THE NOVA SCOTIA MEDICAL BULLETIN

The Scalpel and the Pen—Equal Partners

According to one encyclopedic source, a periodical differs from a newspaper in that, among other things, it purports to present views and opinions of its authors and editors instead of recounting current news. The obvious flaws in that definition notwithstanding, it does have a healthy ring of truth to it where the *Bulletin* is concerned.

True, the *Bulletin* does print what might be termed "information-as-news", but in many respects it is a journal of opinion—and learned opinion at that. Scientific contributions are, when all is said and done, the products of extrapolated opinion, and quite often blatantly state that certain observations have led the author or authors to a certain opinion. And our non-scientific articles are more often than not expressions of opinion in themselves.

Hopefully, the opinions expressed in the *Bulletin's* pages have a meaning and a value beyond that of Shakespeare's "brief shadow", and however much they may strut and fret it is equally to be hoped that the brief candle of their passing will fire the touchstone of opinion in others.

Today, more than ever, the medical community and society as a whole must learn not only to express opinion but to do so productively. It is a time when sane, reasoned, and even forceful comments on the Canadian condition are urgently needed.

It is a time when, as the economy shudders and confusion replaces hope, the too often unheard voices of reasonable men and women must be heard. Possibly it is a time when communities should stop looking for direction and turn toward supplying the seeds of that direction from within themselves.

Physicians, it has often been said, suffer from the isolation of their singular expertise. Their contribution to society and the demands of the profession have tended to block their peripheral vision and to have limited their awareness of broad concepts. While the *Bulletin* doesn't hold this to be true, the fact remains that the potential for leadership and direction in many professions and highly skilled employment catergories has, either through inertia or through imposed limitations, not been realized. Sadly, the smothered potential syndrome can, and possibly has, become a habit.

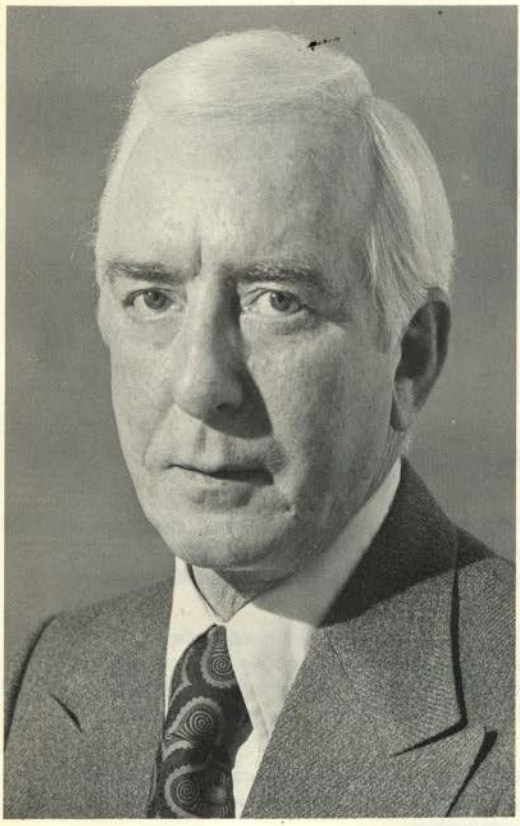
But, as we are prone to tell our patients, it is a habit which can be broken, and unless we are committed to the terminal implications of indifference it is a habit which must be broken.

Opinion — intelligent opinion — can help. A synthesis of many opinions can help even more. That's what the *Bulletin* is here for. Come to think of it, that's what you're here for. □

Dr. Thomas J. McKeough

PRESIDENT
1975-1976

The Medical Society of Nova Scotia



Thomas J. McKeough, M.D., president of The Medical Society of Nova Scotia, has had a distinguished career as a physician, a popular representative in Provincial Government, and as a Cabinet Minister and leader. Born in Sydney Mines, where he still makes his home, Dr. McKeough received his post-secondary education at St. Francis Xavier University, Dalhousie University and the Ottawa University Medical School. He has served as a member of the Sydney School Board and, following his election to the Provincial Legislature some fifteen years ago, successively assumed responsibility for the portfolios of Municipal Affairs, Labour, Trade and Industry, Finance and Economics and, once again, Labour. Currently, he is the official opposition's finance critic. He is married to Marie-Paul Mantha of Ottawa and has six children: Michel, Louise, Daniel, Brian Paul, Marcel and Denise. □

ATLANTIC PRIMER

Much had we suffered in the days of old,
To many grievous hurts become inured;
Down many a garden path have we been lured,
Which gleamed with Fool's and politican's gold.
Now as dumb sheep within our chosen fold,
By proclamation damned, by law secured,
We see the shears once more to be endured,
As by each new taxation we are fleeced,
Shorn naked by the bureaucratic beast.
Here truly should be vital lessons learned:
That Socialism is a dear bought thing;
That bees providing honey also sting;
That Indian gifts are oft' times soon returned,
And Freedom quickly spent, — though slowly earned.

J.W. Reid, M.D.

DOWN EAST ANTHEM

I'm never considered a gourmet,
Or skilled in the kitchen arts.
Nor yet made a tedious journey
For dishes of foreign parts.
The cod and the oyster delight me,
The lobster I place before lamb,
The scallop alone can requite
If I refuse beefsteak or ham.
Salt cod and pork scraps make me merry,
Fish chowder claim as my own,
The shad is old Neptune's best sherry,
With flavour that stands quite alone.
They say there are some who like turkey
That some have a preference for goose.
I take it their reason is murky
Or else they've a screw or two loose!
Though you sample the food of all nations
To the far archipelagoes
Still the best of all kitchen creations
Is salt herring and boiled potatoes.

J.W. Reid, M.D.

SHIP OF STATE

O Nation, no nation, where go you now?
Bedecked with red leaves from your stern to your bow,
Five pilots each trying with wind to o'erwhelm
The frail ship of state and take over the helm
And not one among them sufficiently able
To steer a true course or to keep the ship stable.
The crew of mixed races, discordant and hoarse
Implore the bold captain to alter his course
But the pilots declare that the only solution
Is no change of course but a new constitution.
While high salaried seafarers anxiously shout,
"She'll break on the rocks if she's not put about."
But the tax glutted Ship pops her seams down below,
Her response to the helm erratic and slow,
'til little by little she sinks at the stern —
O Nation, no nation, why don't you learn?

J. W. Reid, M.D.

CANADIAN TOY TESTING COUNCIL

The C.M.A. Council on Community Health reviewed pamphlets and a booklet published by the Canadian Toy Testing Council and believed that these would be useful in doctors' waiting rooms. Up to 25 copies of each pamphlet can be supplied free of charge to those interested. Requests should be sent to:

Mrs. MacFarlane
Canadian Toy Testing Council
P.O. Box 6014
Station "J"
Ottawa, Ontario K2A 1T1
Telephone: (613) 731-2822

Fucidin and Osteomyelitis*

C. E. van Rooyen,** M.D., FRCP(C), D. Petrie,*** M.D., FRCS(C),
B. J. S. Grogono,† M.B., FRCS(C), A. J. Buhr,†† M.D., FRCS(C),
and E. V. Haldane,††† M.D., FRCP(C),

Halifax, N.S.

INTRODUCTION

The antibiotic, Fucidin, manufactured in Copenhagen, Denmark, developed from the fungus *Fusidium coccineum* was isolated in 1953 by the Japanese mycologist, K. Tubaki, from a sample of monkey dung. Initial tests revealed that Fusidium strains were devoid of penicillinamidase activity. Subsequent testing showed them to possess anti-staphylococcal activity and this led to the production of fusidic acid. Although Fucidin has been extensively used in Continental Europe, Britain and elsewhere, it is not yet licensed for clinical use in Canada. Of necessity, our trials have been limited by availability and cost.

