIGINO C. LAURETA, M.D.**

INTRODUCTION

ATROPINE decreases the pressure at the high pressure zone (HPZ) at the gastroesophageal junction thereby compromising its physiologic sphincter function.[1,2] Moreover, it inhibits esophageal peristaltic waves.[3] These promote esophageal reflux and produce esophagitis. This is particularly undesirable in a patient who suffers from esophageal reflux and chronic esophagitis.

The effects of atropine on the motor functions of the esophagus are to be expected because the motor nerves of the esophagus, the vagi, are cholinergic nerves. The anticholinergic drugs that are used for the treatment of peptic ulcer can potentially produce the same adverse effects on the motor functions of the esophagus as those by atropine. Whether these anticholinergic drugs actually produce these effects especially in the recommended dose is not known. The purpose of this study was to determine the effects of a potent anticholinergic drug, glycopyrrolate, on the motor functions of the esophagus.

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**Makati Medical Center.

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MATERIALS AND METHODS

Four young and healthy Pilipino volunteers, two men and two women, were tested for this study.

The motor functions of the esophagus were studied by intraluminal pressure measurements. This method has been previously described.[4] The pressure detecting device consisted of three water-filled polyethelene tubes (P.E. 190; inside diameter, 0.047 in., outside diameter, 0.067 in.) 120 cm long, tied together at the dital end so that the side openings at the distal end were in tandem five cm apart. The tubes were attached to pressure transducers (Statham P32Db) and the pressures recorded on Grass polygraph. The apparatus was calibrated so that one mm Hg pressure produced one mm deflection on the polygraph.

The pressure recording tubing assembly was passed through the nose until the side openings of all three tubes at the distal end were in the stomach. Pressure recordings were made with the subject in the recumbent position. The tubing assembly was withdrawn in stepwise fashion at one half to one cm in-

terval. Pressure were recorded at the lower esophageal sphincter, body of the esophagus, and the upper esophageal sphincter. The responses to swallows of two ml of water were recorded at each level.

The effects of both the injectable and tablet preparations of glycopyrrolate were determined. Two subjects were first tested with the injectable form and the other two with the tablet. In the subjects in whom the injectable form was first tested the normal pressures were first recorded then the tubing assembly was repositioned in the stomach. The recording were repeated half an hour after a subcutaneous injection of 1.5 mg glycopyrrolate, The same subjects were then instructed to take one tablet of glycopyrrolate 30 minutes before each meal and at bedtime for five days after which the intraluminal pressure recordings were repeated. The last tablet was given one hour before the pressure recordings were made. In the two subjects in whom the tablet was first tested the test was repeated with the injectable form at least five days after the last tablet was taken.

The swallowing complex consists of a rise in the average baseline pressure and appears like a plateau and which may be preceded by a brief negative deflection, followed by a positive deflection which represents the peristaltic wave (Fig. 1). The amplitude of the peristaltic wave was determined by measuring the height of the wave from the mean resting pressure to the tip of the wave and expressed in mm Hg pressure.

The velocity of a peristaltic wave was determined by dividing the distance between the two catheter tips (five cm) by the time required for the peristaltic wave to traverse the segment (based on paper speed) as shown in Figure. 1. Only the waves that were clearly progressive were employed in these calculations.

The duration of a swallowing complex was measured from the time of initial deflection to return of the pressure to the baseline (Fig. 1). The duration of the peristaltic wave was calculated from the point of upsweep of the wave to the point where the downsweep reached the baseline. The number and percentage of swallows initiating peristaltic waves and fall in pressure at the lower sphincter were determined for each patient.

Respiratory movements were recorded with a belt pneumograph.

RESULTS

The Normal Pressure Profile of the Esophagus. Sphincter Pressure. In these four normal Pilipinos the lower esophageal sphincter (HPZ) was three to four cm long, the pressure gradually rising from the atmospheric pressure at the fundus of the stomach and abruptly dropping to five mm Hg below the baseline fundal atmospheric pressure as it entered the chest through the hiatus. The mean resting pressure at the peak of the HPZ was seven mm Hg (Fig. 2A). The lower esophageal sphincter responded to 79% of wet swallows with relaxation in the usual manner as indicated by a drop in the resting pressure very shortly after a swallow (Fig. 3).

The upper or pharyngoesophageal sphincter was five to six cm long and the mean resting peak pressure was 15 mm Hg (Fig. 2B). Unlike the lower sphincter the upper sphincter responded everytime to a wet swallow in the usual manner with relaxation indicated by a quick drop in pressure followed just as quickly with a contraction indicated by a

quick rise in pressure.

Peristaltic Waves. The mean amplitude, duration, and velocity of the peristaltic waves are shown in Figure 4. These varied throughout the length of the esophagus originating just below the upper sphincter and dying out before reaching the lower sphincter. The amplitude, duration, and velocity of a peristaltic wave paralleled one another,, i.e. the biggest wave was also the longest and fastest. The biggest waves were about 45 mm Hg with a mean duration of 3.8 seconds and mean velocity of five cm/sec were generated by the middle third of the esophagus. The smallest waves were generated just beyond the distal periphery of the upper sphincter.

Effects of Glycopyrrolate on the Motor Functions of the Esophagus. Sphinc-ter Pressure. The effects of glycopyrrolate on the lower sphincter are shown in Figure 2A and 3. When given by a single subcutaneous injection 1.5 mg of glycopyrrolate reduced the mean resting pressure of the lower sphincter by half. Only 26% of wet swallows initiated relaxation compared to the control of 79% (Figure 3).

When given orally one mg before meals and at bedtime as recommended for five days the last tablet being given an hour before the pressure recordings were made there was no significant effect on the resting pressure. Sixty percent of wet swallows initiated response as compared to the control of 79% (Figure 3).

Whether given by subcutaneous injection or orally as above glycopyrrolate did not have any significant effect on the upper sphincter (Fig. 2B).

Peristaltic Waves. Figure 5 shows the percentage of swallows initiating peristalsis in the four subjects tested. Eighty to 100% of swallows (mean of 94%) initiated peristaltic waves during the control studies. This dropped to 81-95% (mean of 87%) after five days of four tablets a day and 27-60% (mean of 45%) after a subcutaneous injection of 1.5 mg of glycopyrrolate.

The effect of glycopyrrolate on the amplitude of peristaltic waves are shown in Figure 6. Both the tablet and injectable form reduced the amplitude of the peristaltic waves; the effect of the former was less and was confined to the middle third of the esophagus. Following an injection of the drug the waves of the whole esophagus but particularly the distal two-third was affected and the waves that managed to appear were at most half as big as those during the control studies (Fig. 7).

Figure 8 shows the effects of glycopyrrolate on the duration of the peristaltic waves. The duration of peristaltic waves in the distal two-third of the esophagus decreased after both the tablet and injectable glycopyrrolate; the effects of the latter on the peristaltic waves were so profound to allow accurate measurements (Fig. 7).

There was no significant effect of oral glycopyrrolate for five days on the velocities of peristaltic waves as shown in Figure 9.

The velocities could not be determined after the injection because the effects were so great that there were not enough measureable (Fig. 7).

Swallowing Complex. Figure 10 shows the swallowing complexes during control periods and after five days of tablet glycopyrrolate. There was no significant effect although there was a consistent tendency of the swallowing complexes to be longer after oral medication especially on the distal two-third of the eso-

phagus. This was associated with a decrease in the duration of the peristaltic waves.

DISCUSSION

The resting and deglutition esophageal pressures obtained during the control studies in these four subjects are similar to those obtained by others using the same technique.[5,6] The pressures were reproducible in the same subject. Not only the pressures but also the profile are similar to those obtained elsewhere.[3] Locally only one published data using the same technique is available;[4] the present data are similar to these.

It has been shown that the motor functions of the espohagus are profoundly affected by atropine.[1-3] The resting pressure at the lower sphincter was reduced and this was accompanied by acid reflux into the esophagus. The amplitude of the peristaltic waves in the distal two-third of the esophagus were reduced and the percentage of response in terms of initiation of waves to swallows was markedly reduced. These effects are to be expected because the motor nerves of the esophagus, the vagi, are cholinergic.

Because of the foregoing any potent anticholinergic agent would potentially have the same effects. If these effects are produced two things can be expected to follow, namely, varying degrees of dysphagia and esophageal reflux. The dysphagia may not be troublesome but the reduction of pressure at the high pressure zone would incapacitate its physiologic sphincter function and promote esophageal reflux and subsequently a troublesome esophagitis. This effect is very undesirable in a patient who, to begin with, has esophageal reflux for one reason or another.

A number of potent anticholinergic agents are commonly used in the treatment of peptic ulcer. One of these is glycopyrrolate. The intramuscular injection of 1.5 mg of glycopyrrolate reduced the volume of acid and pepsin output by about 90% in patients with peptic ulcer.[7] It has also been shown capable of suppressing the antral, small intestinal, and colonic motor activities.[8-10] The present study showed that glycopyrrolate, like atropine, can markedly depress the motor functions of the esophagus particularly when given in sufficient dose and parenterally; the high pressure at the physiologic sphincter was reduced by 50% and the number of peristaltic waves initiated by swallows by as much as 57%. Moreover, the waves that were initiated were likewise markedly reduced in amplitude. The subjects had to wait for six to eight hours before attempting to eat because the food would not go down. However, when given by mouth in the recommended dose for five days the effects were significantly less; the high pressure at the physiologic sphincter was not affected and the reduction in the number of waves initiated was not significant and did not produce dysphagia in the subjects. Nonetheless, they complained of dryness of the throat and slight blurring of vision.

The subjects tested in this study were healthy and young. Whether the same effects could be produced in older or, more importantly, those with esophageal disease like hiatal hernia or esophagitis due to esophageal reflux was not determined. Glycopyrrolate or any anticholinergic agent should therefore be used cautiously in these patients.

SUMMARY

The resting and deglutition intraluminal pressures in the lower and upper

sphincters and body of the esophagus were recorded in four healthy young Pilipino volunteers, two men and two women. The amplitude, duration, and velocity of the peristaltic waves and the duration of the swallowing complex throughout the body of the esophagus were determined. The average resting peak pressure was 7 mm Hg at the lower and 15 mm Hg at the upper esophageal sphincter. In these four subjects 79% of wet swallows initiated a relaxation of the lower sphincter; the upper sphincter responded to every swallow. The swallowing complex increased more or less linearly from 4 seconds just below the upper sphincter to 12 seconds just above the lower sphincter. Ninety four percent of wet swallows initiated peristaltic waves. The amplitude, duration, and velocity of a peristaltic wave more or less paralleled one another, i.e. the biggest wave was also the longest and fastest. The peristaltic waves decreased toward the distal portion of the proximal 3rd then increased to its peak at the distal portion of the middle and the proximal portion of the distal third of the esophagus and decreased again and dying out before reaching the lower sphincter. The biggest waves were about 45 mm Hg, mean duration of 3.8 seconds, and mean velocity of 5 cm/sec.

The same subjects were studied an hour after an injection of 1.5 mg and again after taking one 1 mg tablet four times a day of glycopyrrolate for five days. The injection of 1.5 mg of glycopyrrolate had the following effects:

1. The resting pressure at the lower esophageal sphincter decreased 50% and only 26% of wet swallows initiated a relaxation. The upper esophageal sphincter was not effected.

2. Twenty seven to 60% of wet swallows initiated peristaltic waves. Of the peristaltic waves that managed to appear the amplitude were profoundly reduced especially in the distal two-third of the esophagus. The effects on the duration and velocity of the waves could not be determined.

3. The effect on the swallowing complex could not be determined because the peristaltic waves that were initiated could not be measured accurately.

With four mg of glycopyrrolate by mouth per day for five days the following results were obtained in the same subjects:

1. The resting pressures of both the lower and upper sphincters were not affected. However, only 60% of the wet swallows produced a relaxation of the lower sphincter compared to 79% during the control test; the upper sphincter responded to all the swallows.

2. Eighty seven percent of the wet swallows initiated peristaltic waves (compared to 94% during control tests). The amplitude of the peristaltic waves particularly in the middle third of the esophagus were reduced but the reduction was not as profound as those produced by the injection of 1.5 mg. The duration of the waves particularly the proximal portion of the distal third and the distal portion of the middle third of the esophagus was likewise reduced. There was no effect on the velocity of the waves.

3. The swallowing complex increased slightly particularly in the distal two-third of the esophagus.

Potent anticholinergic drugs like glycopyrrolate can potentially compromise the sphincter function of the lower esophageal sphincter by decreasing the

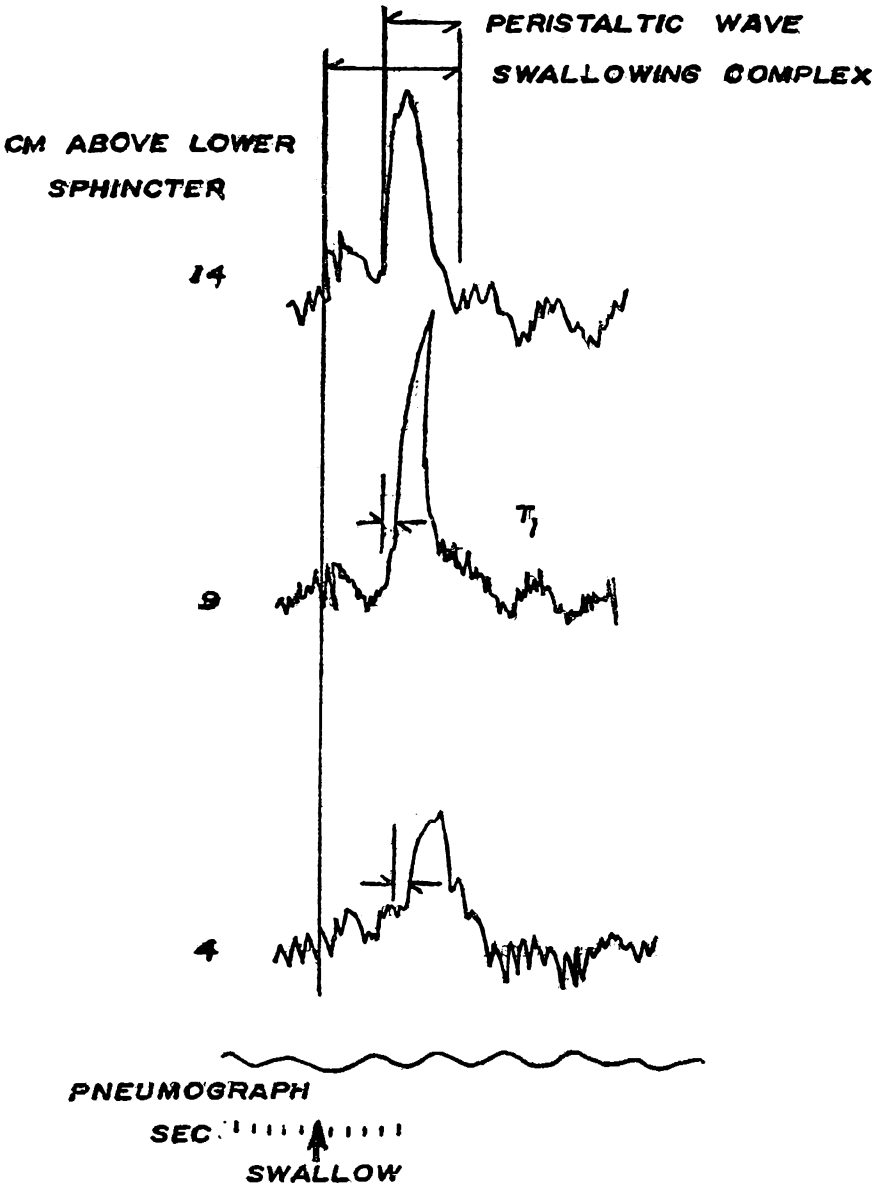

Figure 1. This strip of tracing shows the normal response of the esophagus four to 14 cm above the lower sphincter to a swallow. The method in determining the amplitude, duration, and velocity of peristaltic waves and the swallowing complex is indicated.

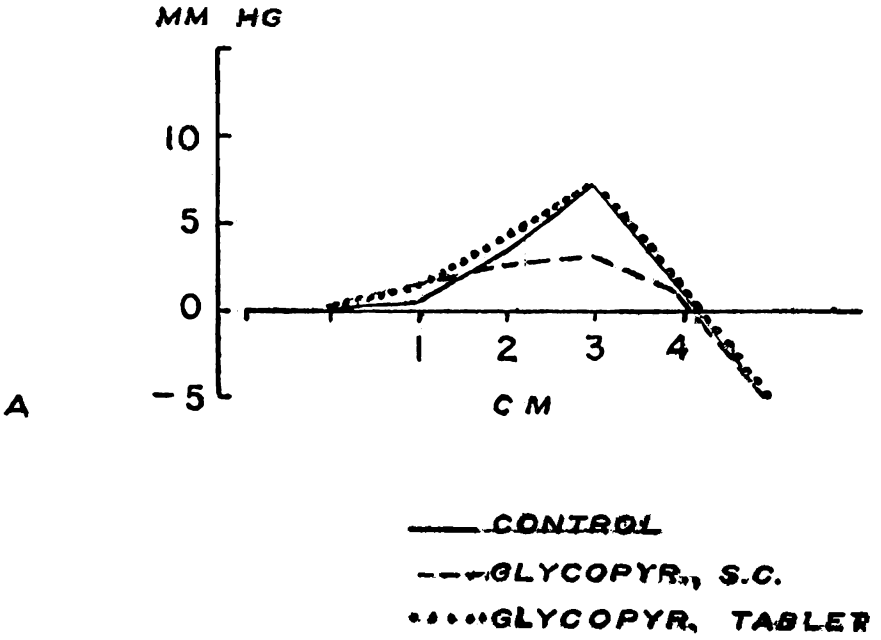

Figure 2A. Mean pressures at the lower esophageal sphincter of four normal subjects before and after glycopyrrolate 1.5 mg by subcutaneous injection and one mg tablet q.i.d. for five days.

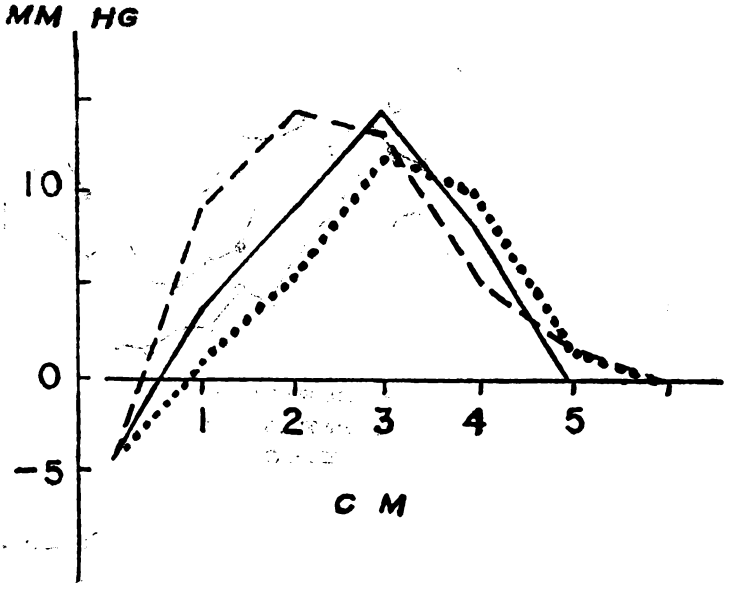

Figure 2B. Mean pressures at the upper esophageal sphincter of four normal subjects before and after glycopyrrolate 1.5 mg by subcutaneous injection and one mg tablet q.i.d. for five days.

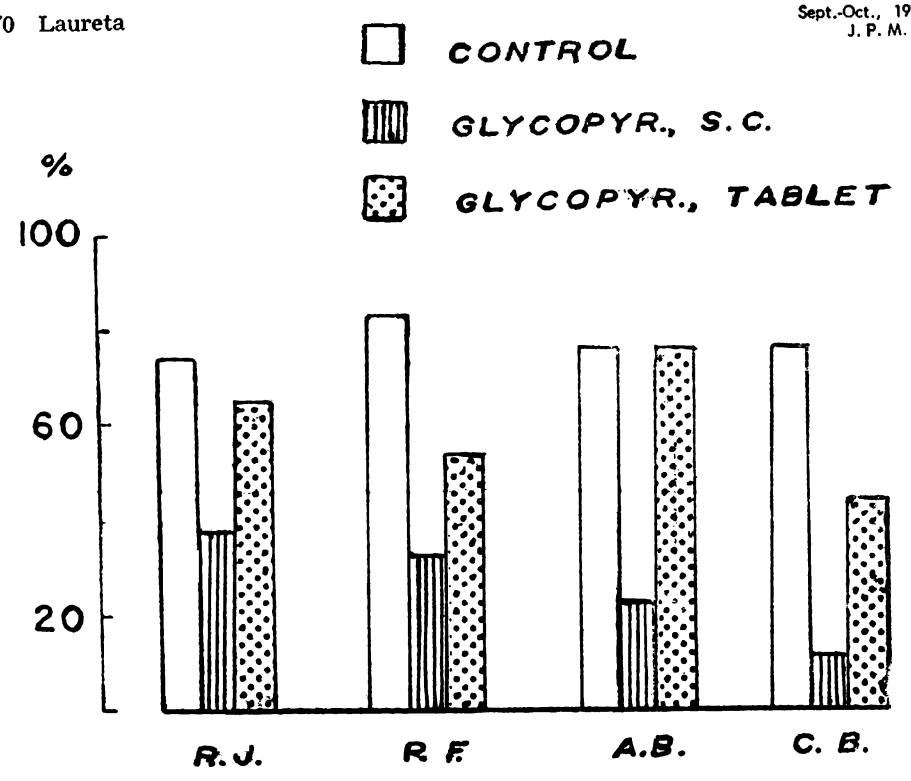

Figure 3. Percentage of swallows initiating fall in pressure at the lower esophageal sphincter in four normal subjects before and after glycopyrrolate 1.5 mg by subcutaneous injection and one mg tablet q.i.d. for five days.