In accordance with the provisions of Section C 08.010 of the Food and Drug Act and Regulations of the Government of Canada, we have obtained sufficient Fucidin for the oral, intravenous and topical therapy of seven selected cases of chronic Staphylococcal osteomyelitis presenting unusually different management problems in orthopaedic surgery and infection control.

Although Fucidin exhibits potent antistaphylococcal activity, it has been emphasized that in order to avoid the development of resistance, Fucidin should be administered in combination with other antibiotics, to derive its maximum effect.

Case 1 P.M.F., age 37 leaped from the second floor of a burning building. He was admitted to hospital with a severe fracture of his pelvis; diastasis of the symphysis pubis and left sacro-iliac joint; comminuted fracture of the upper shaft of the left femur; an undisplaced fracture of the right os calcis and a minor vertebral injury.

He was treated by the insertion of a Steinman pin through the tibial tuberosity and placed in pelvic traction. Subsequently, open reduction and internal fixation with a blade plate were performed over a period of six weeks. During this interval he developed pneumonitis as a complication of smoke inhalation, and infection of the surgical wound site of the left thigh accompanied by osteomyelitis of the left tibia due to *Staphylococcus pyogenes.* He received a course of cloxacillin (Penbritin) and cephalothin (Keflin), but without response. On 17th December, Fucidin was administered by intravenous catheter through the right subclavian vein and he received 500 mg/q8h/5 days.

Response to therapy was good, wound discharge ceased and patient was able to start physiotherapy.

Case II. L.E.L. age 55, fractured his left humerus in 1968, after a pit accident, and was treated by open reduction and internal fixation. Treatment failed, and following several unsuccessful attempts at fixation, the condition resulted in non-union. Subsequently, a plating procedure at Toronto proved successful and union of the fracture resulted. Later, he developed osteomyelitis with a chronic draining sinus of the left arm, for which he received a lengthy course of antibiotic medication.

Organisms found to be present were *Staph.pyogenes* resistant to penicillin, *Pseudomonas aeruginosa* resistant to gentamicin plus several other antibiotics, and Alkaligenes species. These bacteria presented a difficult combination to overcome and it was decided first to eliminate *Ps.aeruginosa* with BB-K8 (A mikacin, Bristol) IV/500 mg/q6h/5 days, and q8h for a further 5 days. Secondly, to eliminate *Staph.pyogenes* with a course of Fucidin IV by the subclavian route, administering 500 mg//8h/10 days.

The patient made a good recovery, the wound became dry and no growth on culture was obtainable.

Case III. G.deW., Age 19. One and half years prior to admission, he was hit by a multiple wheel trailer tractor, which ran over his left foot. All the tarsal and metatarsal bones were crushed. He was treated at Burlington, Ont. and remained in hospital for some 3 months and successfully averted the amputation of his foot. Seen later at the Victoria General Hospital in Halifax, he showed osteomyelitis of the second metatarsal bone with moderate discharge. X-ray findings indicated an area of lucency, together with suggestion of avascular fragments or sequestra at the base of the second cuneiform bone.

Infection was due to a pure growth of *Staph. pyogenes.* Due to the multiplicity of antibiotics which the patient had previously received in hospital, it was not surprising to find that the strain of *Staph.pyogenes* isolated, was resistant to penicillin, tetracycline, streptomycin, erythromycin, chloramphenicol, lincomycin, kanamycin, polymyxin B and carbenicillin.

The following course of antibiotic therapy was employed. Cephalothin IV/1 gm/q6h/10 days; BB-K8 (Amikacin) IV/500 mg/q8h/10 days. This was followed by a second

*From the Depts. of Surgery and Microbiology, Victoria General and Camp Hill Hospitals, Halifax, N.S. (1975).
**Professor Emeritus, Dept. of Microbiology; Consultant, Dept. of Surgery, V.G.H.
***Assistant Professor, Dept. of Surgery, Division of Orthopaedics, V.G.H.
†Assistant Professor of Surgery, Chief of Orthopaedics, Halifax Infirmary.
††Assistant Professor of Surgery, Division of Orthopaedics, V.G.H.
†††Director, Dept. of Clinical Bacteriology, Pathology Dept., V.G.H.

course of antibiotics consisting of Fucidin IV by the subclavian route 500 mg/q8h/3 days, followed by oral therapy with Fucidin PO/250 mg/q8h/4 days, and clindamycin PO/150 mg/q8h/14 days. At the conclusion of treatment, the sinus had closed and purulent discharge had ceased. He still had some tenderness in his left foot, but is able to walk and hopes to return to his occupation as a truck driver.

Case IV. D.C.A., age 28, had suffered for many years from the adverse consequences of multiple birth defects.

At 6 months of age, she received remedial surgery for spina bifida and later a fragment of bone was removed from here right buttock area. Subsequently, she was provided with an ileal bladder. This was followed by a below right knee amputation and a tendon transplantation.

Ureteral and urethral obstruction also received appropriate surgical attention, and a slit urethra was effected to enhance drainage.

On admission to hospital in September 1974, she presented with a decubitus ulcer on the dorsum of her left foot with probable early involvement of infection in the underlying bone. Organisms grown on culture were *Staphylococcus pyogenes, Staphylococcus epidermidis, anaerobic Micrococcus, Streptococcus, Enterococcus, Proteus mirabilis, Pseudomonas aeruginosa* and *Candida albicans.* The patient was allergic to penicillin and in view of the numerous antibiotics she had previously received, she was placed on the following course of therapy in an effort to eliminate each organism seriatim. Gentamicin IV/40/q8h/12 days: tetracycline IV/350 mg/q12h/10 days followed by tobramycin (Nebcin, Lilly) IV/40 mg/q8h/14 days. Following use of these antibiotics, the growth of *Staph.epidermidis, Proteus mirabilis* and *Pseudomonas aeruginosa* ceased. *Candida albicans* and *Staph.pyogenes* still persisted and for these, she received 5-fluorocytosine (Ancobon — Roche) PO/500 mg/q8h/10 days. This was followed by Fucidin PO/250 mg/q8h/14 days, after which no further growth of *Staph.pyogenes* occurred. The ulcer had now healed sufficiently to enable a skin graft to be performed. The immediate prognosis was fair, but the long term function of the foot as a weight bearing area, warranted a guarded prognosis.

Case V. N.M. age 64, a diabetic, sustained a subtrochanteric fracture of the left hip in May 1974. This was treated surgically by internal fixation with a Richards screw and plate. Subsequently, the wound became infected and he developed osteomyelitis with a discharging sinus. Later, debridement of the wound, irrigation and suction, removal of the screw and plate and application of a spica cast were performed. The patient received an intensive course of antibiotic therapy and after a second debridement of the area in December 1974, healing was sufficiently advanced to permit closure and discharge home in April 1975. The infecting organism throughout his illness was *Staph.pyogenes,* resistant to penicillin, ampicillin and cloxacillin, and he received the following antibiotics — ampicillin, cloxacillin, clindamycin and vancomycin, but without response. On October 17, 1974, he was started on Fucidin PO/500 mg/q8h/10 days, followed by diethanolamide fusidate IV via the subclavian vein 500 mg/q8h/6 days — ampicillin IV/500 mg/q6h was given simultaneously. During the combined administration of Fucidin and ampicillin, there was marked improvement in the patient's condition. The hip sinus was also packed with repeated applications of Fucidin Gel.[2,3,4].

Case VI. C. S., age 59. Fell and fractured his left hip. He was treated by internal fixation with a Richards screw and plate. Four months later, X-ray examination revealed that the pin had become dislodged from the head of the femur. This was removed at a subsequent operation where a revision and Girdlestone arthroplasty were performed. Further treatment consisted of traction for 7 weeks plus suction drainage. Bacteriological examination of wound discharge showed the presence of Enterobacter, *B.proteus mirabilis; Pseudomanas* sp; *Achromobacter anitratum* and *Staphylococcus epidermidis.*

Antibiotic therapy consisted of Fucidin IV/50mg/q8h/9 days. Fucidin oral capsules 250 mg/q8h/10 days employed in combination with Gentamicin IV/80 mg/q8h/5 days, and Dalacin C, IV/150 mg/q8h/17 days.