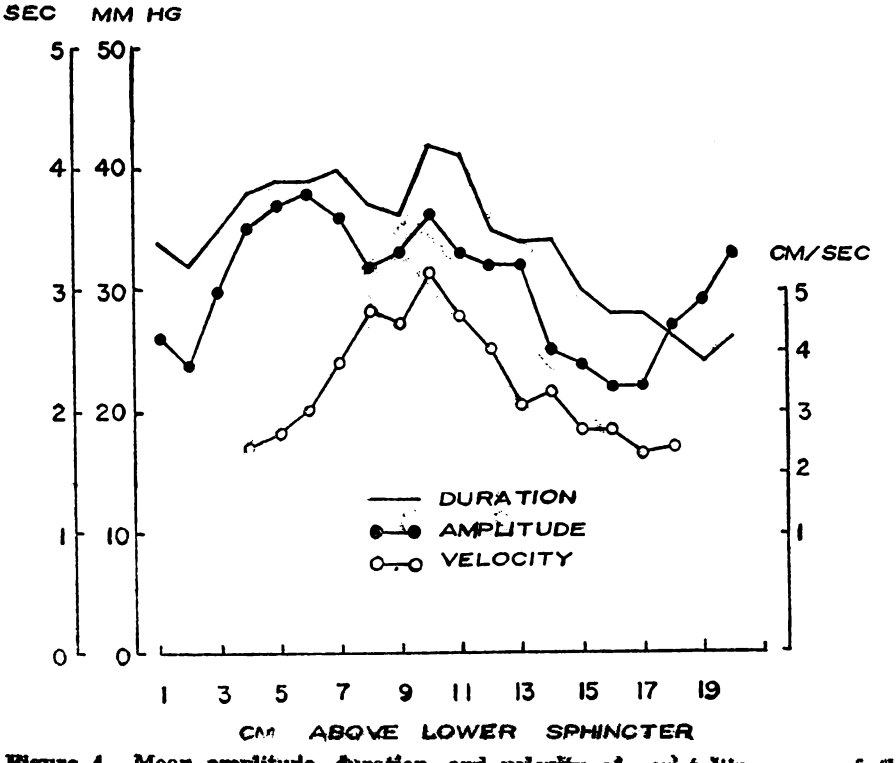

Figure 4. Mean amplitude, duration, and velocity of peristaltic waves of the esophagus of four normal subjects.

Table 1. LOWER ESOPHAGEAL SPHINCTERIC PRESSURES IN NORMAL SUBJECTS BEFORE AND AFTER AN INJECTION OF ONE MG OF ATROPINE.

Esophagel Sphincteric Pressures and Pulse Rates

	Before Atropine		After Atropine	
Subject	Pressure* mm H	Pulse Rate per min	Pressure* mm Hg	Pulse Rate pre min
A	14.0	77	1.5	101
B	8.0	62	1 5	118
C	11.0	68	3.0	102
D	4.0	63	1.0	109
E	9.5	68	2.0	111

*Mean of three pressure recordings.

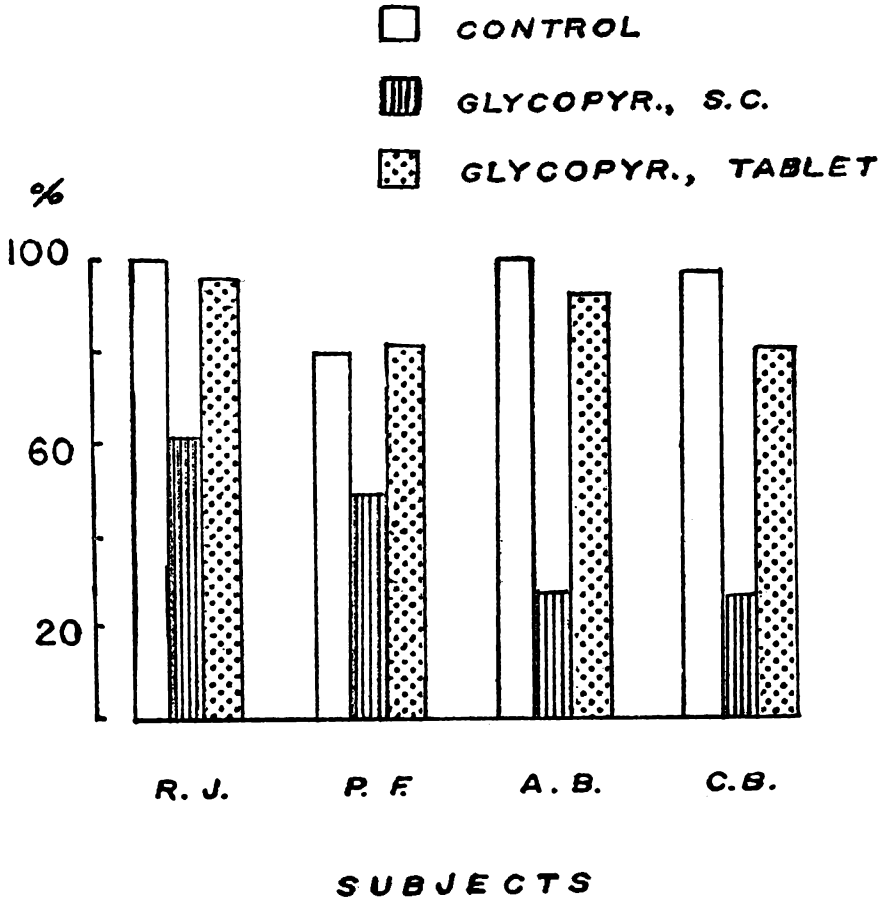

Figure 5. Percentage of swallows initiating esophageal peristaltic waves in four normal subjects before and after glycopyrrolate 1.5 mg by subcutaneous injection and one mg tablet q.i.d. for five days.

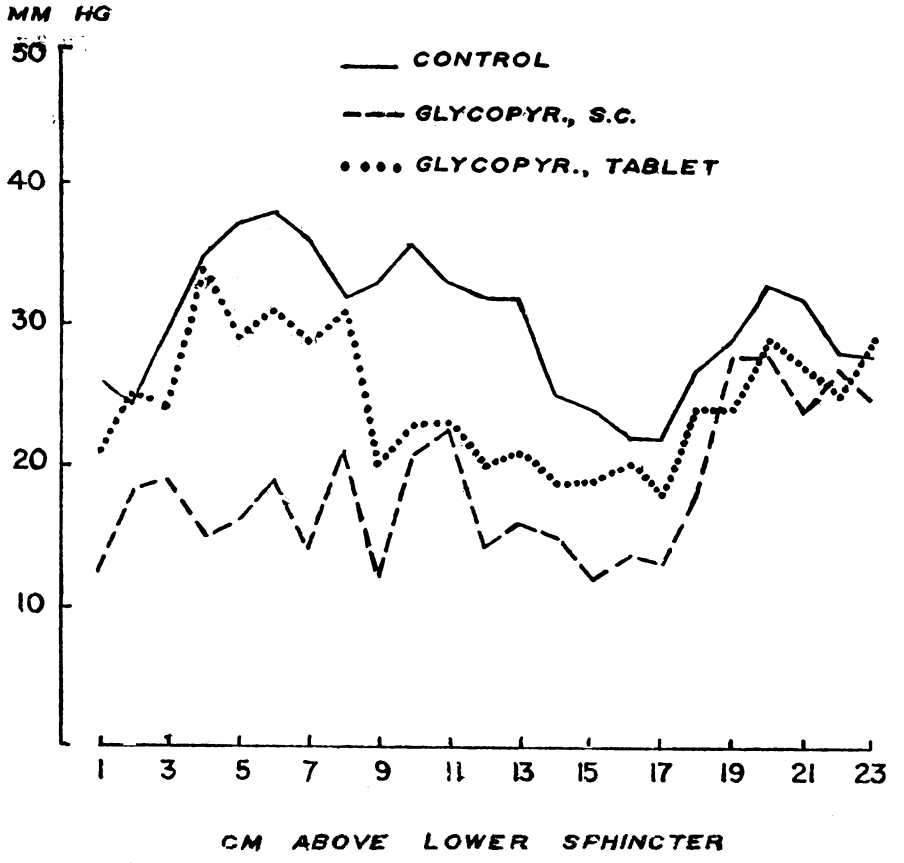

Figure 6. Mean amplitude of esophageal peristaltic waves of four normal subjects before and after glycopyrrolate 1.5 mg by subcutaneous injection and one mg tablet q.i.d. for five days.

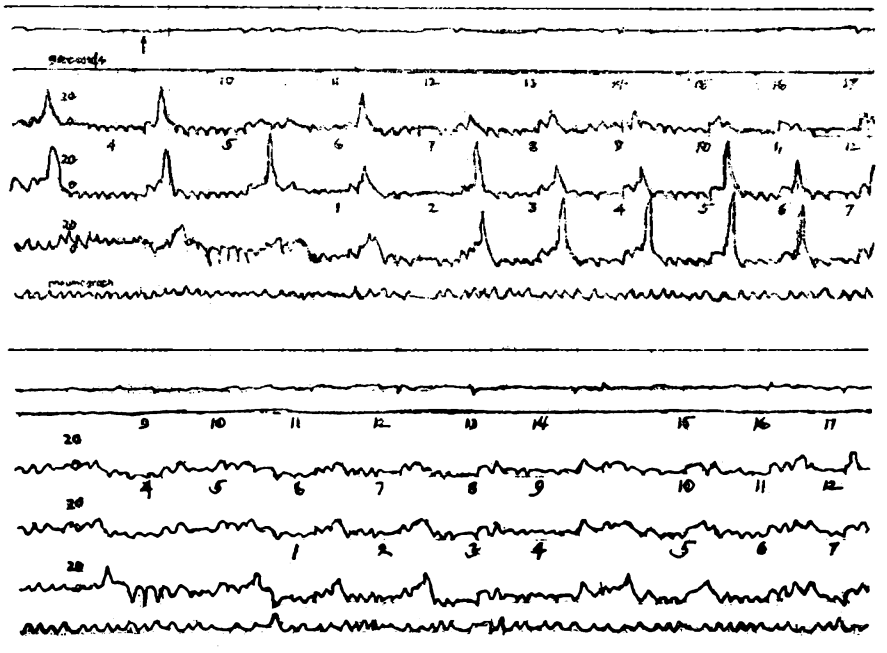

Figure 7. These tracings of one of the subjects show the normal responses of the distal esophagus to wet swallows (upper tracing) and one hour after a subcutaneous injection of 1.5 mg of glycopyrrolate (lower tracing).

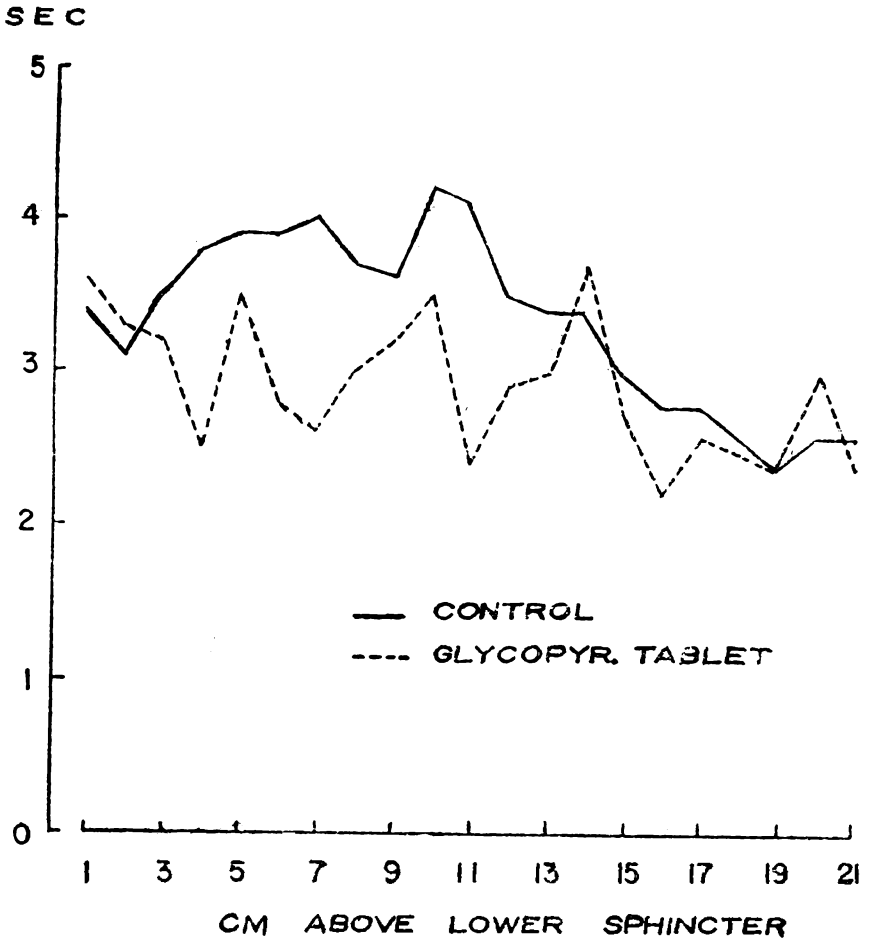

Figure 8. Mean duration of peristaltic waves of four normal subjects before and after glycopyrrolate one mg tablet q.i.d. for five days.

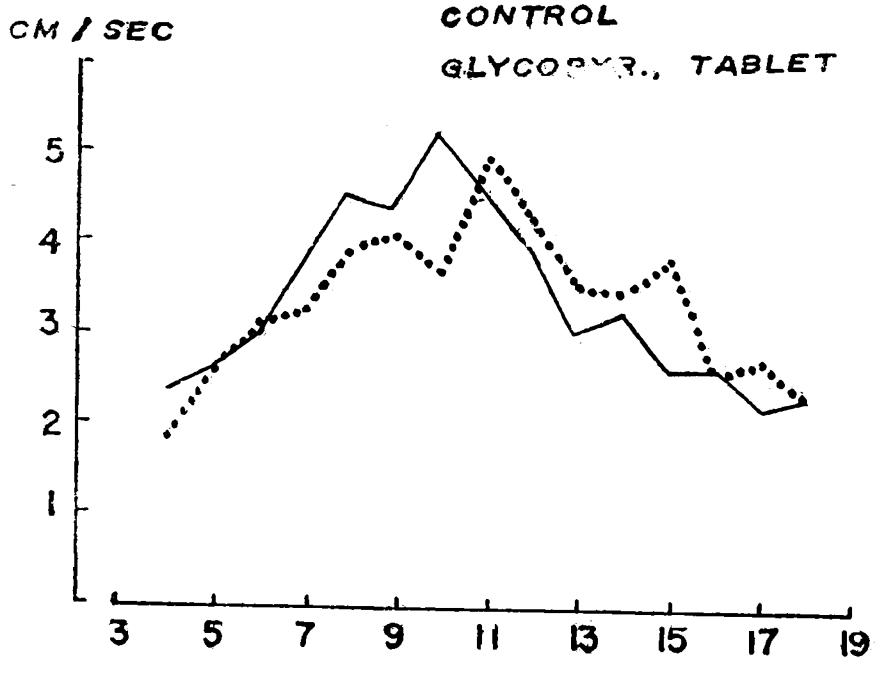

Figure 9. Mean velocity of esophageal peristaltic waves of four normal subjects before and after glycopyrrolate one mg tablet q.i.d. for five days.

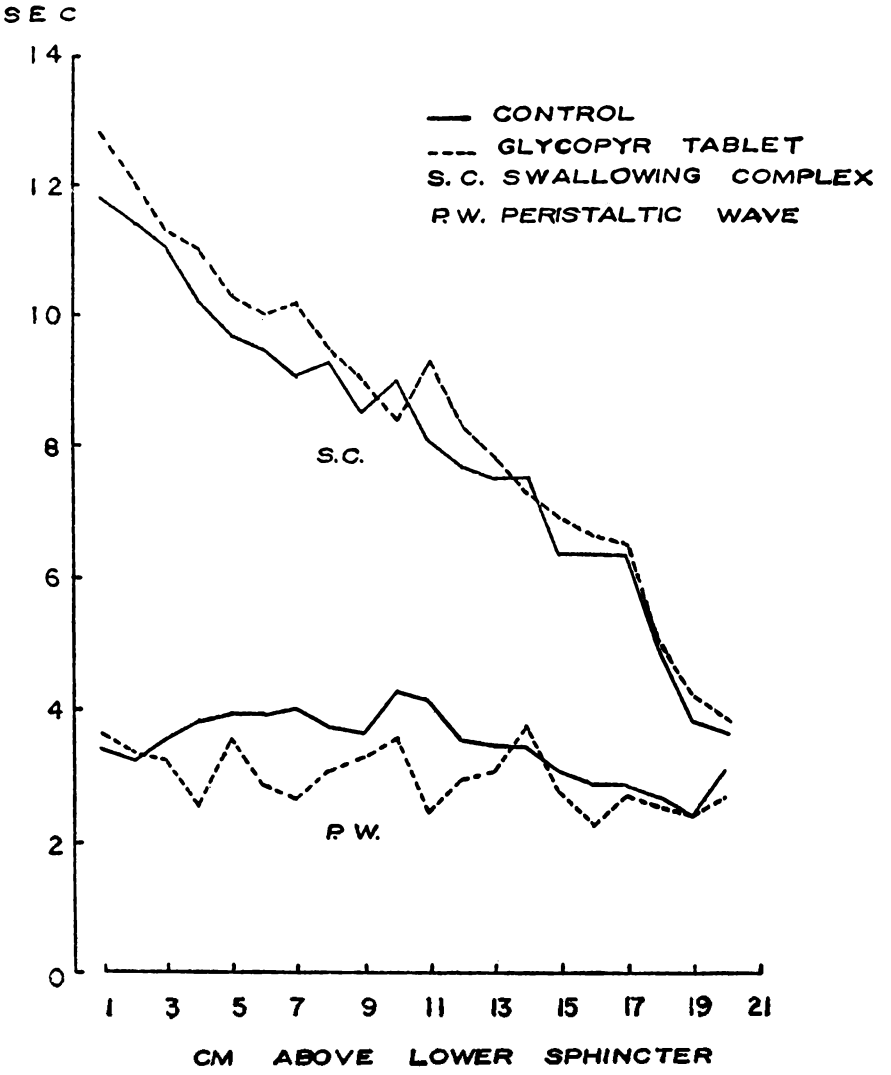

Figure 10. Mean duration of swallowing complexes (S.C.) and esophageal peristaltic waves (P.W.) of four normal subjects before and after glycopyrrolate one mg tablet q.i.d. for five days.

pressure at the HPZ. Potent anticholinergic drugs should be used with particular caution in patients with esophageal reflux or any problem affecting the distal esophagus.

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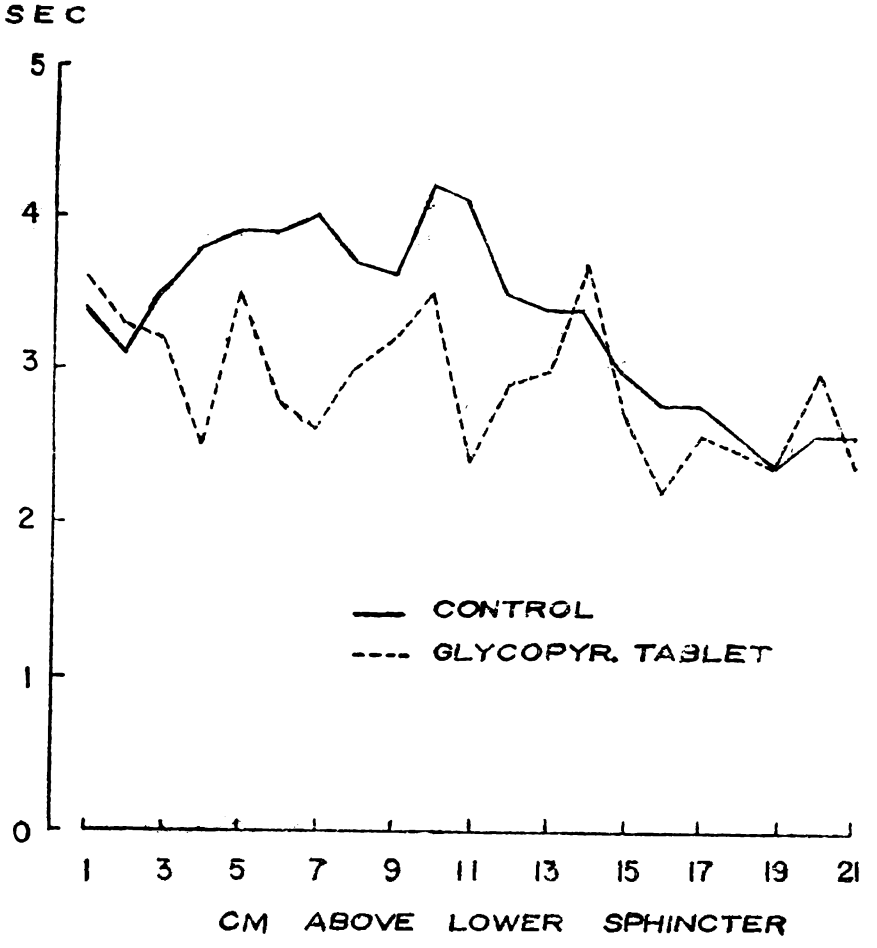

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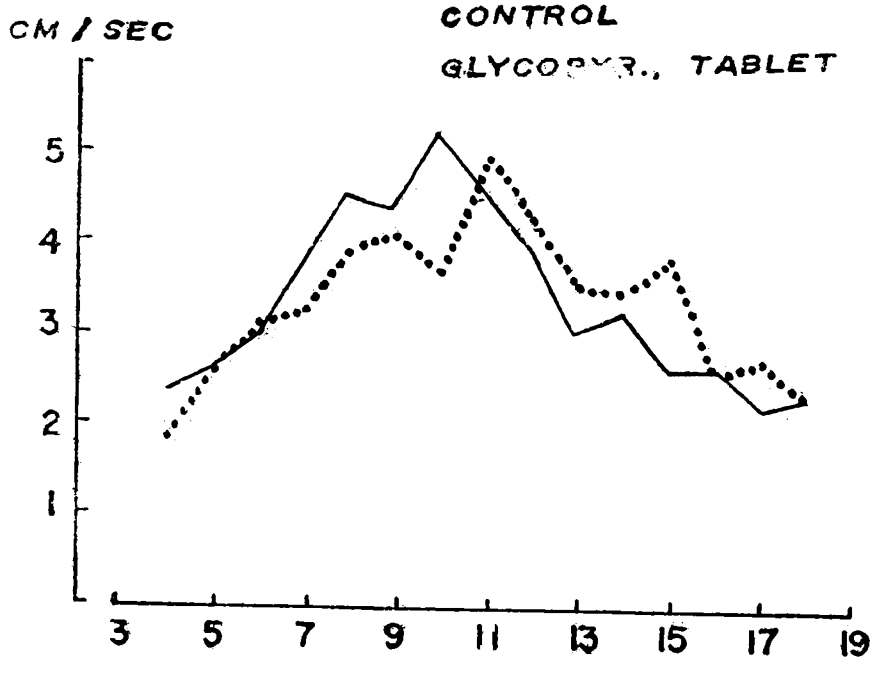

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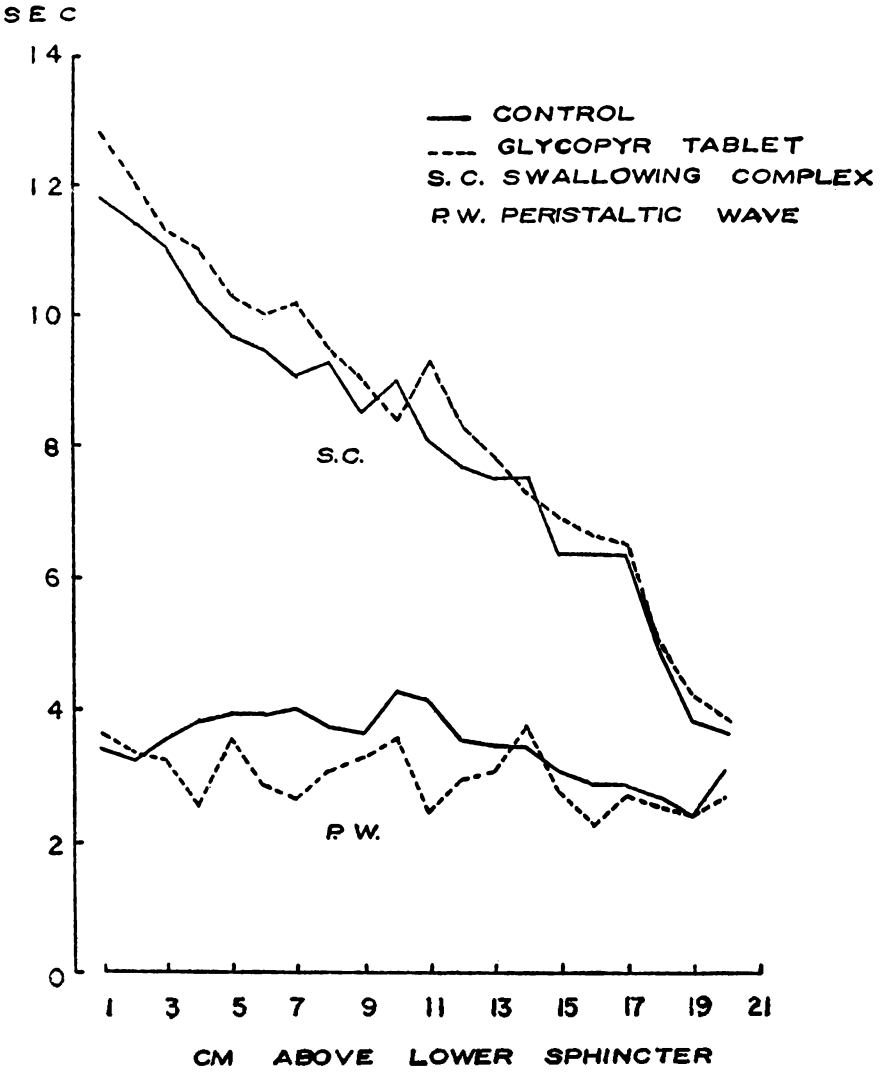

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Trace Elements in Relation to Cardiovascular Disease**●

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CARDIOVASCULAR disease may be considered as a public health problem in the Philippines. Reports of the Disease Intelligence Center, Department of Health show that diseases of the heart has a five year average mortality rate of 35.2 per 100,000 population and constitute 5.1% of the total deaths in the Philippines. In the search for the etiologic factors of cardiovascular disease one has to consider the role of trace elements. In our previous reports[1,2] we reported an increase in the mean values of manganese and copper and a decrease in the mean levels of zinc in the serum of patients with hypertension, old myocardial infarct and diabetes mellitus. Kanabrocki[3] and Wacker[4] also suggested the possible relationship of copper, zinc and manganese to cardiovascular disease. In the present report we shall present findings on the concentration of copper, zinc and molybdenum in the heart, liver and kidneys of 20 normal male healthy subjects that met accidental death and from 25 male patients who died of myocardial infarction.

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MATERIALS AND METHODS

Samples that were analyzed for their trace elemental contents were taken from the anterior wall of the left ventricle, the superior anterior surface of the right lobe of the liver, and the cortex of the kidney. During the collection of the samples, extreme care was taken to prevent metallic contamination with the use of glass or silica knives. Preparation of irradiation standards for copper, zinc and molybdenum, as well as the biological reference materials to check the accuracy of our analytical procedures has been previously described[2]. Preparation of the tissue samples for irradiation and the determination of its trace metals contents by neutron activation technique has already been reported[5].

RESULTS AND DISCUSSION

Figures I, II and III will show the gamma ray spectrum of zinc, copper and molybdenum in the heart, liver and kidney. The results in Tables I to III indicate the values of copper, zinc and

molybdenum in the heart, liver and kidney of normal male subjects that met accidental death. The results in Table IV show that the mean values of zinc, copper and molybdenum in the heart, liver and kidneys of Pilipinos are agreeable to the mean values reported in literature. The results in Tables I to III also indicate that the normal values of copper, zinc and molybdenum in the heart, liver and kidneys of the normal subjects do not vary with their age and occupation. Figures IV to XII will show the scattergram of zinc, copper and molybdenum levels obtained from heart, liver and kidney tissues of normal healthy subjects and patients with myocardial infarction. The results in Table V indicate that the mean concentration of zinc in the heart and liver of patients who died of myocardial infarction, 28.85 $\pm$ 2.07 ug/g and 37.57 $\pm$ 8.38 ug/g respectively were lower than the normal mean values of 30.35 $\pm$ 2.33 ug/g and 47.30 $\pm$ 7.72 ug/g. Our data on the decrease of zinc concentration in the infarcted heart tissue is in good agreement with the report of Wester[6], who reported a significant decrease of zinc level in the injured heart tissues. This decrease might perhaps be related to the disappearance of lactic dehydrogenase, a zinc enzyme from the infarcted heart tissue with an increase in the level of its activity being observed in the serum of patients with acute myocardial infarction[7]. Zinc has been reported to be beneficial to cardiovascular health. Schroeder[8] found that the administration of zinc will reverse the hypertensive effect of cadmium in rats. The mean level of copper in the liver of patients with myocardial infarction of 3.95 $\pm$ 0.82 ug/g was lower than the normal value of 5.01 $\pm$ 1.96 ug/g. Hartman[9] has reported the atherogenic effect of copper. Reinhold[10] found that a deficiency in copper would also result in the defective synthesis of collagen and elastin in the aorta and blood vessels. The mean concentration of molybdenum, 0.83 $\pm$ 0.13 ug/g, 0.76 $\pm$ 0.36 ug/g and 0.74 $\pm$ 0.31 ug/g in the heart, liver and kidney respectively of patients with myocardial infarction were higher than the normal values of 0.32 $\pm$ 0.13 ug/g. 0.52 $\pm$ 0.16 ug/g and 0.41 $\pm$ 0.20 ug/g. Our data on the molybdenum content of the infarcted heart tissue does not agree with the results obtained by Wester[7] who reported a decrease in the concentration of molybdenum in the injured heart tissue, and relate the concentration of this trace element to the degree of fibrosis present in the infarcted heart tissue.

The data that we have obtained our 5 years investigation indicate changes in the concentration of copper, zinc and molybdenum in the heart, liver and kidney of cardiac subjects occuring in association with myocardial infarction. We do hope that the tissue mineral concentration changes that we detected will add significant data to the growing evidence that certain trace elements are associated with degenerative cardiovascular diseases, such as hypertension, atherosclerosis and their sequela. The results that we obtained would not only help in establishing the elemental composition of a "Standard Man" but this study might give us a clue on the biochemical association of the certain trace elements with cardiovascular disease, which would offer information of importance in the control of this public health problem.

SUMMARY

Heart, liver and kidney specimens from 45 adult male subjects were analyzed for their zinc, copper and molyb-

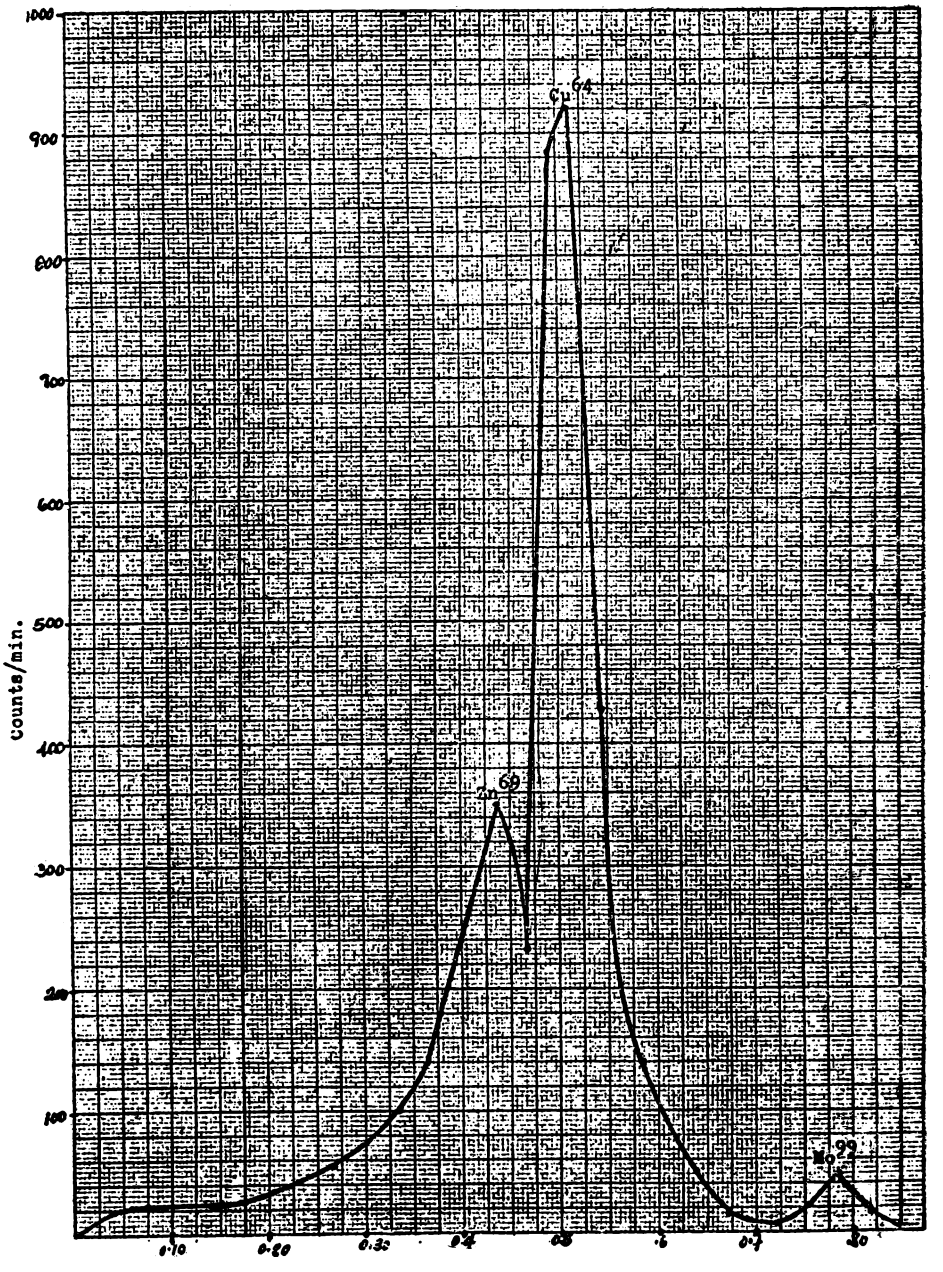

Fig. 1 — Gamma-ray spectrum of Zinc, Copper and Molybdenum in Heart.

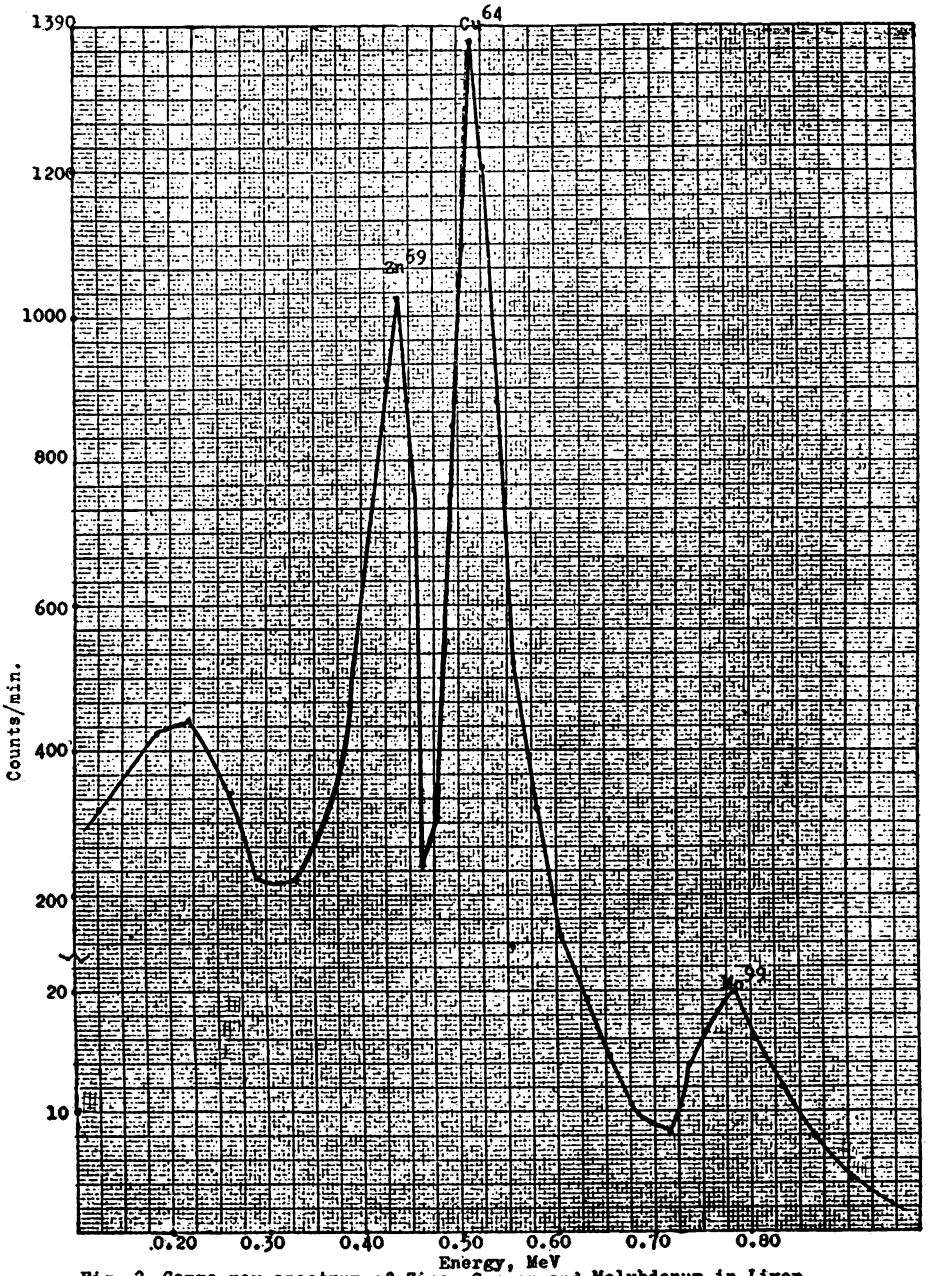

Fig. 2- Gamma-ray spectrum of Zinc, Copper and Molybdenum in Liver

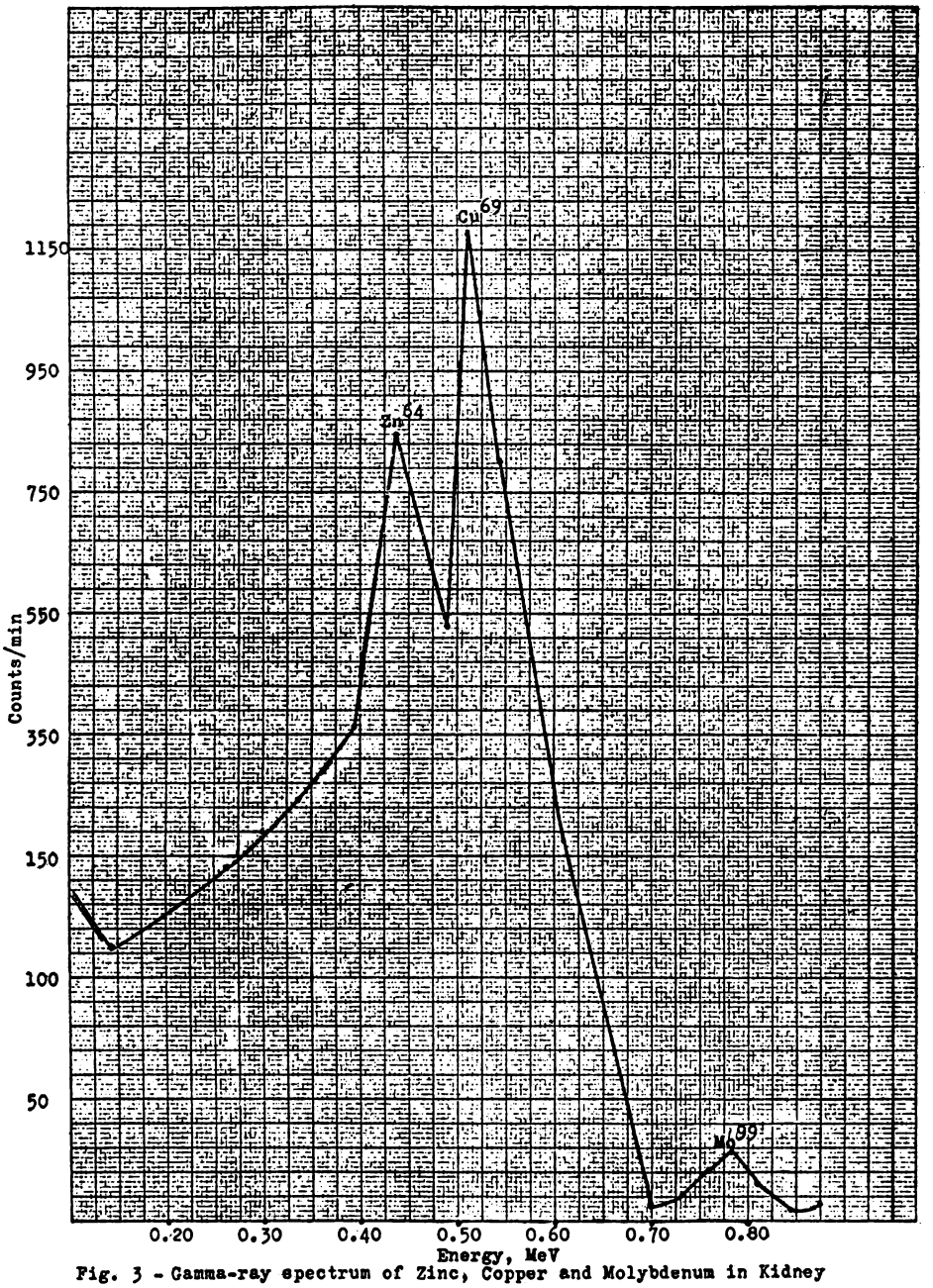

Fig. 3 - Gamma-ray spectrum of Zinc, Copper and Molybdenum in Kidney

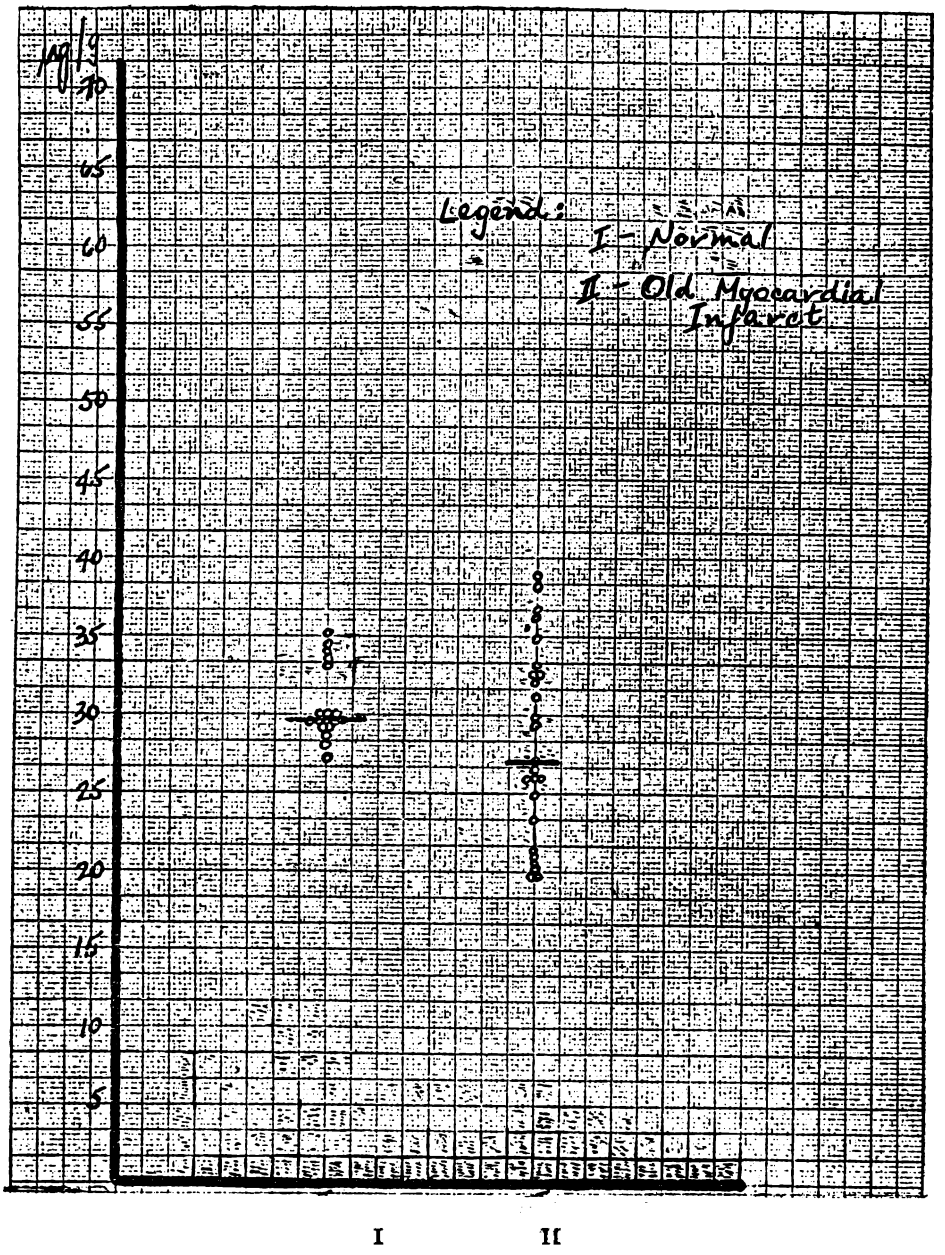

Fig. 4 — Scattergram of zinc levels obtained from heart tissues of normal subjects and patients with old myocardial infarct.