The patient made a slow recovery and is now able to walk with the aid of crutches.

Case VII. This man, age 27, sustained an accidental self inflicted gun shot wound of his right shoulder, at point blank range, whilst duck hunting in a boat. He was treated by removal of the lead shot with surgical debridement of the wound, plus such repairs to traumatized tissues as were possible to effect at the time. For the next 8 years, he experienced intermittent pain, with breakdown of the injured tissues, accompanied by draining sinuses.

On admission to the V.G.H. x-ray examination revealed multiple foreign bodies surrounding the joint area, destruction of the shoulder articulation, partial destruction of the humeral head and its separation from the glenoid cavity. An old fracture through the neck of the humerus was also detected, with bony sequestrum in the area of the humeral head.

At operation, the draining sinus was excised from its base as it extended deep into the shoulder joint; also removed was some cartridge wadding, together with some fragments of fabric of a shirt or hunting jacket which he happened to be wearing 8 years ago. Having removed all visible foreign bodies, the humerus, acromion and glenoid were curretted and the joint cavity irrigated with bacitracin saline solution. The base of the sinus tract which had been directed through the shoulder joint was left open, but the fibrous tissue overlying its anteriorly was closed, as well as the deep tissues, to obliterate the dead space.

Bacteriological culture of wound discharge revealed the presence of *Bacillus bacteroides* and *Staph.pyogenes.* The following combination of antibiotics was selected for specific treatment.

Fucidin IV by subclavian route/500 mg/q8h/10 days.
Dalacin C - IV/150 mg/q6h/10 days.

Patient made a good recovery and he expressed his desire to go on another hunting trip.

DISCUSSION

The following description of Fucidin has been provided by the Manufacturers: "Fucidin (sodium fusidate B.P.) developed in 1962 by Leo research, is the most potent of the three steroid antibiotics (the other two being helvolic acid and cephalosporin P_1). It is chemically and biologically unique, being unrelated to any other antibiotic used in medical practice. The structure of Fucidin is fundamentally different from that of the hormonal steroids and there has been ample evidence during the past five years to show that Fucidin is devoid of demonstrable endocrine effects; indeed, no pattern of toxicity to any system has emerged during this period.

While Fucidin is active against a range of Gram-positive bacteria and Neisseria, interest has centred on its bactericidal effect on most strains of staphylococci, including those which are resistant to other antibiotics. It is widely distributed in the body and of particular significance are the concentrations found in relatively avascular tissues such as chronically inflamed bone, inflamed connective tissue and burn crusts".

Fucidin possesses ability to penetrate relatively avascular sites such as chronic inflamed bone. Likewise its ability to penetrate dead sequestra to produce concentrations greatly exceeding that requisite for inhibition of staphylococcal growth may render it a valuable agent in the therapy of Staphyloccal osteomyelitis.

After a daily dose of 3.0 grams per day for 6 days, the Fucidin concentrations in bone were found to vary from 3.4 to 14.9 μg/g.[5]. The presence of the drug in sequestra was of special interest.[6]

Administered by the oral route, Fucidin appears to be of relatively low toxicity.[7] Small amounts are excreted in urine and higher concentrations appear in bile and faeces when liver function is normal. A daily dose of 3 Gm for 7 days followed by reduced dosage for as long as 6 months, has been recommended.[8]

In selected cases diethanolamidefusidate can be given by the IV route, preferably into a wide bore vein with good blood supply. A total dose of 4 G per 24 hours should not be exceeded.

Possible adverse effects observed have been jaundice, venospasm and thrombophlebitis. Mild gastro-intestinal disturbance and occasional rashes have also been noted to occur. There is no evidence that its steroid nucleus may cause metabolic effects.[9]

Stewart (1964[10] reported that Fucidin concentrations of 4-8 μg/ml were detected in bone. Deodhar et al. (1972)[11] treated cases of osteo and rheumatoid arthristis with 0.75 or 1.5 gm of sodium fusidate daily for 3 to 7 days and observed concentrations of 7 μg/ml in aspirated synovial fluid. Fucidin is widely distributed throughout the body and is slowly excreted so that after doses of 3 G/day (40 mg/Kg) Saggers et al. (1968)[12] found that the plasma concentration rose to 45-200 μg/ml. Fucidin has been shown to be active against many penicillinase producing strains of Staphylococci, but the *in vitro* development of resistant mutants to Fucidin has been observed to occur. It has therefore been recommended by Waterworth (1963)[13] and Garrod, et al. (1973)[14] that Fucidin should be administered in combination with other antibiotics. We have followed this advice and have done so including combination with a newer antibiotic BB-K8 (Amikacin).[15]

The objective of this publication has been to report the use of this antibiotic in Canada, and to add that we consider that it may be a valuable adjunct to therapy in the cases studied. Due to restrictions imposed on access to larger supplies of the drug, we are unable to draw conclusions further than our limited data would permit.

SUMMARY

Seven cases of osteomyelitis presenting management problems in orthopaedic surgery and infection control, have been treated with Fucidin, employing the intravenous, oral and topical preparations, in combination with other antibiotics.

The results have been sufficiently encouraging to warrant more extensive trial of what appears to be a valuable antistaphylococcal antibiotic possessing properties which make it of special interest to the orthopaedic surgeon. □

References

1. **Roser H:** The resistance of Staph.aureus to Fucidin since 1970 compared to other effective antibacterial substances. *Munch. Med. Woch* **116:**1849, 1974.
2. **Ritchie IC:** Packing of abscess cavities. Lancet **2:**1211, 1973.
3. **Morris T:** Technique to improve the rate of healing of incised abscesses. *Lancet* **2:**1093, 1973.
4. **Franklin A, Calver RF:** Fusidic acid gel in the treatment of abscesses. *Practitioner* **212:**388, 1974.
5. **Hierholzer G, Knothe H, Rehn J, Koch F:** Fusidinsaure=Konzentrationen in chronisch entzündetem Gewebe. *Arzneimittelforschung* **16:**1949, 1966.
6. **Rowling DE:** Experience in the management of chronic osteomyelitis. Fifth International Congress of Chemotherapy, Vienna, June 1967.
7. **Barber M:** Toxicity of antibiotics other than penicillin. *Practitioner* **194:**37, 1965.
8. **Arens W, Thiele H:** Uber die Behandlung chronisch eitriger osteomyelitiden mit einem neuartigen Antibiotikum. *Fortschr Med:* **84,** 31, 1966.
9. **Wynn V:** Metabolic effects of the steroid antibiotic Fusidic acid. *Br Med J* **1:**1400, 1965.
10. **Stewart GT:** Steroid antibiotics. *Pharmacotherapia* **2:**137, 1964.
11. **Deodhar SD, Russell F, Dick WC, Nuri G, Buchanan WW:** Penetration of Sodium fusidate (Fucidin) in the synovial cavity. *Scand J Rheumatol* **1:**33, 1972.
12. **Saggers BA, Harwood Hf, Day BH:** Serum levels with sodium fusidate. *Brit J Clin Path* **32:**429, 1968.
13. **Waterworth PM:** Apparent synergy between penicillin and erythromycin or fusidic acid. *Clin Med Winnetka* **70:**941, 1963.
14. **Garrod LP, Lambert HP, O'Grady FO, Waterworth PM:** Antibiotics and chemotherapy. Churchill, Livingstone, London, p.201-205, 1973.
15. **Haldane EV, van Rooyen CE:** Proc. 9th International Congress of Chemotherapy. London, England, July 13-18, 1975.

INSURANCE PROGRAM

SOCIETY MEMBERS

EMPLOYEES OF SOCIETY MEMBERS

THE MEDICAL SOCIETY OF NOVA SCOTIA

THE NOVA SCOTIA DIVISION
OF
CANADIAN MEDICAL ASSOCIATION

For information on how your Society's insurance plans may be of benefit to you and your employees . . .