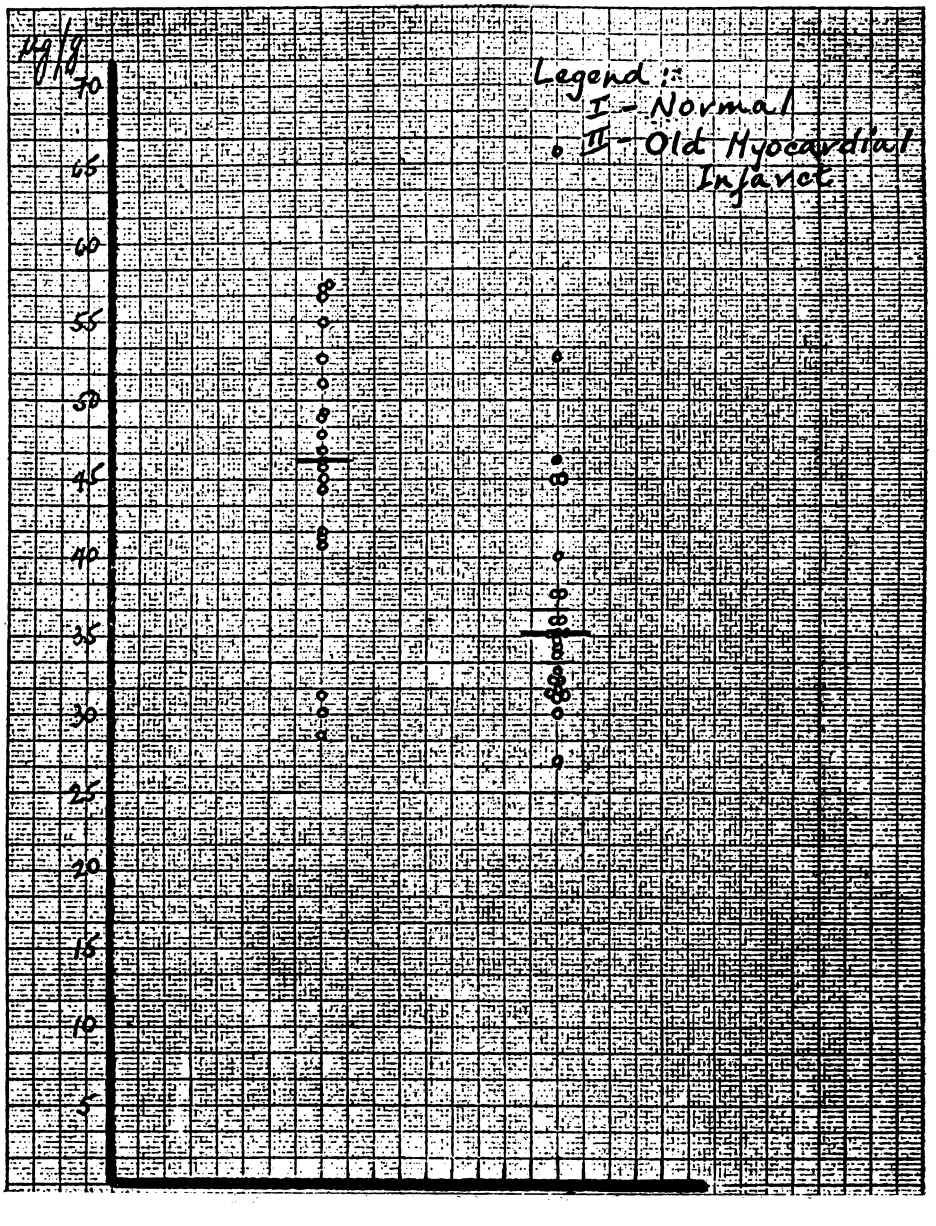

Fig. 5 — Scattergram of zinc levels obtained from liver tissues of normal subjects and patients with old myocardial infarct.

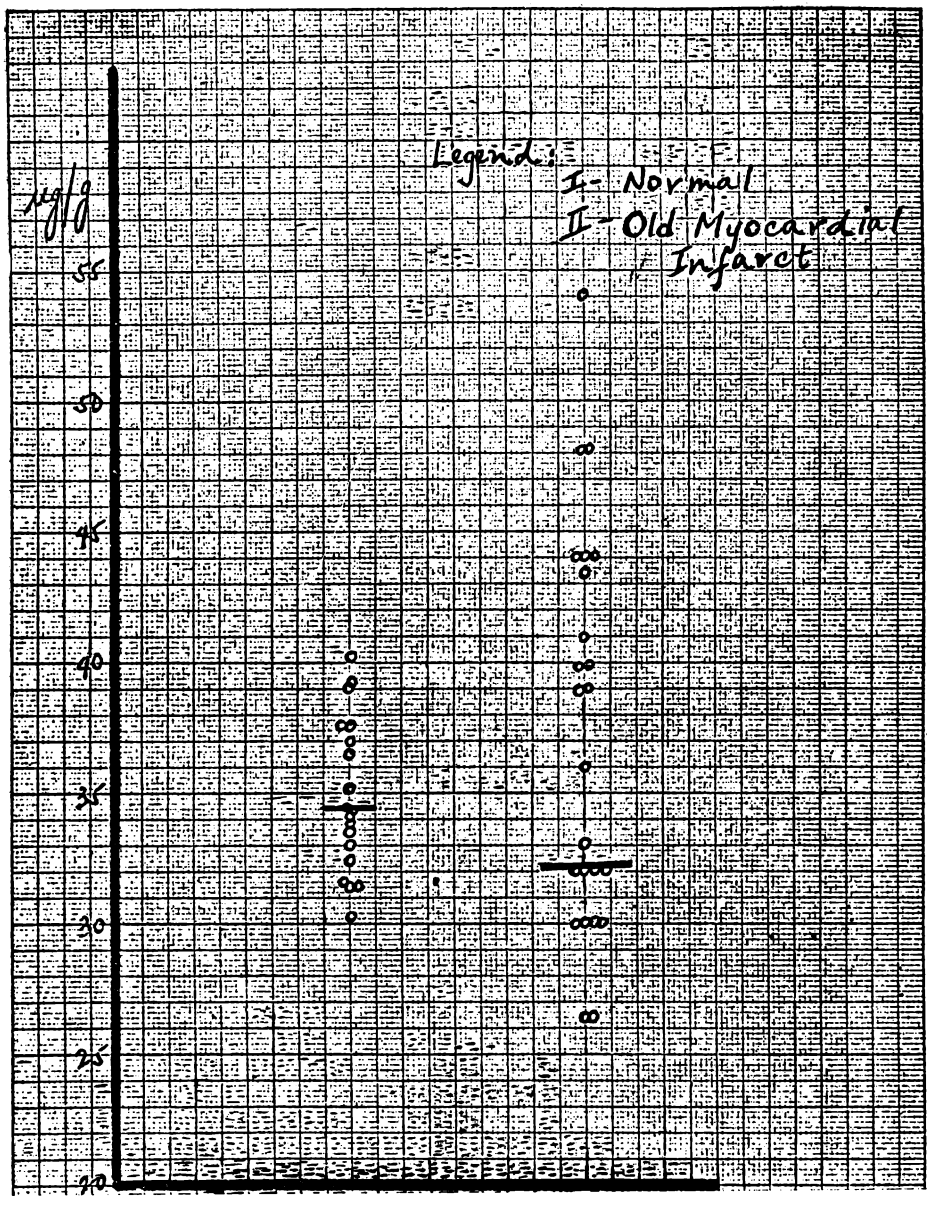

Fig. 6 — Scattergram of zinc levels obtained from kidney tissues of normal subjects and patients with old myocardial infarct.

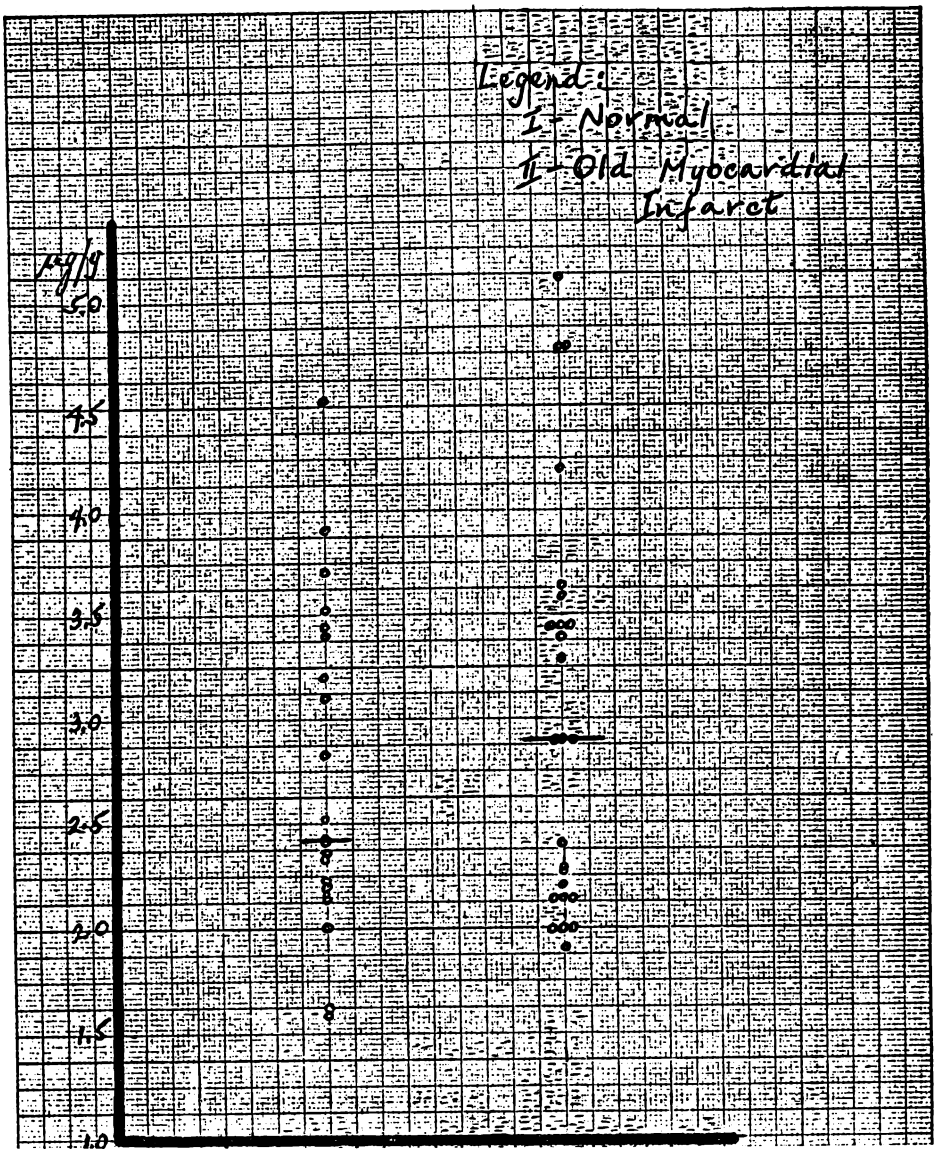

Fig. 7 — Scattergram of copper levels obtained from heart tissues of normal subjects and patients with old myocardial infarct.

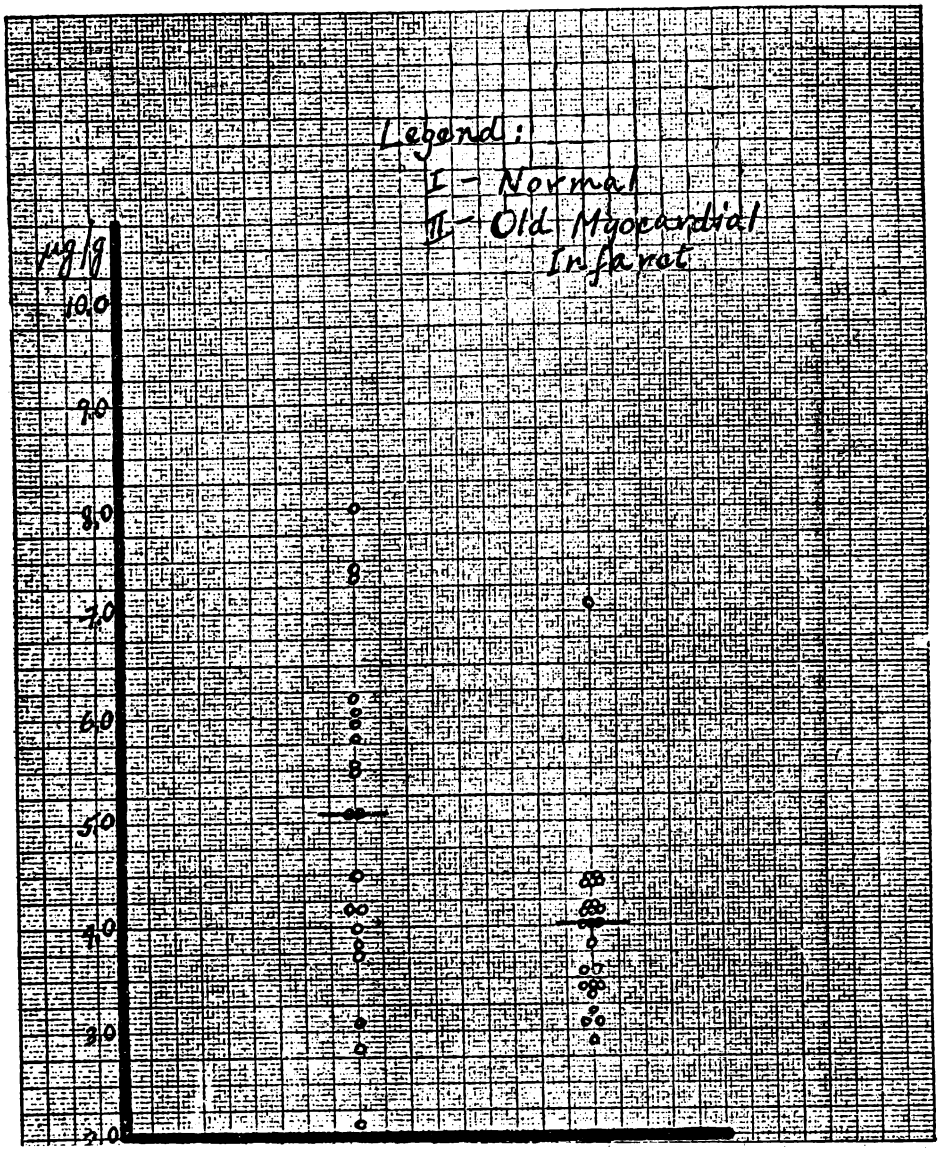

Fig. 8 — Scattergram of copper levels obtained from liver tissues of normal subjects and patients with old myocardial infarct.

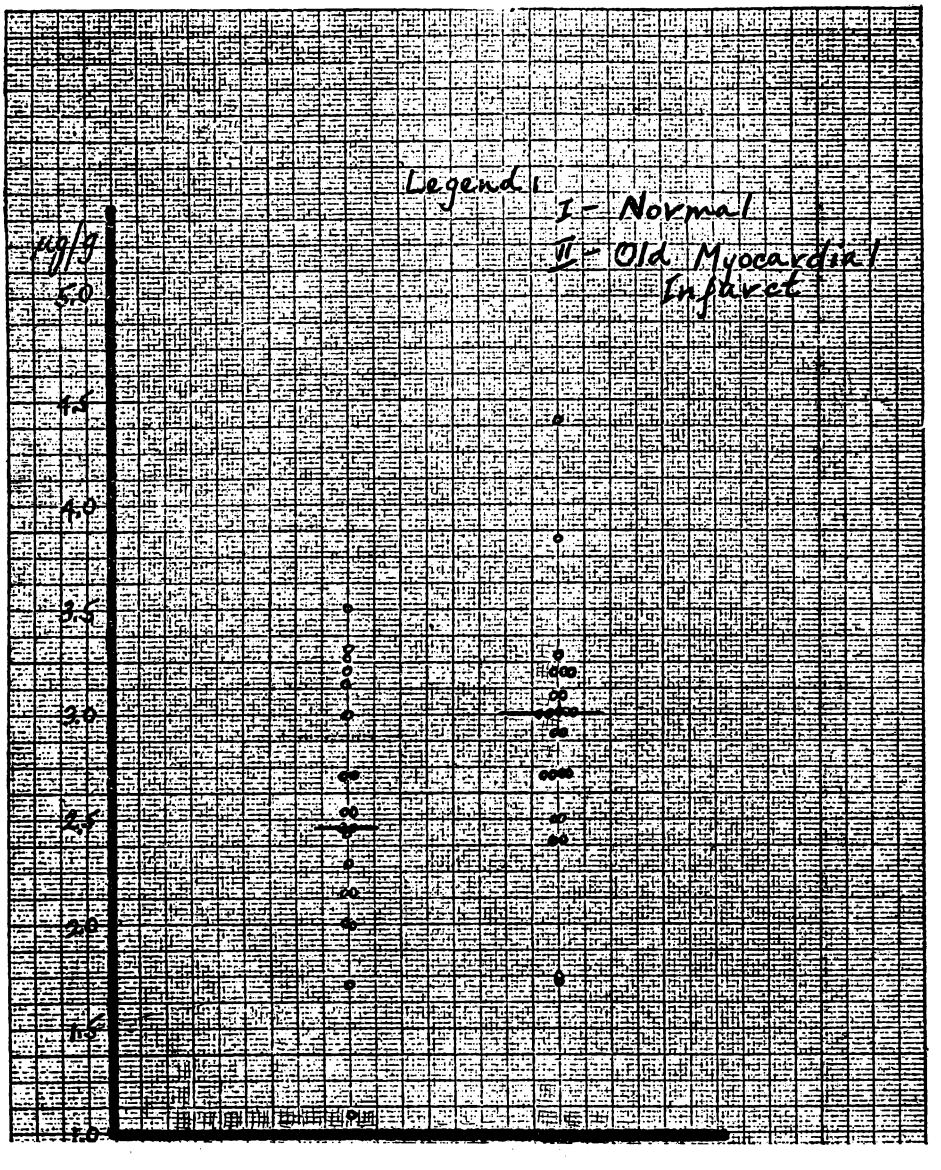

Fig. 9 — Scattergram of copper levels obtained from kidney tissues of normal subjects and patients with old myocardial infarct.

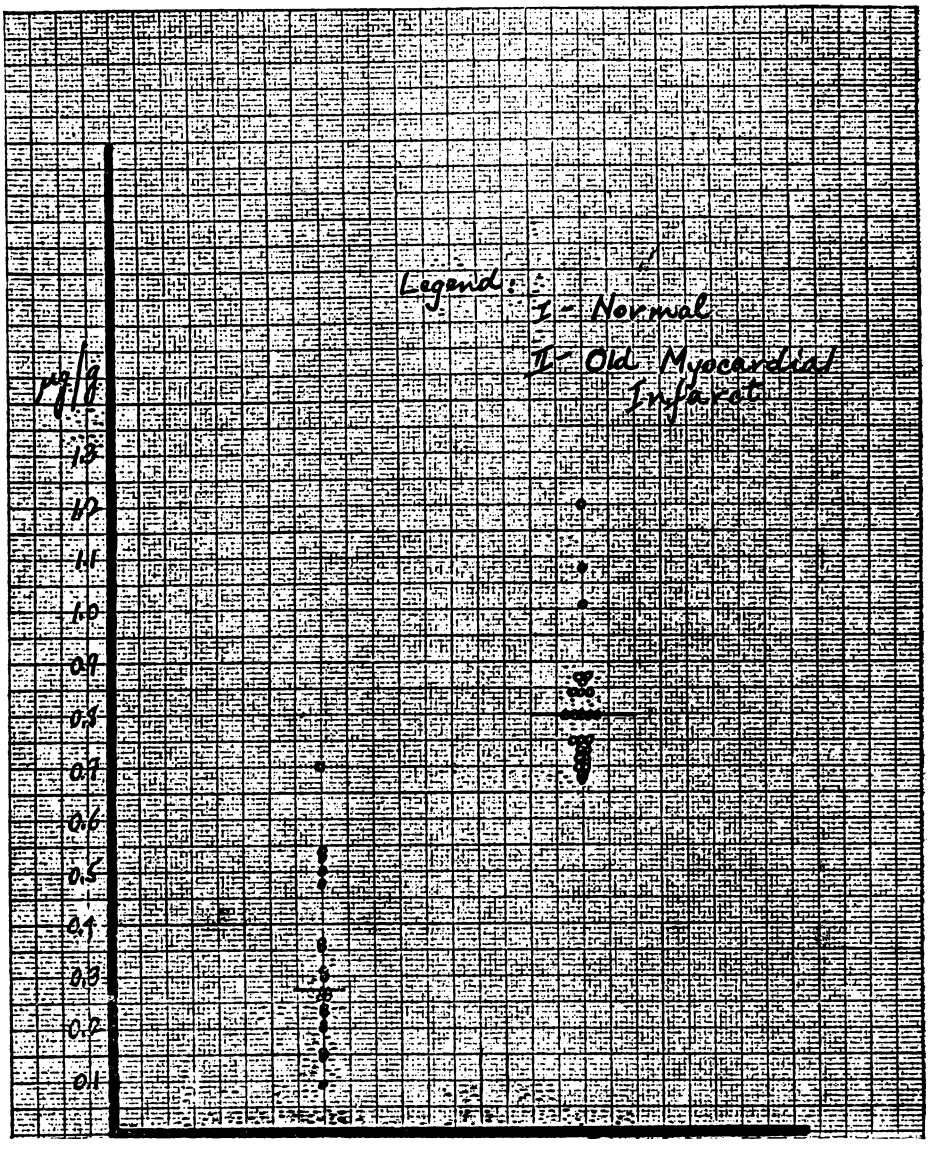

Fig. 10 — Scattergram of molybdenum levels obtained from heart tissues of normal subjects and patients with old myocardial infarct.