PLEASE TURN PAGE

MEDICAL SOCIETY INSURANCE PROGRAM

INSURANCE:
- — Life (Assignable & Convertible)
- — Long Term Disability & Partial Disability
- — Business Expense
- — Accidental Death & Dismemberment

LIFE INSURANCE: (Maximum Available $200,000.00)

Age	Annual Premium per $25,000.00
Under 31	$ 60.36
31-35	$ 70.80
36-40	$ 76.56
41-45	$ 98.04
46-50	$126.96
51-55	$199.68
56-60	$272.04
61-75	$421.92

Special Student Rates Available for $25,000.00

Under 31 $38.04 per year
31 & Over $41.88 per year

LONG TERM DISABILITY: (Lifetime for accident, age 65 for sickness)
(Maximum available $2,000.00 monthly, all sources)

ELIMINATION PERIODS

Age	15 Days	30 Days	60 Days	90 Days	180 Days
Under 31	$22.44	$18.72	$17.40	$16.08	$14.28
31-35	$23.88	$20.04	$18.60	$17.16	$15.24
36-40	$28.08	$23.54	$21.84	$20.16	$17.76
41-45	$35.52	$29.76	$27.60	$25.32	$22.56
46-50	$43.08	$36.00	$33.36	$30.72	$27.24
51-55	$50.88	$42.60	$39.48	$36.36	$32.16
56-60	$60.00	$50.16	$46.44	$42.72	$37.80
61-75	$69.84	$58.32	$54.00	$49.68	$43.92

INTERNES MAY APPLY FOR $750.00 AND RESIDENTS FOR $1,000.00, REGARDLESS OF INCOME

PARTIAL DISABILITY: (Maximum available $2,000.00 per month)
(Maximum six months coverage following full disability)

ANNUAL PREMIUM PER $50.00 MONTH COVERAGE:
$8.16 $6.48 $6.00 $5.52

BUSINESS EXPENSE: (Maximum available $2,000.00)

Age	Coverage For 12 Months	Coverage For 18 Months
Under 50	$18.00	$20.00
51-60	$27.00	$30.00
61-70	$36.00	$40.00

ACCIDENTAL DEATH & DISMEMBERMENT: (Maximum available $100,000.00)
(In conjunction with Long Term Disability)

$9.60 per year for each $10,000.00 unit of principal sum.

Local Anaesthetic Drugs
Some Pharmacology And Physiology

PART I

J. A. Smith,* M. D., F. R. C. P. (C),
Halifax, N. S.

Perhaps no class of drugs is as frequently administered directly by physicians and dentists as local anaesthetics. Considering the relatively low therapeutic ratio, surprisingly few adverse reactions apparently occur. In two articles, it is hoped to review some of the more important aspects of these drugs, including their toxicity , and the physiology relating to them.

NERVE CONDUCTION

In the resting state, the nerve fiber is like a cocked gun. Due to the sodium pump in the nerve membrane, an imbalance of ionic concentration exists between the interior and the exterior of the nerve fiber. Outside (interstitially) the $[Na^+]$ is 150 mEq; inside it is 15 mEq. Outside the $[K^+]$ is 5.5 mEq; inside it is 150 mEq. The sodium pump actively pumps Na^+ from inside the nerve fiber, and the nerve membrane is impervious to its passive return. This results in a deficit of positive ions inside the fiber, and K^+, assisted by the sodium pump, flows in to correct the electrical imbalance. The resulting high interior $[K^+]$ however, is somewhat diminished because of passive outward leakage of K^+ down the concentration gradient. This results in a net deficit electronegative (-50 to -70 mV) with relation to the outside. This is called the resting membrane potential.

Impulses generated in nerve cells inactivate the sodium pump, and make the membrane permeable to Na^+ and K^+ ions, which now move rapidly down their concentration gradients. As the ions move, a sudden reversal of polarity occurs at a critical point, the firing threshold, and the interior becomes electropositive ($^+$20 to $^+$40mV) in relation to the outside. That part of the neuron is now said to be depolarized and is refractory to further conduction until the sodium pump reestablishes the normal ion concentrations and polarity.

This "front" of electrical activity with the resulting internal electropositivity causes similar ion flows in the adjacent segment of neuron, causing electrical reversal, membrane permeability, and depolarization. Thus the wave of depolarization or "impulse" is conducted along a neuron.

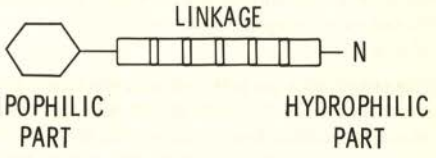
BLOCKING IMPULSE CONDUCTION

Blocking the conduction of an impulse in a nerve can be done in several ways. However, methods such as cutting the nerve and applying a physical toxin are not reversible, and methods such as altering the $[K^+]$ and $[Na^+]$ inside or outside the nerve are not possible. Many substances have been found to have the property of blocking impulse conduction in nerves in a completely reversible and non-toxic manner. The best of these are used as local anaesthetics. Their side effects are tolerably infrequent and usually not severe.

These agents, when present in sufficient concentration at the nerve membrane, prevent depolarization from occurring. They apparently act at certain binding sites on the nerve membrane, displacing Ca^{++} which is necessary for normal conduction. This prevents the attainment of the firing threshold and blocks the passage of Na^+ and K^+ down their concentration gradients, i.e., the whole sequence of depolarization.

RELATIONSHIP OF STRUCTURE TO ACTIVITY

Local anaesthetics have two keys components, one lipophilic and the other hydrophilic. They are connected by a chain of four or five carbon atoms. The lipophilic (aromatic) portion, a derivative of either para-amino benzoic acid or aniline, imparts fat soluble properties to the molecule. The hyprophilic portion, almost always a tertiary amine, imparts water solubility.

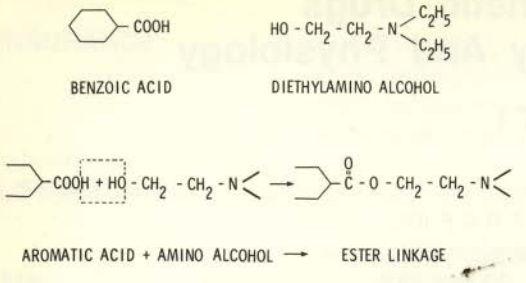


Basic Structure of Local Anaesthetic Molecule

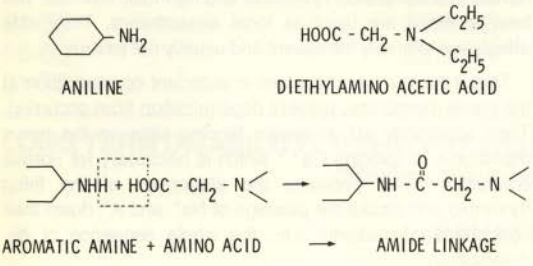
Various alterations in the structure are accompanied by alterations in potency, duration of action, solubility, and toxicity.

When the lipophilic radical is a derivitive of para-amino benzoic acid, it is connected to the intermediate chain via its hydroxyl (OH) tail forming an ester linkage.

*Lecturer, Department of Anaesthesia, Victoria General Hospital, Halifax, N. S.



Examples of ester linked local anaesthetics are procaine (Novocaine) and tetracaine (Pontocaine). When the lipophilic radical is an aniline derivitive, the linkage to the intermediate chain is via an amino group.



Examples of amide linked local anaesthetics are lidocaine (Xylocaine), mepivicaine (Carbocaine), bupivicaine (Marcaine) and prilocaine (Citanest).

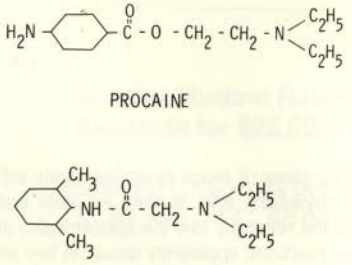
Alkalinization of local anaesthetics has long been known to speed the onset and increase the effectiveness. However, alkaline solutions are unstable and tend to precipitate. Conversely, acidification impairs effectiveness. This is probably the reason that local anaesthetics are less effective in inflamed areas (where the pH tends to be 5 to 6 rather than the normal 7.3).

Local anaesthetics are prepared as amine bases, but are packaged as the acid hydrochloride salt, with pH's of 6 to 7. As an acid salt (cation), they are stable. Acid and base forms, however, coexist and the relative amounts of each depends on the pH of the medium and the coefficient of dissociation (pK) of the particular local anaesthetic.

The pK's of local anaesthetics range from 7.9 for lidocaine to 8.9 for procaine. As a result, when the cation is injected into tissues with a pH of 7.3 to 7.4, the reaction moves to the right, and more base is formed.

It has been found that the base form diffuses much more readily in the tissues to the nerve membrane. There, however, the pH has been found to be a fairly constant 7.2, and the reaction moves to the left, forming more cation. The cation has been found to be the active form, the base form being necessary for the local anaesthetic to diffuse effectively to the site of action.

The site of action is the nerve membrane where it is exposed at the nodes of Ranvier. The nerve impulse jumps from node to node in myelinated nerves.



Example of Ester and Amide Linked Anaesthetics.

SYSTEMIC EFFECTS OF LOCAL ANAESTHETICS

Cardiovascular System

All local anaesthetics, except cocaine and perhaps mepivicaine, cause dilation of peripheral blood vessels, due to a direct smooth muscle relaxant effect. They facilitate their own absorption and shorten their duration of action. Circulating local anaesthetics also tend to lower peripheral resistance and the blood pressure.

Relative to the heart, local anaesthetics increase the refractory period, raise the vertricular excitation threshold, prolong the intracardiac conduction time, and lengthen the QRS interval. They also reduce the contractile force in a dose related fashion and reduce cardiac output. However, these effects are seldom evident or significant in usual clinical concentrations.

All local anaesthetics possess antiarrhythmic properties. Procaine is not useful because of its rapid destruction in the plasma. Lidocaine is the most useful and has the widest safety margin. It is used intravenously in an initial dose of 1-2 mg/kg in 30 seconds followed at a rate of 1 mg per minute. The half life of its cardiac effects is said to be 20 minutes.

Lidocaine is effective in about 85% of ventricular arrhythmias, but only in about 15% of supraventricular arrhythmias. Procainamide (Pronestyl) is more effective in the latter.

The mechanism of action is still somewhat obscure. In nontoxic concentrations, measurable electrophysiological changes are minimal. It alters or abolishes the phase of slow depolarization during diastole in Purkinje fibers, and shortens the duration of action potential and the effective refractory period. Conduction times are not consistantly altered. One might assume that local anaesthetics alter the phase of slow depolarization in other parts of the heart, thus tending to prevent ectopic stimuli from occurring, and when they do occur, tending to prevent their conduction.

Toxic doses exaggerate the effects of slowing conduction, reducing the force of contraction in the heart, reducing peripheral resistance and can produce cardiovascular collapse.

Central Nervous System

Local anaesthetics have interesting and apparently paradoxical effects on the central nervous system. Low doses are anticonvulsant, medium doses are sedative, high doses are convulsant, and extremely high doses are depressant. The mechanisms of these various effects are unclear, but the basic cause is probably a depressant effect.

As an anticonvulsant, approximately equal seizure protection is provided by 2mg/kg of lidocaine, 4mg/kg of mepivicaine, and 10mg/kg of pentobarbital. Lidocaine has the greatest therapeutic dose range between seizure protection and seizure induction. Lidocaine is effective in interrupting grand mal seizures in man, and is especially effective in cases of status epilepticus. The dose is 2-3mg/kg at a rate of 40-50mg/minute. A small dose of a barbiturate will greatly enhance the anticonvulsant property of local anaesthetics.

Slightly higher doses usually cause sedation, but can cause euphoria, excitement, amnesia, vertigo, anxiety, palpitations, tinnitis, diplopia, parasthesias, and flushing. Some of these may appear as premonitory signs of impending severe toxicity.

The most dramatic and dangerous complication of local anaesthetic use is the generalized clonic convulsion. It is seen when the blood level exceeds a certain minimum. Experimental evidence indicates that the initial disturbance is in the limbic system of subcortical and temporal nuclei, probably in the amygdala. If the dose of local anaesthetic is sufficient, the initial hyperactivity is not confined to the amygdala, but spreads to the cortex causing generalized seizures.

The disturbance in the amygdala has been shown to be very similar to that of temporal lobe or psychomotor epilepsy. The mechanism of action is probably not a stimulating effect by the local anaesthetic, but rather the depression of some small cells whose normal function is the inhibition of activity in the amygdala. Diazepam has been found to be quite effective in cases of temporal lobe epilepsy and has been found to be the most effective treatment for convulsions in the newborn, caused by transplacental mepivicaine.

Experimentally, a high plasma CO_2 tension enables seizures to be induced with lesser amounts of local anaesthetic. Conversely, a low CO_2 tension enables higher doses of local anaesthetics to be tolerated before seizures are induced. Thus, hyperventilation is indicated in subconvulsant or convulsant states. Seizures themselves are not thought to be directly harmful to the brain. Brain damage is a consequence of associated cardiovascular and respiratory depression resulting in hypotension and hypoxia. The arterial O_2 tension, for instance, regularly falls to 20mm/Hg in untreated grand mal seizures.

The doses of local anaesthetics given intravenously or for regional block result in blood levels which have no effect on axonal conduction in other peipheral nerves or in the spinal cord. They have, however, an inhibiting effect on poly- and mono-synaptic reflexes. There is also evidence that lidocaine, at least, has a depressant effect on a synaptic transmission in the brain stem. As evidence of this, intravenous lidocaine is a strong cough suppressant.

Other Organ Systems

Local anaesthetics have been shown to have ganglionic blocking activity, neuromuscular blocking activity, anticholinergic, antihistaminic, and antibacterial activity. None of these are reported when they are used alone. They can become significant when administered concurrently with other drugs which may compliment these effects. Local anaesthetics have been shown to depress the rate and force of contraction of uterine nuscle, but appear not to do so in normal clinical dosages.

In the next article will be covered the uptake, metabolism, excretion, and hypersensitivity, and toxicity related to local anaesthetics. □

ONE POINT OF VIEW

The economics of health is a curious discipline, somewhat in the tradition of the theology of indulgences which flourished before Luther. You can count what the friars collect, you can look at the temples they build, you can take part in the liturgies they indulge in, but you can only guess what the traffic in amnesties for purgatory does to the soul after death. Models developed to account for the rising willingness of tax-payers to foot rising medical bills provide similar scholatic guesswork about the new world-spanning church of medicine.

Medical Nemesis
The Expropriation of Health, 1975
Ivan Illich

Application for Participation in - THE CANADIAN MEDICAL ASSOCIATION RETIREMENT SAVINGS PLAN

I hereby apply to the Trustee for participation in the Canadian Medical Association Retirement Savings Plan, ("the Plan") the provisions of which are familiar to me. I understand that the Plan is sponsored by The Canadian Medical Association in conjunction with The National Life Assurance Company of Canada and The Royal Trust Company. I request that the instruments evidencing the terms of the Plan be registered as a Retirement Savings Plan under the Income Tax Act (Canada). I understand that as a consequence of such registration payments out of the Plan can only be made in the form of a life-contingency annuity or as a death benefit and that such payments to me or to my beneficiaries, executors or legal representatives will be subject to tax under the provisions of the Income Tax Act (Canada). However, I understand that I may deregister my Plan by amendment but in so doing I will be required to include in computing my income for a taxation year all amounts received by me in that year from my deregistered Plan.