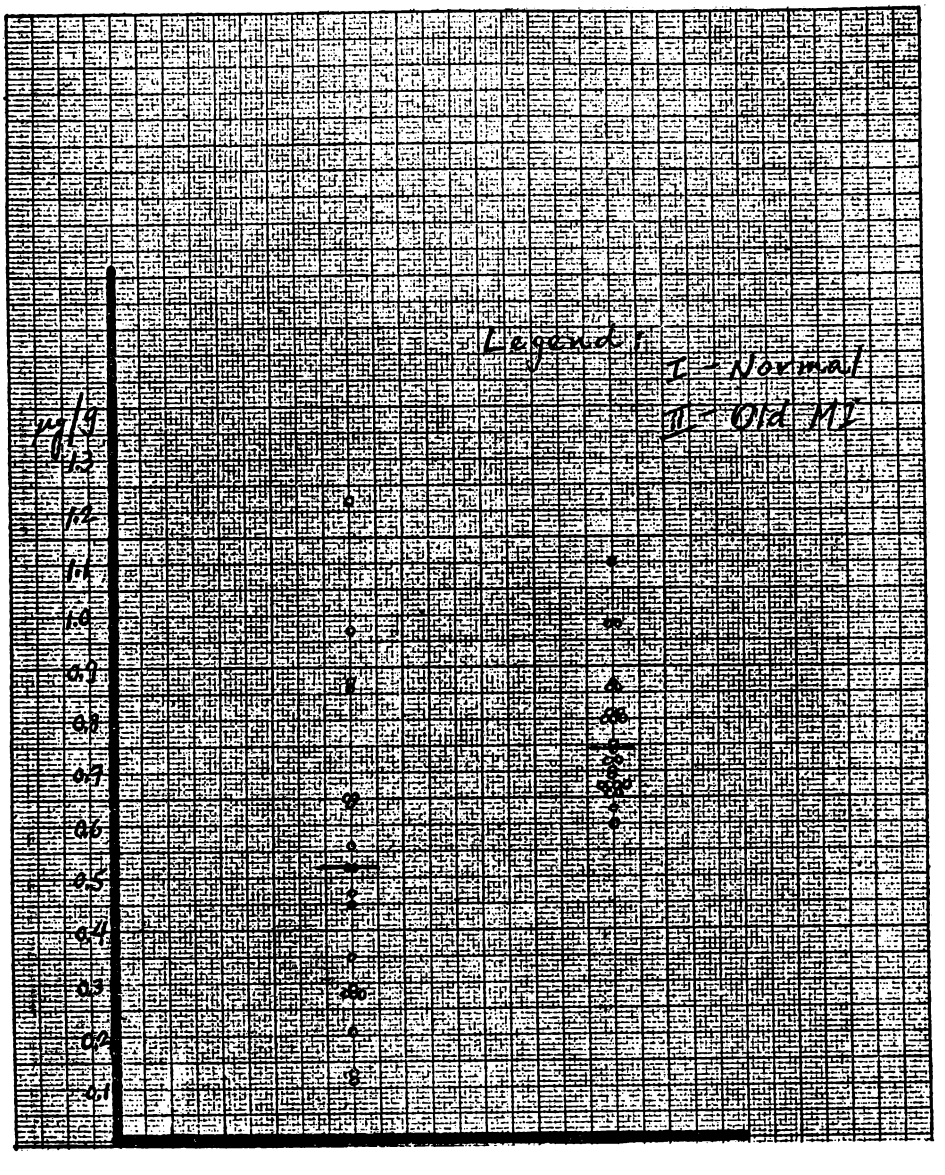

Fig. 11 — Scattergram of molybdenum levels obtained from liver tissues of normal subjects and patients with old myocardial infarct.

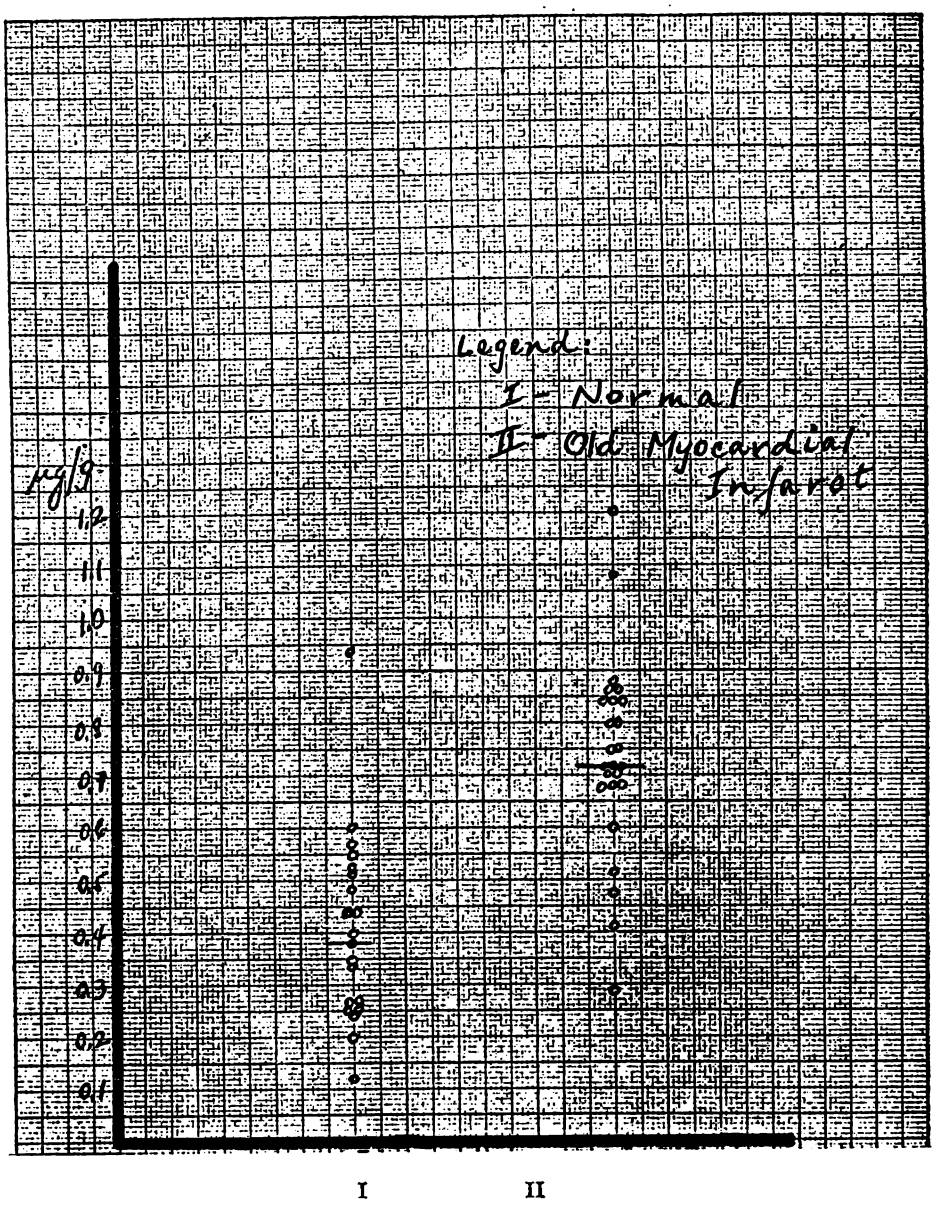

Fig. 12 — Scattergram of molybdenum levels obtained from kidney tissues of normal subjects and patients with old myocardial infarct.

Table I. VALUES OF ZINC IN HEART, LIVER AND KIDNEY OF 20 NORMAL MALE SUBJECTS: ug/g WET TISSUE

Name	Age	Occupation	Cause of Death	Heart	Liver	Kidney
O. D.	40	Soldier	Vehicular accident	30.50	44.50	39.30
R. J.	40	Vendor	Stabbing	29.50	46.00	33.55
Unknown	40	N. A.	Gunshot wound	28.55	40.67	31.83
Unknown	40	N. A.	Stabbing	32.70	49.00	33.20
F. S.	43	Butcher	Stabbing	30.07	45.40	33.89
R. S.	45	Businessman	Stabbing	29.04	42.30	37.10
L. S.	45	Patrolman	Stabbing	30.50	57.45	31.64
F. C.	45	Scavenger	Vehicular accident	26.86	47.80	36.78
H. C.	45	Laborer	Vehicular accident	29.64	28.13	35.48
J. B.	45	Employee	Stabbing	29.64	54.41	35.03
A. P.	45	Driver	Vehicular accident	33.60	41.60	32.53
M. L.	46	Employee	Stabbing	35.29	30.66	37.69
N. C.	47	Driver	Vehicular accident	28.26	55.30	31.68
M. J.	48	Security Guard	Gunshot	33.00	57.64	30.20
A. T.	48	Employee	Vehicular accident	30.19	51.61	34.26
P. D.	48	Security Guard	Karate blow	28.60	32.20	34.40
S. T.	48	None	Vehicular accident	34.80	48.63	40.27
A. D.	48	Employee	Gunshot	27.82	46.90	37.69
M. L.	50	Realtor	Gunshot	29.26	57.41	34.68
A. C.	54	Operator	Stabbing	29.10	49.20	39.20

Table II. VALUES OF COPPER IN HEART, LIVER AND KIDNEY OF 20 NORMAL MALE SUBJECTS; ug/g WET TISSUE

Name	Age	Occupation	Cause of Death	Heart	Liver	Kidney
O. D.	40	Soldier	Vehicular accident	3.10	2.80	3.40
R. J.	40	Vendor	Stabbing	2.02	7.41	2.15
Unknown	40	N. A.	Gunshot	2.19	8.00	2.48
Unknown	40	N. A.	Stabbing	1.62	3.10	2.00
F. S.	43	Butcher	Stabbing	2.20	7.60	2.54
R. S.	45	Businessman	Stabbing	2.43	6.20	2.99
L. S.	45	Patrolman	Stabbing	3.20	5.66	2.01
F. C.	45	Scavenger	Vehicular accident	4.54	5.49	2.72
H. C.	45	Laborer	Vehicular accident	3.26	3.79	1.71
J. B.	45	Employee	Stabbing	1.60	4.14	2.54
A. P.	45	Driver	Vehicular accident	3.40	5.13	3.15
M. L.	46	Employee	Stabbing	3.86	5.14	2.69
N. S.	47	Driver	Vehicular accident	2.84	6.02	2.46
M. J.	48	Security Guard	Gunshot	3.45	4.00	3.44
A. T.	48	Employee	Vehicular accident	2.45	4.49	2.15
P. D.	48	Security Guard	Karate blow	2.30	5.90	1.10
S. T.	48	None	Vehicular accident	3.62	5.32	3.51
A. D.	48	Employee	Gunshot	2.40	4.12	2.32
M. L.	50	Realtor	Gunshot	2.52	2.12	2.48
A. C.	54	Operator	Stabbing	3.52	3.75	3.19

Table III. VALUES OF MOLYBDENUM IN HEART, LIVER AND KIDNEY OF 20 NORMAL MALE SUBJECTS ug/g WET TISSUE

Name	Age	Occupation	Cause of Death	Heart	Liver	Kidney
O. D.	40	Soldier	Vehicular accident	0.15	0.12	0.48
R. J.	40	Vendor	Stabbing	0.23	0.87	0.60
Unknown	40	N. A.	Gunshot	0.21	0.47	0.25
Unknown	40	N. A.	Stabbing	0.48	0.97	0.52
F. S.	43	Butcher	Stabbing	0.70	0.56	0.51
R. S.	45	Businessman	Stabbing	0.54	0.65	0.57
L. S.	45	Patrolman	Stabbing	0.31	0.28	0.20
F. C.	45	Scavenger	Vehicular accident	0.31	0.29	0.12
H. C.	45	Laborer	Vehicular accident	0.50	0.45	0.27
J. B.	45	Employee	Stabbing	0.24	0.21	0.34
A. P.	45	Driver	Vehicular accident	0.27	0.52	0.44
M. L.	46	Employee	Stabbing	0.27	0.13	0.24
N. C.	47	Driver	Vehicular accident	0.36	0.35	0.38
M. J.	48	Security Guard	Gunshot	0.09	0.86	0.35
A. T.	48	Employee	Vehicular accident	0.37	1.22	0.94
P. D.	48	Security Guard	Karate blow	0.53	0.64	0.55
S. T.	48	None	Vehicular accident	0.26	0.28	0.27
A. D.	48	Employee	Gunshot	0.20	0.65	0.44
M. L.	50	Realtor	Gunshot	0.16	0.28	0.25
A. C.	54	Operator	Stabbing	0.26	0.52	0.40

Table IV. COMPARISON OF MEAN NORMAL VALUES OF ZINC, COPPER AND MOLYBDENUM IN THE HEART, LIVER AND KIDNEY OF FILIPINOS WITH REPORTED LITERATURE DATA; ug/g WET TISSUE

	Values of Filipinos			Reported literature values*		
Elements	Heart	Liver	Kidney	Heart	Liver	Kidney
Zinc	30.35 ± 2.33	47.30 ± 7.72	35.02 ± 2.92	20-49(3)	26-68(6)	14-67(5)
Copper	2.88 ± 0.78	5.01 ± 1.96	2.55 ± 0.62	1.9-4.4(4)	5-25(9)	0.03-3.5(6)
Molybdenum	0.32 ± 0.13	0.52 ± 0.26	0.41 ± 0.20	0.05-0.23(2)	1.6(1)	0.03-.63(2)

*Source Kollmer, W. E. et al GSF-Report B 385 (1972)
The number of literature reports on which each range is based is given in parenthesis.

Table V. CONCENTRATION OF ZINC, COPPER AND MOLYBDENUM IN THE HEART, LIVER AND KIDNEY OF NORMAL SUBJECTS AND OF PATIENTS WITH MYOCARDIAL INFARCTION; ug/g WET TISSUE

	Normal subjects			Patients with myocardial infarction		
Elements	Heart	Liver	Kidney	Heart	Liver	Kidney
Zinc	30.35 ± 2.33	47.30 ± 7.72	35.02 ± 2.92	28.85 ± 2.07	37.57 ± 8.38	37.7 ± 7.31
Copper	2.88 ± 0.78	5.01 ± 1.96	2.55 ± 0.62	3.01 ± 1	3.95 ± 0.82	2.83 ± 0.55
Molybdenum	0.32 ± 0.13	0.52 ± 0.16	0.41 ± 0.20	0.83 ± 0.13	0.76 ± 0.36	0.74 ± 0.31

denum contents. The normal mean values of zinc, copper and molybdenum in the heart, liver and kidney of male adult Filipinos was determined and found to be agreeable with the normal mean values reported in literature. The mean concentration of zinc in the heart and liver of patients who died of myocardial infarction, 28.85 $\pm$ 2.07 ug/g and 37.57 $\pm$ 8.38 ug/g respectively were lower than the normal values of 30.35 $\pm$ 2.53 ug/g and 47.30 + 7.72 ug/g. The mean level of copper in patients with myocardial infarction of 3.95 $\pm$ 0.82 ug/g was lower than the normal value of 5.01 $\pm$ 1.96 ug/g. The mean concentration of molybdenum of 0.83 $\pm$ 0.13 ug/g, 0.76 + 0.36 ug/g and 0.74 $\pm$ 0.31 ug/g in the heart, liver and kidney respectively of patients with myocardial infarction were higher than the normal values of 0.32 $\pm$ 0.13 ug/g, 0.52 $\pm$ 0.16 ug/g and 0.41 $\pm$ 0.20 ug/g.

The results and importance of our investigation was discussed.

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Clinical Experience with Transfer and Direct Tumor-Specific Immunity in the Treatment of 24 Advanced Cancer Patients with Observations on "Post-Surgical" Immunoprophylaxis and Local Immunotherapy

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INTRODUCTION

UNTIL RECENTLY, concepts in the treatment of cancer in general have been centered on three major modalities, namely: Surgery, Irradiation, and Chemotherapy. Mathe'[1], however, has succintly emphasized that even the most witty combination of these time-tested approaches takes care only of approximately one-third of the total cancer cell population in the average tumor-stricken victim. There remains, therefore, even after a thorough treatment, the bigger, deceptive, and invisible enemy which must be handled and combatted continuously by the immune defenses of the host down to the "'last cell" in a guerrilla type of "cell-to-cell" contact through the relentless cell-mediated vigilance of a battered immunologic system which manytimes has been rendered incompetent in the latter stages of the warfare.

Because of repeated failures of these orthodox methods (mentioned above) to achieve acceptable cures and survivals, the pendulum of therapeutic posture in cancer has swung from one modality to the other, oftentimes with mixed feeling of confusion even among the sturdiest proponents of a particular modality. It should be emphasized that surgery, irradiation, and chemotherapy are by themselves immunosuppressive procedures and that although their initial effects are encouraging, the patient is frequently overwhelmed and overcome in the latter stages by unopposed and revitalized cancer cells. He, in effect, has become a vulnerable victim, for his defenses have been rendered immunologically impotent by the standard procedures.

During recent years, with some knowledge in human immunology, in a "last ditch" effort to salvage patient survival

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in cancer, Immunotherapy has become a beaconing light to some workers. In its incipient stage, the fascination is great, but there is apparently little to offer to the despondent cancer populace. There is a dearth of local experience in this field as it is abroad. However, it is conceded that the specialty of Cancer Immunology is gradually but steadily taking shape inspite of tremendous difficulties.

It was only during the last decade that we were afforded a clearer understanding of the Human Immune System relative to its behavior in the cancer victim as expounded by Gordon and Ford[2] and by Dmodchowski and Bowen[3]. This has brought us an articulate definition of what actually takes place in the host with respect to tumor-specific antigen recognition, processing, specific cell-mediated activation, and cytoeffector immune response to tumors recognized as non-self that we are provided a means not only for a more effective immunologic approach to the management of cancer but also to elucidate the basic question of how malignant cells manage to escape immunologic destruction.

Through a gradual accumulation of the most recent information on the subject as exemplified by the work of Hellstrom[4], we understand now the sluggish and often suppressed immune system of the advanced cancer patient in contrast to the heightened immunity among non-cancer and cancer-recovering patients. It is with this utter helplessness, impotence, and non-responsiveness of the immune defenses of the cancer victim, and the challenge brought about by the possibility of superactivation and utilization of the immune potentials of the non-cancer and cancer-recovering patients through specific and non-specific immunoactivation that this work was conceived. The allergory is akin to a drowning man who cannot swim. Utterly helpless and doomed to die, he needs a rescuer in the person of a competent swimmer.

In our country, the report of Villasor[5] on the immunopotential effects of BCG in advanced cancer in 1961 and 1965 was initially encouraging, but lasting results were not as dramatic. This however, was a giant step in cancer immunotherapy in our country. The trophoblastic hypothesis of Navarro[6] in the midsixties was challenging and probed into the possibility of further investigation into the "riddle of cancer" in an effort to develop new concepts, diagnostic procedures, as well as methods of treatment. In retrospect, the discovery of Alpha Fetoprotein (AFP) by Abelev in 1963[7] and of Carcinoembryonic Antigen (CEA) by Gold and Freedman in 1965[8] as immunodiagnostic procedures may have mirrored themselves from the human chorionic gonadotropin (HCG) test of Navarro. Gomez[9] in 1967 reported on the "immunosuppressive nature of cancer, "the significance of lymphocytic infiltration at the tumor-host interface, and the possibility of "cancer rejection" in man. Subsequently, in the same year, immunopotentiation techniques were initially employed by the same author[10]. Lately, Pineda[11] ingeniously elaborated on the employment of hemocellular transplant from a healthy syngeneic donor, alone ore combined with BCG administered to advanced cancer patients and reported some beneficial effects in at least two patients but with inconstant and unpredictable results in others.

It is the purpose of this treatise to present a non-heretofore described clinical study on Transfer and Direct Tumor-Specific Immunologic procedures in ad-

vanced human cancer with special attention to effects on tumor regression, survival time, and mortality, as well as observations on immunoprophylaxis. The author is not aware of any similar study undertaken in our country at this time of writing.

MATERIAL AND METHOD

Twenty-four patients with various types of malignant and potentially malignant tumors, most of them in the moderately or far-advanced state form the material of this report. There were 7 males and 17 females with ages ranging from 3 to 63 years.

Complete history, physical examination, pertinent X-rays, and blood counts, particularly the peripheral differential counts including atypical cells when present were routinely performed. Separate studies of leucocytic profiles on 53 cancer patients were also undertaken to determine the role of lymphocytes and other cytopathic effectors of cell-mediated immunity.

The patients were clinically grouped into three, namely: **Group 1** – Patients whose tumors were adequately removed with no recurrence or spread at the start of the treatment, **Group 2** — Patients whose tumors were adequately removed previously but had recurrence or spread at the start of treatment, **Group 3** — Patients whose tumors were not adequately removed and who had recurrence or spread at the start of the treatment.

Survival time was always calculated from the first visit or during the start of the immune treatment in all instances. Six patients were operated on between 1-2 years prior to immune treatment but survival times in these patients were counted not from the time of operation but from the immunotherapy.