I request that future contributions be apportioned to The National Life Assurance Company of Canada, Group Savings Policy No. G.A. 485 and to the Canadian Medical Association Investment Fund managed by The Royal Trust Company in the percentages as specified on the form below. I understand that this percentage allocation may subsequently be varied by written notice in accordance with the provisions of the Plan.

I understand that all premiums (contributions) made in the year or within 60 days after the end of the year are receiptable for income tax purposes subject to the amount of premium deductible as specified under the provisions of the Income Tax Act (Canada).

I undertake, upon request, to provide proof of age satisfactory to the issuer in respect of any annuity contracts provided to me as a benefit under these plans.

I hereby appoint The Canadian Medical Association to act as my Agent in the negotiation of contracts and agreements to carry out the provisions of the Plan.

If I am domiciled in the province of Quebec, I further request that my application be approved in accordance with the provisions of Order In Council No. 280 of the province of Quebec, with all consequences this involves.

Return to - THE CANADIAN MEDICAL ASSOCIATION – 1867 Alta Vista Dr., Ottawa, Ontario K1G 0G8

In order to take advantage of 1974 tax relief your contribution herewith must be in lump sum. Future contributions may be made monthly, quarterly, or annually and allocated to the Common Stock or Annuity Fund in the proportions you designate on each contribution date.

A statement of account recording your current and accumulated contributions will be mailed to you at the month end after your contribution is received.

C.M.A.R.S.P. APPLICATION

for office use only

Dr. / Mr. / Mrs. / Miss

NAME _____
(Family Name) (Given Names)

ADDRESS _____
No. & Street Apt. No.

_____
City Province

_____
Postal Code

DATE OF BIRTH ____ ____ ____ Day Month Year

Sex ☐ Male ☐ Female

Language Choice ☐ French ☐ English

SOCIAL INSURANCE NO. _____

BENEFICIARY _____
(Family Name) (Given Names)

RELATIONSHIP OF BENEFICIARY TO YOU _____

NOTE: In the event of your death, your benefits in the Insured Annuity Fund will accrue to the beneficiary named and may be used to purchase one of a variety of annuities. Your benefits in the Common Stock Fund are considered as part of your estate and disposition should be by your will. There are tax advantages in bequeathing these assets specifically to your spouse.

ALLOCATION OF CONTRIBUTIONS

Percentage of contributions to be invested in the Common Stock Fund (C.M.A.I.F.—Fund "A") ____ %
Percentage of contributions to be invested in the Short Term Deposit Fund ____ %
Percentage of contributions to be invested in the Insured Annuity Fund ____ %
TOTAL 100%

_____ _____
(WITNESS) (SIGNATURE OF APPLICANT)

DATE _____ PLEASE READ REVERSE SIDE

If you would like to receive information on the automatic contribution system - Pre-Authorized Payments Plan, please check this box ☐

If this application is being submitted by a C.M.A. member's spouse, please print your own name in full and indicate your own C.M.A.R.S.P. account number if you have an account.

NAME _____ C.M.A.R.S.P. No. 11-_____

DETACH AT PERFORATION AND MAIL COMPLETED APPLICATION TO MD MANAGEMENT LTD., 1867 ALTA VISTA DRIVE, OTTAWA, ONT. K1G 0G8.

WITH CMARSP AND CMARHOSP

The Canadian Medical Association Retirement Savings Plan

&

The Canadian Medical Association Registered Home Ownership Savings Plan

YOU SAVE ON TAXES AND COMMISSIONS

These two CMA sponsored tax deferred savings programs provide a number of options for members to save money and reduce taxes. You pay no sales commissions or other "loading" charges, but you still receive professional management of the money you invest.

IF YOU ACT BEFORE FEBRUARY 28
YOU CAN REDUCE YOUR 1975 TAXABLE INCOME BY $5,000*

A Reminder to Current Members

If you are one of the 13,000 plus CMA members enrolled in the Canadian Medical Association Retirement Savings Plan (CMARSP) this is a timely reminder to be sure to take full advantage of the deductions allowed from taxable income, even if you have to borrow to complete your 1975 contributions to CMARSP. Interest on money borrowed for contributions to a registered retirement savings plan is fully deductible from taxable income.

Your contributions can be allocated to the Common Stock Fund, the Short Term Deposit Fund or to the Insured Annuity Fund in what ever portions you wish. You may also open a CMARSP account for your spouse and thus take advantage of income splitting for lower taxes now and in the future. For more information contact CMA in Ottawa or your Provincial Branch.

CMARHOSP Offers Additional Tax Saving Opportunities

If you did not own a home in 1975 you can reduce your 1975 taxable income by an additional $1000 by investing in the Canadian Medical Association Registered Home Ownership Savings Plan. Funds accumulated in this Plan can be used to purchase a new home or furnishings for it, **or** they can be transferred to a registered retirement savings plan.

**Maximum allowable annual contributions: CMARSP $4000 – CMARHOSP $1000*

IT IS NOT TOO LATE TO ENROLL
IN EITHER OR BOTH THESE PLANS
APPLICATION FORMS ARE PROVIDED FOR YOUR CONVENIENCE

If you have yet to take advantage of the tax savings and sound investment management available to CMARSP and CMARHOSP members, now is the time to do so. For more details call or write Mr. R.P. Bannerman, Vice-President of MD Management at CMA House, Ottawa (613) 731-9331. Because of the limited time left to obtain 1975 tax relief through these plans, applications forms are provided on the preceding and following pages. Please fill in completely, including Social Insurance Number which is required to issue tax receipts. Please forward your personal cheque (separate cheques for each plan) together with your completed application form or forms to:

MD Management Limited
1867 Alta Vista Drive

FOR OFFICE USE ONLY

HOSP-S-052

THE CANADIAN MEDICAL ASSOCIATION
REGISTERED HOME OWNERSHIP SAVINGS PLAN

NAME Dr. / Mr. / Mrs. / Miss _____
(Family Name) (Given Names)

ADDRESS _____
No. & Street Apt. No.

_____
City Province

_____
Postal Code

DATE OF BIRTH ____ ____ ____
Day Month Year

Sex ☐ Male ☐ Female

Language Choice French ☐ English ☐

SOCIAL INSURANCE NO. _____

I hereby apply to The Royal Trust Company for a Canadian Medical Association Registered Home Ownership Savings Plan ("the Plan") in accordance with the terms of the Plan. I request that my plan be registered with the applicable taxation authorities.

I hereby declare:

1. that I am at least 18 years of age and of the age of majority in accordance with the applicable laws;
2. that I am a resident of Canada;
3. that I have not previously been a beneficiary of a registered home ownership savings plan;
4. that I do not own or have an interest in a partnership that owns, in either case whether jointly or otherwise, real property in Canada, any portion of which was used as a dwelling place by any individual at any time in the calendar year up to the date of this application.

I hereby authorize the Canadian Medical Association to act as my agent for the general administration and promotion of the Canadian Medical Association Home Ownership Savings Plan and I elect that my contributions shall be invested in the Canadian Medical Association Investment Fund in the following proportions.

(a) _____% to be invested in "A" units; (Common Stock Fund)

(b) _____% to be invested in "B" units; (Fixed Income Fund)

I agree that this investment direction shall apply to future contributions to the Plan unless and until by notification in writing I advise the Plan that subsequent contributions shall be invested in different proportions.

_____ _____
(WITNESS) (SIGNATURE OF APPLICANT)

DATE: _____

Local Anaesthetic Drugs
Some Pharmacology And Physiology

PART II

J.A. Smith,* M.D., F.R.C.P.(C),.

Halifax, N. S.

PREAMBLE

In the previous article, we reviewed the physiology of nerve conduction and how it may be blocked, the pharmacological nature of local anaesthetics, and some structure activity relationships.

We will now discuss the fate of local anaesthetics in the body, toxicity, and hypersensitivity.

UPTAKE AND DISTRIBUTION OF LOCAL ANAESTHETICS

Uptake of Local Anaesthetics

Local anaesthetics are absorbed from tissues in relation to the local vascularity and the vasodilating effect and dosage of the particular local anaesthetic. Resulting blood levels depend not only on the above, but also on the rate of inactivation and/or removal from the plasma.

Absorption can be slowed by the addition of adrenalin. This promotes local vasoconstriction and prolongs the duration of action. The optimum concentration of adrenalin is 1:200,000. Higher concentrations do not significantly improve vasoconstriction and increase the incidence of side effects from possible intravascular injection.

Except cocaine, all local anaesthetics are readily absorbed through intact mucous membranes — the rate depending on the vascularity. Blood levels following application of local anaesthetics to the laryngeal mucous membrane and mucous membranes that are inflamed may approach those attained through intravenous injection.

Distribution of Local Anaesthetics

Initially local anaesthetics in the blood are distributed disproportionately to the highly perfused organs. Redistribution begins immediately, as binding occurs with plasma proteins (chiefly albumin) and affinities of certain local anaesthetics for certain tissues make themselves felt. Bupivicaine (Marcaine) for example, is the most highly bound to plasma proteins. Lidocaine (Xylocaine) and mepivicaine (Carbocaine) have the greatest affinities for fatty tissue, liver, kidney, and brain. The destruction of procaine in the plasma is rapid, so high blood levels are unlikely.

Local anaesthetics also distribute themselves between the plasma and erythrocytes in specific ratios, varying for each agent. The ratios for each are proportional to the protein binding capacity. The degree of protein binding is related to the duration of action; bupivicaine being the longest acting local anaesthetic currently in use. Its presence in the blood is prolonged by being highly protein bound.

Organ Barriers

Local anaesthetics cross all organ barriers with relative ease. Blood-brain equilibrium after intravenous injection occurs in ten minutes. The placental barrier is crossed with ease. Lidocaine appears in the fetal blood in two to three minutes following maternal injection, and remains measurable for 45 minutes. Passage to the fetus is related to the degree of protein binding. Bupivicaine, being the most highly bound to protein in the maternal blood, will exhibit the lowest fetal — maternal ratio of blood levels.

The barrier presented by the dura of the spinal cord is more formidible, but there is evidence that local anaesthetics cross in some quantities, both via the nerve root sheaths following peridural injection, and via the blood stream. Following peridural injection, peak maternal blood levels occur in 20-40 minutes, in the fetus in 30-45 minutes. The lidocaine levels in infants born within 15 minutes of peridural injection average 50% that of the mother. Procaine is metabolized by the placenta and fetal blood levels seldom approach 50% of the maternal levels. Bupivicaine levels in the fetus average 20-30% those of the mother.

All local anaesthetics are not as highly bound to fetal protein as to maternal. It follows then that a dose that is partitioned between protein and plasma to yield non-toxic levels in the mother could produce toxic levels in the fetus.

Prilocaine (Citanest) crosses the placenta easily and fetal levels may approach or even exceed those of the mother. It is apparently poorly metabolized by the fetus, in contrast to lidocaine and mepivicaine.

Accumulation of Local Anaesthetics

Accumulation of local anaesthetics in the plasma and tissues depends on the rate of administration, absorption, inactivation, and excretion. The half life of lidocaine, for example, is about 90 minutes, and 45% of an injected dose is still unchanged in the body after two hours. Hence, accumulation can occur and the plasma level may be expected to rise with consecutive doses which exceed the removal rate.

*Lecturer, Department of Anaesthesia, Victoria General Hospital, Halifax, N.S.

A safe rate of administration seems to be 1 mg/min, but doses as high as 3.5 mg/min for five days have been reported without adverse effects. The maximum single dose of lidocaine into the tissues is 4-5 mg/kg.

The maximum single dose of bupivicaine is 150 mg. Not more than 400 mg in 24 hours should be given.

THE FATE OF LOCAL ANAESTHETICS IN THE BODY

The disposal of local anaesthetics by the body is related to the chemical structure. Those with an ester linkage (e.g. procaine, tetracaine) are destroyed chiefly in the plasma by pseudocholinesterase. Procaine is rapidly hydrolysed to form para-amine benzoic acid and diethylaminoalcohol. The former is excreted largely by the kidneys, the latter is further metabolized. Tetracaine is hydrolysed much more slowly. Since procaine and succinylcholine are both destroyed by pseudocholinesterase, prolonged effects of either may be expected when one is given in the presence of the other. No cases are reported, but people with absent, low, or atypical pseudocholinesterase might be expected to have a prolonged duration of action from procaine and other ester-linked local anaesthetics.

The amide linked local anaesthetics (lidocaine, mepivicaine, bupivicaine, prilocaine) are metabolized chiefly in the liver by enzymatic hydrolysis. Prilocaine is also metabolized to some extent in the kidneys. Several pathways of metabolism in the liver have been identified.

The stability and resistance of amide-linked local anaesthetics to non-enzymatic hydrolysis may be appreciated when one realizes that lidocaine, for example, is stable in the presence of strong acids and alkalis, and it can be boiled and autoclaved repeatedly without significant loss of potency.

Cocaine is eliminated almost entirely unchanged by the kidneys and about 10% of injected lidocaine appears in the urine unchanged. There is evidence that acidification of the urine aids excretion. There is also excretion of small amounts of local anaesthetics in the bile.

ADVERSE EFFECTS OF LOCAL ANAESTHETICS

We must distinguish between hypersensitivity and toxicity. Toxicity is related to the concentration in the blood. The higher it is and the longer it remains high, the more likely a toxic effect. Hypersensitivity is true allergy.

Hypersensitivity

Allergy is uncommon and is apparently limited to the ester linked local anaesthetics, especially procaine. Dermatitis, edema, urticaria, bronchospasm have all been reported. Cross allergies may exist between procaine and structurally related chlorprocaine, tetracaine, and procainamide.

A complicating factor is that the preservative methylparaben, usually added to local anaesthetic solutions, has also been shown to be allergenic. The parabens are also derivatives of para-amino benzoic acid (a component of all ester linked local anaesthetics) and are widely distributed in nature. So one can see not only that direct allergy to methylparaben is possible, but also a cross allergy to any ester linked compound, and all without apparent prior sensitization.

Contrary to popular belief, there is no documented case of allergy to the amide-linked local anaesthetics. Most occasional reports have not been properly investigated and could have been due to the preservative methylparaben or a reaction to sudden absorption of adrenalin, which is a common constituent of local anaesthetic solutions. DeJong states "hypersensitivity to lidocaine and related compounds is so rare as to be virtually negligible". It must be realized that anyone allergic to procaine could exhibit a cross allergy to amide-linked compounds containing methylparaben. For people with such possible allergies, the preparations of lidocaine and marcaine marked for epidural, and lidocaine for intravenous use should be chosen, since they do not contain methylparaben. Even with these agents, however, it is wise to do skin testing prior to use.

Cytotoxicity

There is no cyto- or histotoxicity caused by the usual doses and concentration of local anaesthetics. Reports of tissue reaction at injection sites are usually found to be due to infection or hematoma. In days past, tissue reaction could be caused by metallic ions (Cu, Ni, Zn) mobilized from metal syringes or medicine cups by the extra acidity imparted to the local anaesthetic by the adrenalin antioxidant sodium bisulphite.

Central Nervous System Toxicity

When excessive levels of local anaesthetic are reached in the blood, central nervous system toxicity occur with generalized convulsions. These have an abrupt onset, a violent character and have potentially serious consequences, apparently from associated hypoxia from respiratory and circulatory impairment.

The prevention of seizures is of prime importance although the rapid absorption of injected local anaesthetics is, at times, unavoidable, One can do no more than avoid direct intravenous injection, use the least amount of agent possible (milligrams, not milliliters), use a vasoconstrictor when possible, and have an intravenous running. It is difficult to administer oxygen, start an intravenous, and give drugs to a convulsing patient.