IMMUNOLOGIC TECHNIQUES

Therapeutic manuevers depending upon the presenting need were as follows:

1. Administration BCG alone given directly to the cancer patient particularly after adequate tumor removal. In this sense, the therapy may be termed a "Post-Surgical" immunoprophylaxis. The BCG, given mainly as a recall antigen and non-specific immunopotentiator was given intracutaneously at the time of diagnosis at a dose of 0.5 to 1.5 cc similar to the technique of Villasor[5] once or twice depending upon the initial Delayed Hypersensitivity Reaction (DHR). When the first injection produced a violent or satisfactory reaction (3 to 5 cm of initial redness), no second dose was given. When the DHR was poor or timid, a second dose was given 10-20 days after the first. The scarification techniques as advocated by Mathe'[1] was not used in this series, although this author is contemplating its use on future patients.
2. Tumor — Specific Antigen (TSA) administered directly to the patient. This was either given alone or in combination with BCG. This maneuver was also given as a "post-surgical" immunoprophylaxis. The TSA was either allogeneic, syngeneic, or autologous in origin. No typing compatibility was required for allogeneic (nonrelated) TSA as long as the cancer cell type was similar.

Tumor-specific Antigens which are actually protein complexes were usually

given subcutaneously either fresh or treated with mitomycin as recommended by Mathe'[1]. In this series we prefer the former and sometimes use a little ether to reinforce antigen identification. Mitomycin inactivation was used only in 2 patients (cases 12 and 24). The TSAs were obtained by simple venipuncture in the following manner:

(a) As solubilized antigen (detached from the cell) taken from the serum of the same or another cancer patient (same blood type and tumor) as defined by Pilch and Golub[12] and demonstrated clinically by Griffiths[13].

(b) As cell-bound antigen either from the same or another patient with the same cancer cell type from coelomic cavity fluids which were positive histologically for cancer, or from resected tumors or involved nodes.

The antigens from resected tissues were minced in a sterile manner in the operating room, and ground before subcutaneous implantation through an incision separate from the main operative wound. Those obtained from body fluids and sera were injected similarly mixed with bacterial products or enzymes such as polyvalent bacterial vaccines, varidase, or BCG. Part of the resected tumors was submitted for biopsy and another part was stored in the freezer for future antigenic utilization.

3. Transfer Immune Factors in form of serum and white blood cells or whole blood administered to the cancer patient subcutaneously from a sensitized human donor preferrably but not necessarily syngeneic (related) and of the same blood type as the patient. Sensitization consisted of the donor having received either TSA as described above, or TSA-BCG combination, or BCG alone when TSA was not available. Transfer Immune Factors were given periodically, at first 2 times a week for 2-3 weeks, then weekly for 1 month then once every 15 to 30 days there-after when signs of clinical remission appeared. This was sustained for a total average of 15 to 18 transfers.

In this set-up, Transfer Immunity consisted of the following possible constituents, namely:

(a) Transfer Factor (TF) as originally demonstrated by Lawrence in 1955[14].

(b) Immune RNA is also a possibility as demonstrated by Mannick and Egdahl[15] and confirmed by Sabadini and Sehon[16]. This factor, however, is mainly obtained from animals (rodents, sheeps, monkeys) rather than humans and is easily inactivated by tissue ribonuclease.

(c) Serum Factors —

(1) Unblocking Serum Factor (USF) — described by Hellstrom, et al[17] which abrogates the "blocking" of cell-mediated tumor immunity among cancer patients also earlier reported by the same workers[4].

(2) Antibody — Dependent Cellular Cytotoxic factor (ADDC) also called the "arming" antibody, lym-

phocytedependent antibody, and "Synergistic" cytotoxicity as recently investigated by MacLennan[18] and Perlmann[19]

4. Local Immunotherapy in cases of cutaneous and subcutaneous cancers either as a local recurrence or metastatic spread to he subcutaneous tissues. In this series an ointment consisting of a combination of fibrinolysin and desoxyribonuclease was applied locally on the cutaneous and subcutaneous tumors daily as abvocated by Kelin[20]

In cases of metastasis, or when adequate solid tumor removal was impossible because of extensive growth or spread, inductive chemotherapy usually with cyclophosphamide with or without steroids was initially utilized to reduce tumor burden to at least 10^5 cells (Mathe'[1]), or to shrink the lesions to not greater than 1 cm. per cluster even when multiple as advocated by Southam[21] to render these residual cells vulnerable to eventual immunologic maneuvers.

When initial chemotherapeutic induction has been achieved, or when peripheral lymphocytic population has significantly been reduced to levels below 5,000, the drug was promptly withdrawn and transfer or direct immunity was administered and periodically given until host resistance has been overhelmingly potentiated. As soon as immunotherapy was started, chemotherapy was absolutely omitted so as not to offset positive immune responses.

Radiotherapy was utilized only in three instances: one for ovarian suppression in a breast cancer, one for recurrent epidernoid skin cancer, and the other, for a neck mass in reticulum cell sarcoma. Chemotherapy and radiotherapy, therefore, were only adjunctive and inductive modalities and were not necessary in the treatment.

High dosages of amino-acids and inosine were given during the whole period of the treatment to potentiate immune cell regeneration and immunoglobulin synthesis as part of a multimodality concept of treatment in cancer.

For Transfer Immunity, only healthy donors were selected having the same blood type and preferrably but not necessarily related (syngeneic) with the patient. The donors usually received TSA with BCG combined, or BCG alone. Full knowledge of the procedure was required and consents were signed by both donor and patient. The cases in this series reflected only those whose families or friends fully consented to the procedure since great difficulty was encountered in the process.

A separate group of 33 patients with various types of advanced cancer who had either surgery or chemotherapy but without immunotherapy as described herein was used as control.

RESULTS

Of the 24 patients, 21 were operated on but only 14 had adequate removal of their tumors, one of whom was a huge recurrent breast tumor which was treated like a primary lesion. Eight of these patients had no demonstrable spread or recurrence at the time of immunotherapy while six showed either recurrence or systemic spread. Five patients had

only exploration and biopsy, while two had primary surgery leaving distant metastases unaltered. Three patients were diagnosed mainly by unequivocal radiologic signs (see table 1).

The diagnoses of the different tumors are listed in table 2. These were obtained prior to immunologic treatment. Nine patients had ductal infiltrating carcinomas of the breast, two had choriocarcinoma, and two had reticulum-cell sarcoma. The remaining eleven had one diagnosis each, namely: primary neurogenic cancer of the right lung (neurilemmoma), adamantinoma, bronchiolar carcinoma, lung carcinoma (radiologic), tongue carcinoma (epidermoid), mediastinal cancer (radiologic), adenocarcinoma of the pancreas, ovarian carcinoma, esophageal carcinoma (radiologic), giant cell tumor of the humerus with fracture, and epidermoid skin carcinoma, interorbital area. For detailed information of the clinical materials see Plate 1.

TUMOR EFFECTS

Specific cytopathic effects on tumor of patients whose malignancies were adequately removed are seen on table 3 and demonstrated the following:

(1) Dramatic dissolution of pulmonary, subcutaneous, cutaneous, nodal metastasis or recurrences and effusions with stabilization of bone lesions in 3 patients: 2 with breast carcinnoma, 1 with choriocarcinoma (see figures 1, 2, and 3).

(2) Intermittent or partial dissolution and growth slowing of recurrent cutaneous and pectoral incisional lesions in 1 patient with recurrent breast cancer one year after radical mastectomy, and a recurrent ovarian carcinoma removed 1 1/2 years previously.

(3) Absence of recurrence in seven patients with adequate removal of: breast cancer in four, adamantinoma in one, giant cell tumor in one, and tongue cancer in one. One of the breast cancers in this group was huge local recurrence 24 months after a pervious radical procedure. There was no recurrence 9 months after a second operation with subsequent immunotherapy.

(4) Marked slowing of bronchiolar cancer adequately removed 24 months previously, and an epidermoid skin cancer removed one year previously.

Tumor effects on patients whose malignancies were either inadequately removed or not removed at all were noted as follows:

(1) Moderate to marked slowing of: a massive neurogenic pulmonary growth, an esophageal cancer with temporary remission and restored ability to swallow, and two breast cancers, one of whom is still alive after 72 months.

(2) Progression of tumor growth was observed in: one lung cancer with mediastinal extension, one pancreatic cancer, one choriocarcinoma, two reticulum-cell sarcomas, and one mediastinal cancer.

SURVIVAL TIME

Survival times calculated from the first visit or at the start of immunotherapy are seen in table 4. Group 1 consisting of 8 patients had a survival time range of 9-96 months with a mean of 35.87 months. As of this moment seven of eight patients (87.5%) as still alive.

Group 2 consisted of 6 patients with a survival time range of 6-60 months and a mean of 27.16 months. Five of six patients are still alive (83.33%).

Group 3 had only two patients: One survived 30 months, the other only two months, a mean survival time of 16 months. Both patients have died.

Group 4 consisted of 8 patients with a survival time range of 1 to 72 months with a mean of 12.25 months. All have died except one (12.5%). Of the total 24 patients, 13 are alive (54.1%) at the time of writing. The overall mean survival time was 24.16 months.

The Control Group consisting of 33 patients with their respective organ cancer listed in table 5 had an age range of 4 to 78 years. 17 were males and 16 were females. The mean survival time were 2.7 months (range 1-18 months). One female patient with a sluggishly growing ductal breast cancer survived 18 months. All patients died at the end of the follow-up.

RESULTS OF IMMUNOLOGIC PROCEDURE —

The result of the immunologic procedures employed are seen in table 6. BCG was used alone on cases 2, 3, and 4 of Group 1. Only one had eventual recurrence and died (66.6%). TSA alone was used on cases 1,6,7,8,12,13,15 and 24. Six of eight patients (75%) are still alive, four from Group 1, one from Group 2, and one from Group 4.

Transfer Immunity utilizing only BCG which alone was available at each particular instance was used on cases 9,11,16,-17,18,19,21 and 23. Only 2 of 8 patients (25%) are alive, all from Group 2.

Transfer Immunity utilizing BCG and TSA to sensitize the donor plus direct employment of TSA and BCG on the patient was used on cases 5,10,14, 20, and 22. Three of the five patients (60%) are alive, one from Group 1, and 2 from Group 2.

POST-SURGICAL "IMMUNOPROPHYLAXIS"

This was done on 8 patients in Group 1, on one patient in Group 2, on one patient in Group 3, and on three patients in Group 4. Only 7 patients (7 of 8 patients or 87.5%) all in Group 1, are alive, giving an overall survival rate of 53.84% for all groups. TSA was used in 6 patients, TF was used in 4, and BCG in 3. The results are seen in table 7. Interestingly, two cases (1 and 7) with low malignancy (adamantinoma and giant cell tumor) had no recurrence 30 and 47 months after therapy, respectively.

Lymphocytic Profiles

Of the 53 patients separately studied for peripheral lymphocyte profiles, 36 were terminal cases while 17 were in the process of clinical remission. Of the terminal subjects, 13 had lymphos below 10%, 8 with lymphos between 10-15%, 8 had between 16-20%, 5 had 21-30%, while only 2 had over 30%. Of the remitting cases, no patient had below 10% count, 10-15% count, or 16-20% count. Eleven had counts between 21-30% while 6 patients had over 30%. The results can be viewed in table 8. Atypical lymphos as an expression of blastogenic responses were observed on two patients. In one of these, a significant eosinophilia was observed (35%). The same patient had a dramatic dissolution of metastatic lesions. Examples of unfavorable and favorable lymphocyte responses are seen in table 9.

This author was able to observe significant lymphocytic increases with inosine and essential amino-acids in conjunction with immunotherapy. In one remitting patient (case 14) for instance, an initial count of 25% on 8-2-75 increased to 37% on 8-16-75 without significant change in the total WBC. A similar observation was seen in cases 9, 10, 17, and 23 who were maintained on these adjuvants throughout the length of their treatment.

Local Immunotherapy

Local Immunotherapy with combined fibrinolysin and desoxyribonuclease was uwsed in the cutaneous and subcutaneous lesion on cases 9, 10, and 14. Case 9 had intermittent flattening while cases 10 and 14 had dramatic disappearance reflecting also probably not only local but also systemic immune responses resulting from TSA and TF.

DISCUSSION

The study of cancer has often fascinated surgeons, pathologists, radiologists, and biologists alike. Surgeons often capitalize on the excisional approach and have been able to prolong survival times in cases of purely localized malignancy. When the extent of the lesion is precarious, the long term results are poor and it becomes the duty of the chemotherapist and radiotherapist to render adjuvant aid at a stage when host resistance has obviously waned. Frequently, the latter two modalities enhance rather than check tumor growth particularly when doses are inadequate because of their inherent capacity to further immunosuppress biologic defenses in the same manner that surgery does to the patient, the difference being that surgery produces a rebound immunologic response probably because of tumor burden reduction as hypothesized by Simmons[22].

It is now known that the above mentioned modalities can only cure about one-third of the cancer patients when treating perceptible disease[1]. This leaves a considerable amount of imperceptible tumor cells which comprises the residual, insiduous, and upredictable enemy. This is that particular state of affairs that brings recurrence and eventual demise of the immunobiologically helpless cancer patient. Many-times, one would only hope that the left-over cell burden would not exceed the capacity that can be handled by the existing immune defense in a particular patient. It is in this concept that a multimodality approach to cancer treatment has been advocated by Haskel[23].

The role of immunotherapy in the treatment of cancer although slow in its development, has lately gained momentum with a better understanding of "biologic immunodynamics". The finding by this author in 1967[10] of the immunosuppressive behavior of cancer as revealed by absence or scanty lymphocytic infiltration at the tumor-host interface has given insight into the need of some maneuver that would bring about a potentiation of the host resistance. Experience has shown that most patients with advanced cancer and, therefore, with considerable tumor burden have an almost absolute refractory immunosuppression not responsive to ordinary nonspecific immunostimulants such as BCG or other bacterial vaccines as advocated by Villasor[5], or to non-sensitized hemocellular transplant as reported by Pineda[11], hence, the unpredictability of these immunologic procedures.

In advanced cancer patients with severe immunosuppression, intracutaneous

BCG did not produce a reaction (7 patients) even after repeated inoculations, showing obvious anergic status. In some patients with minimal immunosuppression, however, hemocellular transplant itself could be beneficial probably because of Hellstrom's USF. This is one of the components (serum factors) this author relied on during transfer immunization.

Physiology of the Immune System

There are unequivocal evidences to show that immunity of tumors are exercised by the Cellular or Lymphocytoid Division rather than by the Plasmacytoid Division of the Immune System as amply described by Gordon and Ford[24]. The schema of the Physiology of the Immune System is seen in figure 4. The sensitized T-lymphocyte which has matured through the thymus and, therefore, thymus oriented is the obvious cytopathic effector, However, if the T-lymphocyte is not tumor-specifically sensitized, then the USF is non-effectual since the unopposed cytopathic effector mechanism has no specific direction or target cell. For this reason, non-specific hemotransplant is of no physiologic value. **The most ideal and rational approach is tumor-specific sensitization and/or transfer immunity from a healthy, syngeneic, specifically sensitized donor.**

The Plasmacytoid or Humoral Division which is represented by the B-cell or bursa oriented cell, so called because in the chicken these cells are derived from the hindgut bursa of Fabricius, is in man derived from the lymphoid follicles of the Peyer's Patches and probably the appendix. These plasmacytes elaborate immunoglobulins or serum antibodies which are mainly responsible for immune responses in bacterial infections, foreign body and allergic reactions. They seldom take part in tumor immunity. Moreover, by creating antigen-antibody complexes with tumor receptor sites, they may actually enhance tumor growth producing the so-called "Serum Blocking Factor" SBF) earlier reported by Hellstrom[4] (see figure 5). This is the more plausible explanation of cancer patients who inspite of high titres of tumor antibodies are unable to "reject" their own tumor lending credence to the hypothesis of the immunosuppressive behavior of cancer in its autonomous stage[10].

Tumor-Specific Antigen

One of the various new properties which characterize cancer cells is the acquisition of protein complexes which have not been present or defined in the cell prior to malignant change. The existence of these TSA in both animal and human tumors has been recognized for years[3]. The malignant cell may carry a variety of antigens, either intracellular or at the cell surface. These antigens may be recognized as "foreign" or "non-self" by the host's immune system, and an immune response may be mounted specifically against the antigens and against the tumor cells that bear them. The immune response is usually believed to be cell-mediated (Lymphocytoid Division) and the mechanics is similar to a transplantation rejection process. It is to be emphasized here that the cancer cell is distinct from the antigen itself. It is therefore, with practical importance that we distinguished our approach in securing the TSA into the so called "solubilized" or cell-free, and the "cell-bound" antigens, the former obtained by simple venipuncture, the latter by surgical excision, aspiration of coelomic fluids, or biopsy.

Griffiths[13] has shown that cancer cells

abound in the blood in 42 of 70 patients (60%) even among silent, localized colonic cancers. It is obvious, therefore, that the score could be up to 90% when it comes to cell-bound antigens in cases of full-blown metastatic cancer. This author, moreover, predicts an almost 100% availability in the peripheral blood in cases of solubilized antigens. In the future, it will be an expedient plan to set up a bank of fresh frozen cancer tissues of various types as a vaccine pool similar to the one described by Mathe'[1] at the Institute of Cancer and Immunogenetics in France.

In this report, the author has introduced specific immunization by way of immunoprophylaxis, cancer suppression, and transfer immunity with the end in view of a well-directed specific immune response. From the data presented, there was no recurrence of the tumor 30, 21, 18, 9, 42, 47, and 96 months, respectively, in Group 1, all patients being presently alive (100%). One patient aged 30 (case 6) suffered no recurrence and is alive 42 months after initial surgery and immunization inspite of one pregnancy during the follow-up period. There was only one patient (case 2) whose growth slowed (24 months) but developed metastases and died. There were two patients in group 2 with TSA immunization. One had a dramatic dissolution of pulmonary metastases and is alive today 60 months after initial immunization (see figure 2). The other patient had growth slowing of an epidermoid carcinoma of the interorbital skin but latter died of cerebral spread 24 months after immunotherapy. One patient in Group 3 and one in Group 4 had marked slowing of growth, but eventually, of the 8 patients with direct TSA administration in all groups, six (75%) are alive between 24 to 96 months after immunotherapy. Deaths in Groups 2 and 3 merely reflect the factor of tumor burden which runs pare' pasu' with tumor-induced immunosuppression and is oftentimes a decisive element in determining immunologic victory or defeat.

It has been conceded by cancer immunologists that tumors with sizes over 1 cm. are difficult to disintegrate immunologically. The experience in this series, however, have shown that metastasis as big as 1 inch even when in multiple clusters all over the body dissolved dramatically as early as one to two months time as exemplified by cases 10, 11, 12, and 14 (see figures 1, 2, and 3). Some big solid tumors may pose as impenetrable barriers, although a "second set" type of homograft-like rejection may occur similar to the "Gell's perivascular islands" of Jones[25] which can cause an acute ischemia, necrosis, and dissolution regardless of tumor size.

The specificity of tumor antigens to induce corresponding specific reaction is exemplified by the work of Hellstrom and associates[26] who observed inhibition of various tumor cultures by autogenous or allogeneic leukocytes from patients with the same type of tumor in 88 to 91% as against 3 to 7% of normal cell cultures. Most interestingly, leukocytes from cancer patients caused destruction of allogeneic tumor cells of the same type but not tumors of other histologic types. The recent clinical trial by Marcove, et al[27] of autogenous vaccines in the treatment of osteogenic sarcoma merits attention.

Southam[24], in his experiments in mice observed that tumor-takes of transplanted methylcholanthrene-induced sarcoma were only 50% less in immunized than non-immunized animals. Experience in

man although not well controlled, showed that reduction of takes was not more than 50% of control values, and to get approximately to that degree, it takes a ratio of 1,000 leucocytes to 1 tumor cell for an effective cell-to-cell contact.

The preparation of the tumor-specific antigen itself deserves mention. According to Southam[21], the most effective form of tumor vaccine is the intact tumor cell, either viable, or metabolically alive but treated with chemicals, bacterial products or irradiation to prevent cell propagation but retains as well as reinforces its antigenicity as suggested by Rios and Simmons[38]. This author suspects that in big solid tumors antigenicity is nil if the host-tumor interface remains as a thick barrier leaving no means of "immunologic exchange" between the tumor and the host, thereby perpetuating unchecked tumor growth. When the tumor eventually finds its way to the blood stream, immunosuppression has gone too far for the host to take care. Thick TSA tissues when not comminuted adequately and attenuated as described prior to subcutaneous implantation may produce a "take" which occurred in one patient in earlier experiments. The lesson was learned and subsequently corrected.

When severe immunosuppression has prevailed, TSA alone may be too weak to evoke a response. The use of TSA in combination with BCG becomes an alternative. This is a simpler method devoid of moral and donor problems when compared with Transfer Immunity. Recent reports by Powles[28] showed dramatic results among patients with acute myelogenous leukemia using stored viable tumor cells plus BCG. Fefer, quoted by Simmons[22] described 12 patients who received subcutaneously their own leukemic cells, lethally irradiated in vitro with 10,000 rads plus intravenous infusions of peripheral lymphocytes from a normal identical twin. Complete remissions occured in 87% of cases with six patients having complete remission at 11 to 44 months without chemotherapy. The cultured cell-BCG immunization technique of Sokal and Aungust[29] is merely a variation.

Recently, Rosato[30], et al used Vibrio cholera neuraminidase as an adjunctive treatment with monthly injections of autochthonous tumor cells to 25 patients with various types of cancer. Six who received the full course of 6 injections are all alive without clinical evidence of progression more than 8 months after the start of treatment. It is clear, therefore, that the TSA may need some sort of immunopotentiation in the more advance ype of cancer with severe immunodepression. The adjunctive treatment apparently reinforces the TSA by causing a DHR through the following mechanisms, namely: 2) production of a less rigid cell surface structure allowing easier membrane deformation and phagocytosis of the TSA by macrophages, b) unmasking of antigens allowing greater recognition, and (c) facilitation and accessibility of antibodies to antigenic receptor sites on the surface of the cancer cell. Employing cytotoxicity assays in vitro using autologous target cells grown in tissue culture, Rosato[30] observed cytolysis without tumor enhancement or "blocking" effect in 4 of 5 patients in whom this was measured, In this series, TSA combined with BCG was not used alone but in conjunction with Transfer Immunity by reason of exigency. Of 5 patients where this was used (case 5, 10, 14, 20, and 22), 3 or 60% are alive. The non-response of patients in group 4 (cases 20 and 22) was

due to overwhelming tumor load and immunodepression.

Transfer Immunity

Lawrence[14] in 1955 was the first to report on the rtansfer of delayed hypersensitivity responses to tuberculin and other antigens in man with dialyzable extracts of human peripheral lymphocytes. This was termed the "Transfer Factor" (TF). In 1960, specific accelerated rejection of skin homografts in man were found to be mediated by this factor by the same authors[31]. Although its use has been confirmed in non-cancer immune deficiency diseases such as Wiscott-Aldrich syndrome, its more dramatic role in recent years has been focused on malignancy. It is similar but distinct from Immune RNA of Pilch and Golub[12], the difference being on the fact that the former is obtainable from the lymphocytes of man while the latter mostly from that of animals and is, moreover, inactivated by tissue ribonuclease while the TF is not. Ribonuclease, however, can be inactivated in turn by low molecular weight dextran.

Southam[21] refers to Lawren's TF as "Instructional Immunotherapy" for although it does not contain the antigen to which immunity is conferred, nor is antigenic of itself, it somehow transmits information which "instructs" the recipient's immune system to respond to the same antigen which sensitized the donor. The appeal then for such non-antigenic material for immunotherapy is obvious based on the assumption that healthy donors who have built up immune resistance to a wide variety of cancer cells could offer their leucocytes to the cancer recipient who is unable to defend himself against the malignancy. This was precisely the concept utilized by this author in this treatise. With the administration BCG to the donor, he acquires a heightened, non-specific immunity, but with the addition of TSA, he develops, in effect, a specific, hightened immunity when transferred "instructively" to the cancer patient and confers not only a recall DHR but also a specific cytotoxic instigator to a remarkable degree.

When using transfer elements including serum instead of just only leukocytes as originally used by Lawrence[14], this author also availed of two serum factors aside from the possible availability of Immune RNA. The serum factors, previously mentioned are: (1) USF of Hellstrom, and (2) ADCC factor of MacLennan and Perlmann.

Two patients, in Group 2 where transfer BCG was used are both alive (cases 9 and 11) 41 and 12 months, respectively. The rest of the patients who received transfer BCG all died, one belonging to Group 3 and five from Group 4. One of the above survivors (Case 11) had dramatic dissolution of abdominal spread and ascites. The over-all effectivity for all groups with transfer BCG was a poor 25% reflecting severe refractory immunosuppression. In comparison, the effectivity of 50% for combined Transfer and Direct Immunity utilizing TSA plus BCG for both approaches seems encouraging and should be used more often in advanced cases. It is observed however that transfer BCG was used more often than transfer TSA. The reason is reluctance on the part of the donor in accepting the procedure for fear of cancer propagation. However, the argument itself is not valid, first, because the TSA is initially deactivated by pre-treatment as previously described, and second, because of the concept of Immunologic

Surveillance in healthy individuals as advanced by Burnet[32].

Survival Time and Mortality

The mean survival time in this series of 35.8 months in Group 1 and 29.2 months in Group 2 is indeed encouraging. For example, in Group 1 we had a superextended survival of 96 months in one patient and over 40 months in two, and the rest between 9-30 months with only one death. The mean survival among patients given autologous tumor cells treated with Vibrio cholera neuraminidase after surgery by Takita, et al, as quoted by Simmons[22] was only 17.4 months.

Although the mean survival time in Group 2 was only 29.2 months, the longest survivals for this group were 60 and 41 months, respectively. The rest had between 12 to 24 months with only one death at the end of the follow-up. Group 3 and 4 did not fair well (16 and 12.2 months mean, respectively), although one patient who is still alive has a 72-month survival time. These results speak cogently for themselves when compared with the 33 control patients without immunotherapy who had a mean survival time of 2.7 months, all of whom have died.

Comparison with the BCG group of Villasor[5] (see table 10) which had 7 survivors out of 43 patients (16.2%) at 24 months, the survival in this series were 10 out 24 patients alive 24 to 96 months (41.6%), while the actual number of living patients is 13 (54.1%) which is highly significant. The results in Group 1 and 2 are inspiring and should invite more attention and study as well as employment of bigger and adequately controlled series. It is, moreover, obvious from this data that tumor burden is a critical factor if immunotherapy is to succeed. The poor results in Groups 3 and 4 are witness to this fact.

Lymphocytic Responses

The study of peripheral lymphocytes in this series deserves mention since they are the principal agents of immunity against tumor cells. As early as 1922 MacCarty[33] has already mentioned the significance of lymphocytic infiltration around breast cancers as a determinant in host rejection of the tumor and a favorable prognostic sign relative to sur vival. It is unfortunate that this observation was discredited for half a century before eventually gaining some support.

Evidences have shown that lymphocytes become significantly reduced in a good number of patients whose progress is dismal. As a matter of fact, the decrease or increase of the lymphocyte population is of prognostic significance which will presage whether the patient is going to succumb to the disease or get well in the not too distant future. In the authors' personal unlisted experience, the forst and most accurate prognosis were on those patients whose lymphocyte counts slumped below 10% pare' pasu" with very high total WBC counts beyond 15,000.

The appearance of atypical cells in two patients (cases 10 and 18) was suggestive of blastogenic repsonse which according to Pilch and Golub[12] is indicative of prior sensitization of lymphocytes to tumor antigens. This may, therefore, be interpreted to represent detection or recognition of TSA by the host.

The appearance of significant eosinophilia in one patient (also with atypical lymphos) with dramatic tumor dissolution indicated either the presence of a

foreign agent, an allergic reaction, or an antigen-antibody repsonse. By elimination, the latter may be the most likely mechanism to explain this occurrence. This antigen-antibody phenomenon has been amply expounded by Wetherley-Mein[34] who claimed that eosinophils are involved in the initiation of antibody synthesis. It appears that antigen-antibody complexes could be phagocytosed by eosinophiles. Defense against pathogenic effects of immune complexes by eosiphiles is significant in the light of Hellstrom's SBF[4]. Other functions of the eosinophiles are fibrinolytic activity and histamine inactivation whose relationship to cancer is still unknown.

"Post-Surgical" Immunoprophylaxis

Cancer Immunoprophylaxis in the strict sense of the word refers to immunoprocedures performed on the non-cancer patient to prevent a future occurrence of the actual cancer. In this study the term immunophylaxis was used rather loosely and was preceded by the word "post-surgical" to qualify succinctly what this author had in mind. The word was used only with respect to those patients who had actual removal of the tumor and were given either BCG, TSA, both, or with TF.

From the figures in this study, immunoprophylaxis was effective only when the tumor was adequately removed. The figure of 87.5% effectivity (7 of 8 patients) clearly justifies the procedure, although a bigger series would be more convincing. Moreover, immunoprophylaxis may be effective even with tumors of low malignancies as seen in two patients. To date, only two other human experiments had been done aside from this present series. One was by Bjorklund[35] who inoculated small groups of elderly men with a vaccine containing a mixture of human tumor cell in the hope that the resulting homograft immunity would inhibit the development of future cancers. Up to the present, however, no follow-up reports had been published. The flaw in this experiment, however, is that the prophylaxis was made late in life, although it can be opined that this is the age when tumors occur more frequently and, therefore, demands prevention. The other study was a collaboration between the group from Sloan-Kettering Institute, and that from Ohio State University Medical School[36] with the primary objective of studying homograft rejection phenomena and TSA. In that experiment, nearly 300 volunteers in the Ohio Penitentiary received living tissue culture cell homografts of various human cancer cell lines. Long-lasting homograft immunity directed toward TSAs was demonstrated in these men. The follow-up was between 14 to 20 years, and although it was difficult to trace every body because of frequent change of abode, those who were accounted for ten years or more from the time of inoculation (about one-third of the original number) showed only two known cases of cancer (2%). Although no conclusion was possible, immunoporphylaxis, either post-surgical or the true preventive measure is a fascinating procedure which will do doubt find its place in our future conduct with cancer-prone patients.

Local Immunotherapy

The subject of local immunotherapy for superficial lesions merits attention. Klein, et al[20], in his experiences with basal-cell and breast cancer (recurrent) as well as mycosis fungoides using locally applied dinitrochlorbenzene (DNCB), streptokinase-dornase, and PPD showed eradica-

tion of skin cancers in 95% in a group of 90 patients. The mechanism is brought about by DHR to haptens of relatively small molecular weight producing selective antitumor effects against malignant and premalignant epidermal lesions and lead to their eradication. Of three patients where local immunotherapy was used in this series, all responded with either flattening or complete disappearance of cutaneous and subcutaneous lesion (100%).

The Donors

The donors selected for transfer immunity were preferrably of the same blood type and related to the patient. This is merely to avoid the usual problem with histocompatibility antigens encountered with non-syngeneic donors during subsequent transfers. The experience here, however, has shown that non-related isotyped donors did just as well with excellent results even after over 12 transfers (cases 10 and 14). A history of hepatitis not only in the prospective donor but also in the patient is an absolute contraindication to transfer immunity. TSA in this case is the logical recourse.

Adjunctive Therapy

The discussion of immunotherapy will not be complete without certain factors which may be responsible for adequate lymphocyte production. Protein is one of the most vital raw material which can accelerate cell production. Preferrably, this should be in essential amino-acid form when assimilated by the patient in order to facilitate prompt synthesis without undergoing too much digestive work when introduced orally. Interestingly, amino-acids in contrast to the usual natural complex protein, passes through the gut into the portal system to the liver readily without much ado and there undergo rapid protein synthesis. It is even more effective when administered intravenously.

Hypoproteinemia is a common observation among advanced cancer patient probably because of nausea, inanition, poor absorption, and deficient protein synthesis. This results in poor body resistance and immunodepression. Patients given amino-acids, however, regain their serum protein values and, consequently also, their lymphocyte and antibody capacities, and frequently experience some kind of remission.

The role of Inosine in reversing lymphopenia either after chemotherapy, radiotherapy, or because of cancer immunosuppression itself has been firmly established by Kondo and Aoyama[37] in 1965. Lymphocyte regeneration is probably by way of the Inosine-Ribosephosphate-AMP-ADP-ATP pathway facilitating nucleotide and protein synthesis even under conditions of hypoxia. In this series at least 20% of the cancer patients were brought to satisfactory lymphocytic levels either after inductive chemotherapy or during the immediate cost-surgical period. This phenomenon cannot be explained solely by the effect of immunotherapy alone.

SUMMARY

Twenty-four patients with various types of cancer were given transfer and Direct-Specific Immunizations which at times were reinforced with BCG under conditions of exigency. The patients were grouped as follows: **Group 1**— Tumors adequately removed, no metastasis or spread, **Group 2** — Tumors adequately removed previously but with existing spread or metastasis at time of immunotherapy, **Group 3** — Tumors not ade-

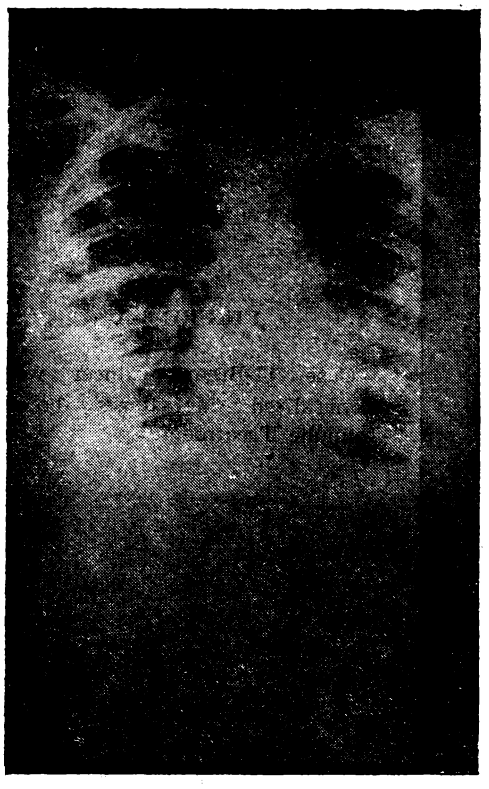

FIGURE 2-A

Case 12-Choriocarcinoma with Pulmonary Metastases before Immune Treatment.

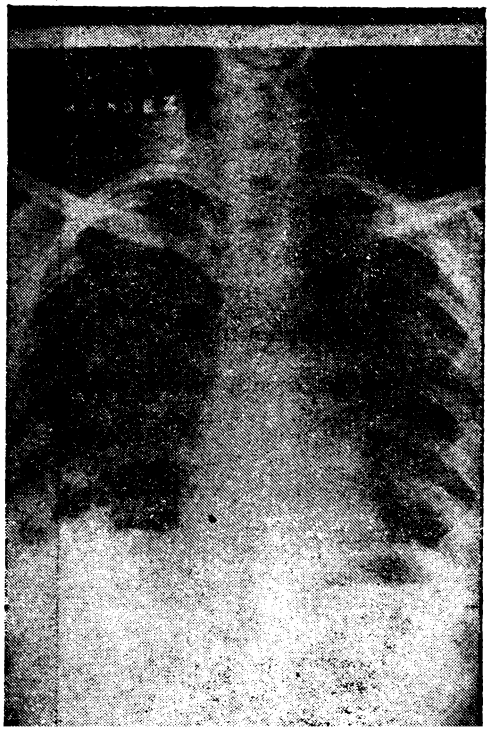

FIGURE 2-B

Case 12-Two months after Immunotherapy.

Sept.-Oct., 1976
J. P. M. A.

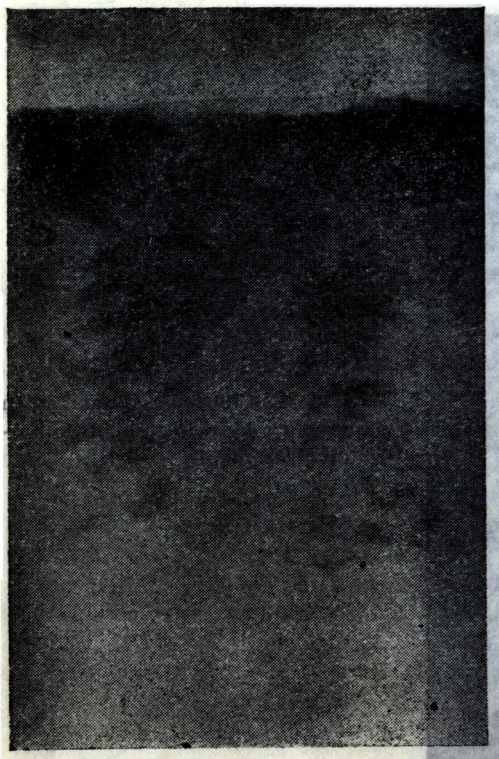

FIGURE 3-A

Case 14-Breast Cancer with Generalized Metastases before Immune Treatment.

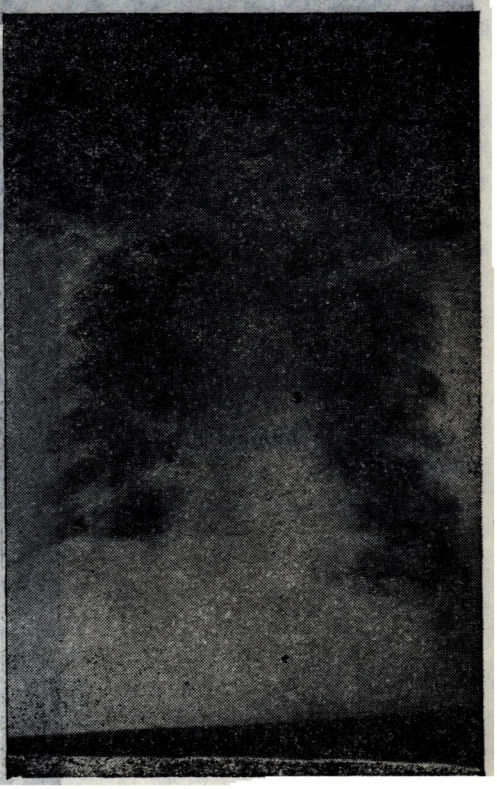

FIGURE 3-B

Case 14-One month after Immune Treatment.

PHYSIOLOGY OF THE IMMUNE SYSTEM

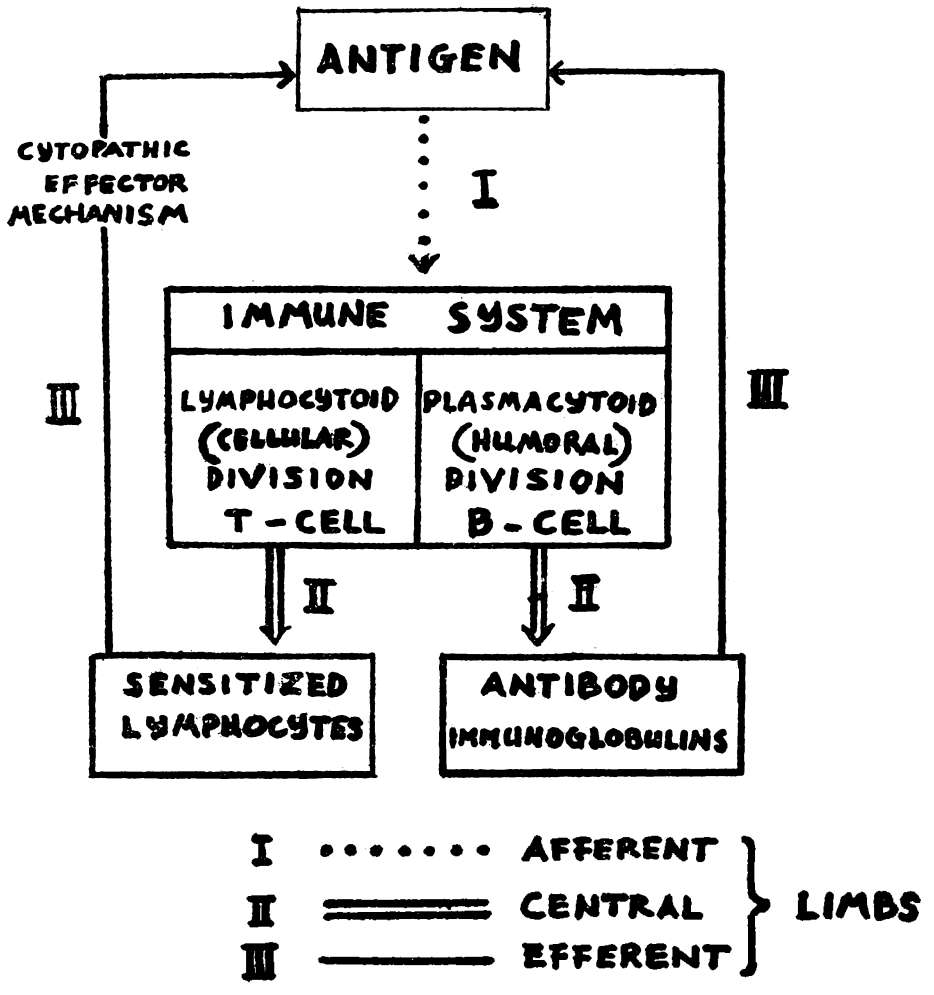

FIGURE 4

quately removed, with local or systemic spread, Group 4 — Tumors not removed, with local or systemic spread.

In group 1, all are alive except one (7/8 or 87.5%) between 9 to 96 months (mean 35.8 mo.) with recurrence of tumor only in one patient. In Group 2 (6 patients), four had dramatic dissolution of the spread and recurrence, two had growth slowing and all are alive except one (5/6 or 83.3%) 6 to 60 months (mean 27.1 mo.). In Group 3 (2 patients), all died with a mean survival time of 16 months. In Group 4 (8 patients), only one is alive (12.5%) after 72 months, with a mean survival time of 12.2 months. Control studies in 33 advanced cancer patients without Immunotherapy revealed a mean survival time of 2.7 months, with no living patient after that period. Survival time was calculated from the first visit or in-

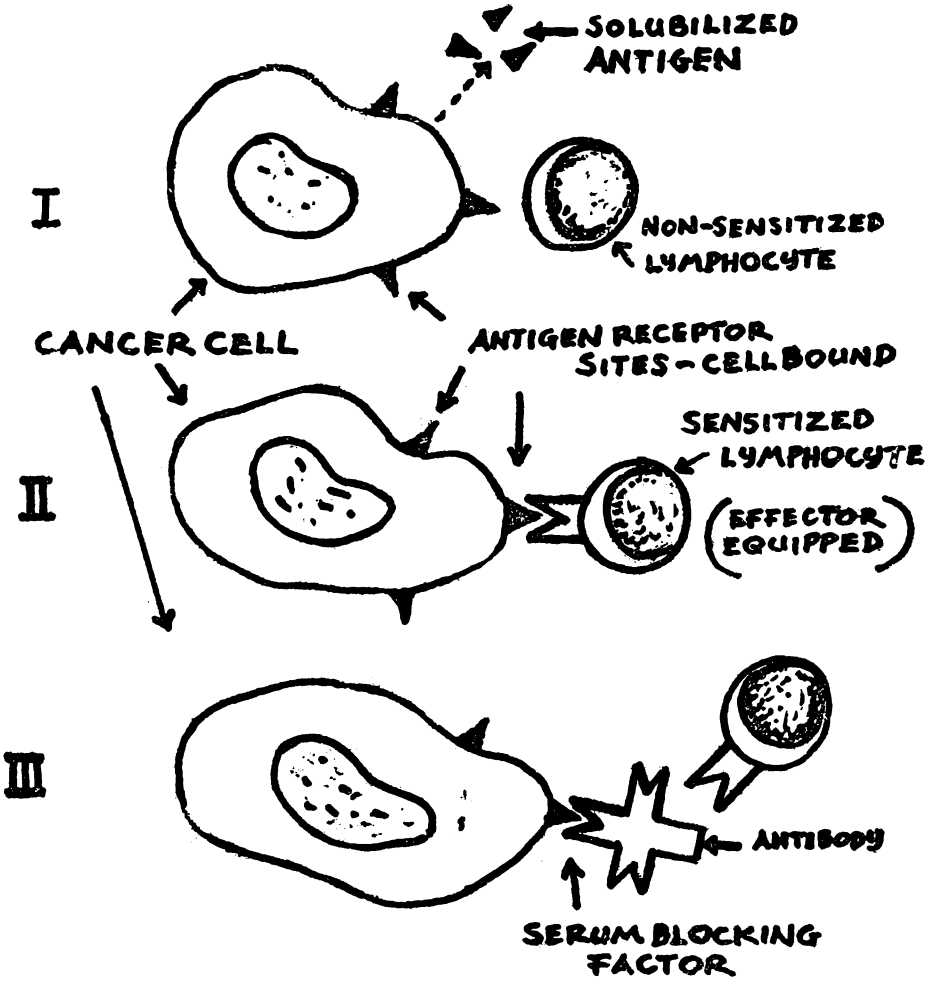

FIGURE 5

stitution of immunotherapy and not from the previous operation. Comparison with Villasor's series was discussed. Included in this study was an experience with local immunotherapy for cutaneous lesions.

Tumor burden was a critical factor as shown in Groups 3 and 4. The results in Groups 1 and 2 were encouraging and invite more attention, study and employment of bigger series.

"Post--Surgical" Immunoprophylaxis was discussed relative to its effectivity (7/8 or 87.5%) in Group 1 and an overall survial rate of 53.8% for all groups. The role of lymphocytes as cytopathic effectors of cell-mediated immunity as well as the prognostic significance of its peripheral population has been emphasized. The presence of atypical cells and significant eosinophilia in some patients and their relationship to antigenic recognition and tumor antigen-antibody interaction was mentioned. Finally, the regenerative potential of Amino-acids combined with Inosine in conjunction with Immunotherapy was revealed by improvement in lymphocyte levels which cannot to explained solely by immunotherapy alone.

Plate 1. TRANSFER AND DIRECT TUMOR-SPECIFIC IMMUNITY. SPECIFIC TUMOR EFFECTS AND SURVIVAL

Group	Case	Age	Sex	Cancer	Tumor Effects	Survival Time in Months	Present Status
1 —	1	50	F	Jaw	NR	30	A
	2	51	F	Lung	MS	24	D
	3	50	F	Breast	NR	21	A
	4	53	F	Breast	NR	18	A
	*5	54	F	Breast	NR	9	A
	6	38	F	Breast	NR	42	A
	7	3	M	Bone	NR	47	A
	8	63	M	Tongue	NR	96	A
	*second operation for local recurrence						
Group 2 —	9	55	F	Breast	PD	41	A
	10	36	F	Breast	DD	20	A
	11	52	F	Ovaries	PD	12	A
	12	22	F	Trophoblast	DD	60	A
	13	48	F	Skin	MS	24	D
	14	47	F	Breast	DD	6	A
Group 3 —	15	54	F	Breast	MS	30	D
	16	52	F	Trophoblast	PG	2	D
Group 4 —	17	50	F	Lungs	MS	10	D
	18	58	M	Lungs	PG	2	D
	19	7	M	RES	PG	5	D
	20	58	M	Pancreas	PG	3	D
	21	62	M	Esoph.	PD	3	D
	22	61	F	RES	PG	2	D
	23	60	M	Mediast.	PG	1	D
	24	55	F	Breast	MS	72	A

Legend: NR— No recurrence, MS — Marked slowing of growth, PD— Partial dissolution, DD — Dramatic dissolution. PG— Progression of growth, RES — Reticulo-endothelial system D — Dead, A — Alive

Plate 1. CLINICAL MATERIAL

Classification			No. of Patients
A. With Surgery			(21)
1. Adequate Tumor Removal		14	
a) no spread		8	
b) with spread		6	
2. Inadequate Tumor Removal		2	
3. Exploration or biopsy only		5	
B. Radiologic Diagnosis Only			(3)
Total			24)

Table 2. DIAGNOSES OF MATERIALS

Tumor	No. of Patients
Duct Carcinoma, Breast	9
Choriocarcinoma	2
Reticulum-Cell Sarcoma	2
Esophageal Carcinoma (radiologic)	1
Neurogenic Sarcoma, Lung	1
Giant Cell Tumor, humerus with fracture	1
Adamantinoma	1
Epidermoid Skin Cancer	1
Bronchiolar Carcinoma, Lung	1
Lung Carcinoma (radiologic)	1
Tongue Epidermoid Cancer	1
Mediastinal Cancer (radiologic)	1
Adenocarcinoma, pancreas	1
Ovarian Carcinoma	1
TOTAL	24

Table 3. SPECIFIC TUMOR EFFECTS WITH TRANSFER AND DIRECT TUMOR-SPECIFIC IMMUNITY

Classification		No. of Patients
A. Tumors Adequately Removed		(14)
1. Dramatic dissolution	3	
2. Intermittent or partial dissolution	2	
3. Absence of recurrence	7	
4. Marked slowing of growth	2	
B. Tumors Inadequately or Not Removed		(10)
1. Moderate to marked growth slowing	4	
2. Progression of tumor growth	6	
TOTAL		24

Table 4. SURVIVAL TIME AND EFFECTIVITY RATE

Group	No. of patients	Range-mo.	Mean-mo.	Survival Ratio	% Alive.
1	8	9—96	35.87	7/8	87.50
2	6	6—60	27.16	5/6	83.33
3	2	2—30	16.0	0/2	0.00
4	8	1—72	12.25	1/8	12.50
All Groups	24	1—96	24.16	13/24	54.10
Control	33	1—18	2.7	0/33	0.00

Table 5. ORGAN CANCERS IN 33 CONTROL PATIENTS —

Organ Site	No. of Patients
Lungs	9
Breast	7
Liver	4
Skin and Subcutaneous Tissue	3
Colon, Rectum	2
Cervix	1
Pancreas	1
Esophagus	1
Intestines	1
Bone Marrow	1
Muscle	1
Bone	1
Pleura	1
TOTAL	33

Table 6. IMMUNOLOGIC PROCEDURES

Agents Used	Case	Group	Tumor Effects	Result	% Alive
A) BCG Alone	2	1	MS	Dead	
	3	1	NR	Alive	2/3 (66.6%)
	4	1	NR	Alive	
B) TSA Alone	1	1	NR	Alive	
	6	1	NR	Alive	
	7	1	NR	Alive	
	8	1	NR	Alive	6/8 (75%)
	12	2	DD	Alive	
	13	2	MS	Dead	
	15	3	MS	Dead	
	24	4	MS	Alive	
C) TFusing BCG	9	2	MS	Alive	
	11	2	DD	Alive	
	16	3	PG	Dead	
	17	4	MS	Dead	2/8 (25%)
	18	4	PG	Dead	
	19	4	PG	Dead	
	21	4	MS	Dead	
	23	4	PG	Dead	
D) TF Using TSA +BCG	5	1	NR	Alive	
	10	2	DD	Alive	3/5 (60%)
	14	2	DD	Alive	
	20	4	PG	Dead	
	22	4	PG	Dead	

Legend: DD-Dramatic dissolution, NR-No recurrence, MS-Marked Slowing, PG— Progression of Growth.

Table 7. IMMUNOPROPHYLAXIS

Group	No. of Patients	Alive %	Dead
1	8	7(87.5%)	1
2	1	0 (0%)	1
3	1	0 (0%)	1
4	3 (biopsy only)	0 (0%)	3
Total	13	7(53.84%)	6

Table 8. LYMPHOCYTE PROFILES IN 53 CANCER PATIENTS

A. Terminal Patients		(36 Patients)
Lymphocyte Count:		
Below 10%	13	
10—15%	8	
16—20%	8	
21—30%	5	
over 30%	2	
B. Remitting Patients		(17 Patients)
Lymphocyte Count:		
Below 10%	0	
10—15%	0	
16—20%	0	
21—30%	11	
over 30%	6	

Table 9. UNFAVORABLE AND FAVORABLE RESPONSES RELATIVE TO LYMPHOCYTIC PROFILES AMONG CANCER PATIENTS

(a) **Unfavorable** — (untreated)

(1) Patient E.T., 33 yrs., F — Breast Cancer
Initial Counth — WBC — 17,000 **lymphos**—14 Eost-2
Su'bseq. Count — WBC — 19,000 **lymphos**— 7 Eos-0
Result: died

(2) Patient R.T., 40 yrs., M — Lung Cancer
Feb. 3, 1967 — WBC — 13,500 **lymphos** — 19 Eos-1
Feb. 14, 1967 — WBC — 25,000 **lymphos** — 9 Eos-1
Result: died

(b) **Favorable** — (With Immunotherapy)
Patient L.S., 36 yrs, F (Case 10) — Breast Cancer
Jan. 19, 1974 — WBC — 17,000 **lymphos** — 3 Eos-11
March 29, 1974— WBC — 17,000 **lymphos** — 25 Eos-35
atypical
(lymphos seen)

Result:
Dramatic Tumor
Dissolution, Alive

Table 10. COMPARISON BETWEEN SPECIFIC AND NON-SPECIFIC IMMUNOTHERAPY

Workers	No. of Patients	Survival Time	Survivors	%
Villasor	43	at 24 months	7	16.2
This Author	24	24—96 months	10	41.6
(do)	(do)	6—96 months (present survivors)	13	54.1

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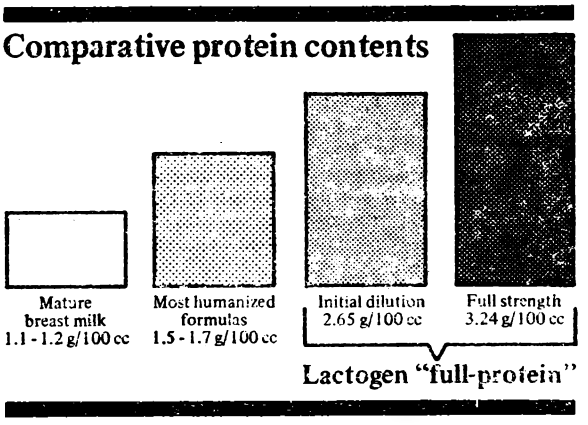

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NORTH AVENUE, Q.C.

Statement of Receipts & Disbursements
March 16—September 30, 1976
(With Comparative Figures for July August & September)

RECEIPTS	July, 1976		August, 1976		September, 1976		TOTAL March 16—Sept. 30 '76	
Journal								
Membership dues (₱10.00 share)	₱ 2,482.00		₱ 3,636.00		₱ 3,110.00		₱ 45,196.00	
Receivable collected-Advertisements —	—		—		7,750.00		25,900.00	
Dollar exchange rate differential	5,670.51		—		—		5,670.51	
Subscription income	84.74				1.50		720.44	
Postage cost refunded	———	₱ 8,237.25	———	₱ 3,636.00		₱10,861.50	161.82	₱ 77,648.77
Administration								
Affiliation fee-Specialty Society	₱ —		₱ 3,700.00		₱ 4,400.00		₱ 8,100.00	
Membership dues	11,630.00		15,526.00		13,202.00		192,188.30	
Registration fees (70% PMA Share)	—		—		—		39,305.00	
69th A.C. Commercial Exhibit income	9,100.00		2,100.00		1,400.00		34,720.00	
Interest income	10,913.30		2,721.48		1,760.00		28,912.27	
Miscellaneous	794.76	₱ 32,438.06	1,243.00	₱25,290.48	70.00	₱20,832.00	2,535.19	₱305,760.76
Other Receipts								
Membership dues (component society's share)	479.00		2,238.00		1,036.00		14,234.00	
Registration fees (30% host society's share)	—		—		—		16,845.00	
Commercial Exhibits (30% host society' share)	3,900.00		900.00		600.00		14,880.00	
Most Active District Award (donated by Dr. Jesus V. Tamesis	—		—		—		3,000.00	
Receivables-San Juan Project Physicians	—		—		—		795.00	
Advances Refunded	368.00		—		—		3,463.25	
Temporary deposit (Employees' SSS, Medicare, premiums deductions, etc.)	369.18		730.43		779.10		7,085.55	
Collections for host society (raffle tickets, etc.)	75.00	₱ 5,691.18		₱ 3,868.43		₱ 2,415.10	28,525.00	₱ 88,827.80

	July, 1976		August, 1976		September, 1976		TOTAL March 16–Sept. 30 '76	
Fund Receipts								
PMA Building Fund	₱ 2,656.00		₱ 5,630.10		₱ 600.00		₱ 39,587.60	
Matef & DBP Fund	36,027.23		24,052.85		20,014.47		281,699.09	
PMA-Physicians Fund	7,738.92		5,630.10		600.00		25,713.14	
PMA-Abbott Research Award Fund	—		—		9,000.00		23,500.00	
PMA-FAPHEPI Fund (Interest income)	—		—		—		3.48	
Narciso-Perez Fund	9,705.92		1,595.00		2,519.07		16,619.99	
PMA Medical Indigency Proj. Fund	—		600.00				600.00	
Calamity & Disaster Fund	—		535.00		25,020.00		25,555.00	
Medicine Week Fund (Interest income)	—		—		—		52.68	
PMA-Weight Reduction Fund interest income	—		—		—		12.00	
WMA Fund (Interest income)	414.58	₱ 56,536.65		₱38,043.05	629.13	₱58,382.67	1,043.71	₱414,386.69
		₱102,903.14		₱70,837.96		₱92,491.27		₱886,624.02
LESS-DISBURSEMENTS:								
Journal								
Salaries & honoraria			450.00		565.00		3,238.58	
Transportation expenses-clerks	26.35		28.70		90.95		356.50	
Postage, telegraph & delivery service	15.00		9.75		400.00		1,086.05	
Supplies	—		—		120.00		241.00	
Subscription refund	—		—		—		86.40	
Printing	—		20,640.08				43,918.96	
Emergency Allowance	50.00		50.00		50.00		350.00	
Miscellaneous	50.60	₱ 591.95	330.00	₱21,508.53	—	₱ 1,225.95	405,60	₱ 49,683.09
Administration								
Salaries	8,968.50		8,968.50		7,571.10		56,850.96	
Light, telephone & water	1,008.60		1,103.94		631.21		5,723.53	
Office supplies	1,895.90		1,667.11		2,268.90		10,748.57	
SSS, Medicare & ECC Contributions	542.15		542.15		610.75		3,220.30	
Postage, telegraph & delivery service	519.36		484.17		841.37		5,753.20	
Security service	961.76		989.70		961.76		5,946.26	
Auditing service	400.00		—		1,200.00		2,600.00	
P R O	—		1,000.00		1,000.00		2,000.00	
Legal services	—		—		—		125.00	
Expenses-Comelec	—		—		—		5,150.92	
Expenses-House of Delegates	4,498.53		2,942.44		2,419.80		27,057.14*	

*₱6,125.00 cost of office equipment included

	July, 1976		August, 1976		September, 1976		TOTAL March 16–Sept. 30 '76	
Expenses-69th Annual Convention	20.16		—		—		₱ 26,272.14	
Expenses-Medicine Week Celebrations	—		—		180.45		180.45	
Transportation expenses-Council	4,936.00		11,195.00		5,483.75		33,143.80	
Transportation expenses-Clerks	202.15		263.60		242.65		1,227.65	
Representation Allowance-President	1,717.05		1,674.04		800.32		4,191.41	
Representation Allowance-Pres-Elect			758.00				758.00	
Representation Allowance-Secretary	500.00		800.00		—		3,600.00	
Representation Allowance-Treasurer	—		500.00		-		2,000.00	
Representation Allowance-District Council	410.40		370.00				780.40	
Representation Allowance-Councilors-at-Large	200.00		182.00				382.00	
Gratuity pay	—		—		3,750.00		3,750.00	
Emergency Allowance	800.00		800.00		800.00		5,600.00	
Various expenses chargeable to prior period	—		—		—		16,056.77	
Miscellaneous	3,305.93		988.51		308.99		7,696.93	
Subscription-Newspaper	—		—		—		200.00	
Office Equipment	184.40		4,684.25		3,990.50		9,534.15	
Office & Building Maintenance	193.00		270.00		2,943.36		3,456.36	
Fire Insurance-Building	—		—		—		1,957.00	
Travel Insurance-Council	3,654.06		—		—		3,654.06	
Overtime & Emergency Labor	803.66		572.74		472.34		2,007.32	
Uniform Allowance-Personnnel	2,958.00		—		—		2,958.00	
Nutrition Project Social Concern	—		1,000.00		1,500.00		2,500.00	
Contribution to Narciso-Perez Fund	1,000.00	₱ 39,679.61		₱41,756.15		₱37,977.25	1,000.00	₱258,082.32
Other Disbursements								
Temporary deposits	50.00		35.00				2,483.59	
Salary Advances	—		—		2,000.00		2,000.00	
Employees' salary loan (SSS)	914.51		—		—		2,072.83	
Fund due to host society, 69th Annual Convention (Partial)	18,395.00		—		—		43,395.00	
Advances to host society-70th A.C.	—		—		—		5,000.00	
Advances for PMA Family Planning Project, WAPMA, etc	—		—		—		3,483.25	

	July, 1976		August, 1976		September, 1976		TOTAL March 16–Sept. 30 '76	
Component society's share in dues	—		—		58.00		265.00	
Registration fees refunded (4 life members)	—		—		—		140.00	
Membership dues refunded (double payment)	—		—		—		90.00	
SSS & Medicare contributions (employees share)	382.50	₱ 19,742.01	382.50	₱ 417.50	355.45	₱ 2,413.45	₱ 2,197.25	₱ 61,126.92
Fund Disbursements								
MATEF & DBP Fund	₱25,982.02		9,513.18		21,146.80		94,952.13	
Culture & Arts Project-Calamity & Disaster Fund	—		2,393.50		3,137.85		5,531.35	
PMA Abbott Research Award Fund	—		—		—		12,103.06	
PMA Medical Indigency Project Fund	—		—		120.00		120.00	
PMA Abbott Scientific Speakers fund	—		758.00		—		758.00	
Narciso-Perez Fund	4,000.00		9,000.00		—		13,000.00	
Most Active District Award Fund		₱ 29,982.02		₱21,664.68	3,000.00	₱27,404.65	₱ 3,000.00	₱129,464.54
Total Disbursements		₱ 89,995.59		₱85,346.86		₱69,021.30		₱498,356.87
EXCESS OF RECEIPTS OVER DISBURSEMENTS (Disbursements over Receipts)		12,907.55		(14,508.90)		23,469.97		388,267.15
Add-Fund Balance Beginning		1,701,758.87		1,714,666.42		1,700,157.52		1,335.360.34
TOTAL CASH (In Banks & On Hand & Short term investments) September 30, 1976		₱1,714,666.42		₱1,700,157.52		₱1,723,627.49		₱1,723,627.49

PHILIPPINE MEDICAL ASSOCIATION

North Avenue, Quezon City

Cash on Hand & In Banks & Short Term Investments
September 30, 1976

Petty Cash	₱ 300.00
Cash on Hand	4,027.99
CBTC-c/a (General Fund)	105,354.47
CBTC-s/a	1,749.90
PNB-s/a	3,622.95
CBTC-s/a	3,878.49
Bank of America — s/a	39,763.50*
CBTC-c/a (Matef & DBP Fund)	79,972.97
CBTC Time Deposit (Matef & DBP Fund)	38,302.99
Pasay City Rural Bank	20,000.00
Pasay City Development Bank-Time Deposit (Matef & DBP Fund)	23,497.11
FNCB-Time Deposit (Matef & DBP Fund)	32,850.00
CBTC-s/a (WMA Fund)	41,579 63
CBTC-s/a (PMA Building Fund)	22,460.00
CBTC-s/a (PMA Special Fund)	4,516.01
PNB-c/a (PMA Special Fund)	2,000.00
CBTC-s/a (Dr. Romeo Y. Atienza Memorial Fund)	4,000.00
CBTC-s/a(Narciso-Perez Fund)	3,619.99
CBTC-s/a (Culture & Arts Project Fund)	3,326.59
CBTC-s/a (PMA Medical Indigency Project Fund)	4,895.46
CBTC-s/a (Population Council Fund for Family Planning Project)	2,775.86
CBTC-s/a (PMA Medicine Week Celebration Fund)	3,062.17
CBTC-s/a (Weight Reduction Clinic Fund)	1,040.13
CBTC-s/a (PMA FAPHEPI FUND)	110.16
	₱446,706.37

Money market placements — Matef & DBP

	Issue Date	Maturity Date	Interest Rate		
FNCB P.N. No. 018574	8/ 4/76	11/ 4/76	13%	₱343,161.60	
FNCB P.N. No. 018533	7/27/76	10/26/76	13%	363,076.17	706,237.77

Money market placements — General Fund & PMA Physicians Fund

FNCB P.N. No.	8/ 4/76	10/ 4/76	12 1/2%	₱346,040.16	
FNCB P.N. No.	7/27/76	10/26/76	13%	₱224,643.19	570.683.35
					₱1,723,627.49

RESERVE FOR —

Matef & DBP Fund	900,384.52
WMA Fund	41,579.63
PMA Physicians' Fund	186,204.32
PMA Building Fund	165,804.26
PMA Special Fund	6,516.01
Dr. Romeo Y. Atienza Memorial Fund	4,000.00
Narciso-Perez Fund	3,619.99
Culture & Arts Project Fund	933.09
PMA Medical Indigency Project Fund	5,375.46
PMA Abbott Research Award Fund	11,396.94
PMA Abbott Scientific Speakers' Fund	6,538.36
PMA Medicine Week Celebrations fund	2,881.72
PMA Weight Reduction Clinic Fund	1,040.13
Calamity & Disaster Fund	22,417.15
Population Council of New York fund (for PMA Family Planning Forums & Seminars)	2,775.86
PMA FAPHEPI Fund	110.16
Journal Operating fund	90,136.07
General Operatin fund & other reserves	271,913.82
	₱1,723,627.49

*US $5,680.50 deposit recorded in the books at the conversion rate of ₱7.00 to U.S. $1.00.

HILARION C. DE DIOS, M.D.
National Treasurer

PREPARED BY:
(Sgd) JOSEFINA B. CRUZ
Accountant

Republic of the Philippines
Department of Public Works and Communications
BUREAU OF POSTS
Manila

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(Required by Act 2580)

The undersigned, HILARION C. DE DIOS, M.D., Business Manager of the JOURNAL OF THE PHILIPPINE MEDICAL ASSOCIATION (title of publication), published Bi-monthly (frequency of issue), in English (language in which printed), at Quezon City (office of publication), after having been duly sworn in accordance with law, hereby submits the following statement of ownership, management, circulation, etc., which is required by Act 2580, as amended by Commonwealth Act No. 201,

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Business Manager: HILARION C. DE DIOS, M.D.	North Avenue, Dil., Q.C.
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Total	10,200

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Business Manager

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