Some possible premonitory signs of an impending seizure have been mentioned (euphoria, excitement, anxiety, palpitations, tinnitis, diplopia, parasthesias, and flushing). At the first sign of these stop administering the local anaesthetic, give oxygen and ask the patient to hyperventilate, which will raise the seizure threshold. Premedication with diazepam may be beneficial as a preventive measure.

Treatment of Seizures

Seizures are usually brief due to rapid redistribution and removal of the local anaesthetic from the circulation. Proper resuscitation apparatus, oxygen and ambu bag, drugs, barbiturates, vasopressors and muscle relaxants, should always be available when local anaesthetics are administered.

Patients should be protected from self-injury, hypoxic or hypotensive injury by hyperventilating them with oxygen and using vasopressors. It may be necessary to use short-acting muscle relaxants to make adequate oxygenation possible.

Barbiturates remain the mainstay of therapy, but as little as possible should be given as there is evidence that their depressant effects are additive to those of local anaesthetics.

Cardiovascular Toxicity

Most investigators agree that cardiovascular collapse is always secondary to central nervous system and respiratory center depression. Treatment with oxygen, intravenous fluid, and vasopressors is indicated for cardio-vascular collapse.

Local Anaesthetics in Epileptics

There is no evidence that epileptics have greater sensitivity to local anaesthetics. Paradoxically, local anaesthetics may be used to terminate epileptic seizures.

Prilocaine

A unique kind of toxicity can occur with prilocaine. Excessive doses (more than 600 mg) can lead to the appearance of a dusky cyanosis. This is due to the formation of methemoglobin as a result of a break-down product (ortho-toluidine). The cyanosis appears more serious than it really is. Only 15% of the hemoglobin may be involved. The treatment is oxygen. □

References

1. **deJong, Rudolph H:** Physiology and Pharmacology of Local Anaesthesia; Springfield. Ill. Thomas, 1970.
2. **Covino, B. G:** Local Anaesthesia I; *N. Engl. J. Med.* **286:** 975-83, May 1972.
3. **Covino, B. G:** Local Anaesthesia II; *N. Engl. J. Med.* **286:** 1035-42, May 1972.

GUIDELINES FOR AUTHORS

Reference to these guidelines and recent issues of the Bulletin will help authors in preparation of their papers. Send the original typed copy to the Editor and keep a carbon copy.

The entire manuscript (including references and tables) should be typed double-spaced, with a generous margin on the left, on only one side of the pages. Do not underline unless the type is to be set in italics. Standard abbreviations (**e.g.,** hr, mg, ml) are acceptable without definition; less-common abbreviations should be written in full the first time they are used. Give generic as well as proprietary names and the manufacturer's name for drugs.

References. Identify references by numbers within the text, and list them in numerical order on a separate sheet [see (f)].

Figures. Provide an unmounted glossy print of each, clearly marked on the back with a SOFT marker, indicating top, figure no., and author's name. Show scale when relevant. Do not write legends on them [see (h)].

The usual framework of a paper is as given in (a) to (h) below, starting each section on a new page and numbering pages consecutively to the end of (h).

a) Front page, showing title, author(s) and degrees, whether the author is in family practice or the institution where the work was done, and address for correspondence.

b) Brief summary.

c) Introduction.

d) Materials and methods, then Results; **or** Case report.

e) Discussion.

f) References.
Examples: **Journal papers** — EBBERT, A., Jr. Two-way radio in medical education. J. Med. Educ. 38: 319-28, 1963. **Books** — MAJOR, R. H., and OELP, M. H. Physical Diagnosis, 6th ed. Philadelphia, Saunders, 1962, p. 51. **Contributions in books** — Voheer, H. Disorders of uterine function during pregnancy, labor, and puerperium. **In:** Pathophysiology of Gestation, ed. by N.S. Assali. New York, Academic Press, 1972, vol. 1, pp. 145-268.

g) Tables (each, including heading and footnotes, on a separate page).

h) Figure legends (all listed on one page); state magnification of photomicrographs.

Malignant Lumps in the Neck* (A Five Year Review in Nova Scotia)

M. Yousuf,** M.D. and G. M. Novotny,*** M.D.,

Halifax, N.S.

It is generally accepted that metastatic carcinoma in the neck nodes comprises the most prevalent source of a malignant cervical mass. The primary site, in most cases, is in the head and neck region. It is also agreed that primary thyroid cancer is the most frequent single source of malignancy in the neck.

Incidence

To assess the experience with malignant neck masses a survey of 130 admission records was done on patients who were followed in the Nova Scotia Tumour Clinic in the period from 1968-1972 inclusive. We did not include cases who presented with masses in the supra clavicular region representing metastatic nodal deposits from primary sites below the clavicle. Primary lymphoreticular tumours were also excluded.

Of 130 patients in this survey, 122 presented with metastatic cervical node deposits from primary carcinomas in the head and neck. In comparison, only 24 patients had a primary malignancy in the cervical region. Most of these latter cases also had metastatic cervical nodes at the time of initial presentation.

The primary sites in the head and neck region for the metastatic cervical lumps are shown In Table I. Majority of these metastases originated from the oral cavity, accounting for 74 cases, followed by hypopharynx and thyroid gland. Tonsillar fossa was the commonest individual primary site followed closely by piriform sinus, inferior alveolus, floor of the mouth, posterior third of the tongue, anterior two thirds of the tongue, and thyroid gland.

Of all the primary malignant tumours appearing as neck masses, thyroid neoplasms were the commonest, accounting for 15 cases, 7 of which presented with simultaneous cervical nodal metastatic deposits. (Table II)

We were particularly interested in the records of ten patients who came with metastatic neck masses from so called cryptic primary sites in the head and neck region. This represents about 8% in this series. In all, except one, of these cases the primary source of carcinoma was subsequently discovered either on thorough follow up examination or after histological examination of the excised surgical specimen in case of thyroid tumours. The distribution of these primary sites is shown in Table III. Seventy per cent of these resided

*From the Department of Otolaryngology, Dalhousie University, Halifax, N.S.

**Teaching Fellow, Department of Otolaryngology, Dalhousie University.

***Professor and Head, Department of Otolaryngology, Dalhousie University.

TABLE I

Distribution of head and neck primary lesions metastasizing to cervical lymph nodes

		TOTAL: 122
A. Oral Cavity	74	
Upper lip		0
Lower lip		6
Buccal mucosa		2
Superior alveolus		2
Inferior alveolus		11
Floor of mouth		11
Anterior $^{2}/_{3}$ Tongue		10
Posterior $^{1}/_{3}$ Tongue (and vallecula, and lingual surface of epiglottis)		11
Tonsillar Fossa		15
Palate		4
Minor Salivary glands		2
B. Nasopharynx	4	
C. Nose	1	
D. Hypopharynx	14	
Piriform Sinus		12
Post Cricoid		1
Posterior Pharyngeal Wall		1
E. Supraglottic Larynx	6	
Laryngeal Surface of Epiglottis		2
False Vocal Cord and Arytenoid		4
F. Glottic Larynx	7	
True Vocal Cords and Ant. Commissure		7
G. Subglottic Larynx	1	
H. Thyroid	10	
F. Major Salivary Glands	5	
Parotid		3
Submaxillary		2

TABLE II

Distibution of primary malignant tumours in the neck.

	TOTAL: 24
A. Thyroid	15
B. Parotid gland	4
C. Submaxillary gland	3
D. Miscellaneous	2
1) Embryonic mesenchymal	1
2) Malignant Thymoma	1

in the oropharynx, hypopharynx and nasopharynx, and the remaining 30% in the thyroid gland.

One patient also included in the above table presented with metastatic squamous cell carcinoma involving cervical lymph nodes, but he died during the initial hospital admission. The primary site in this case was strongly suspected to be in the nasopharynx but it was not confirmed either ante or post-mortem.

TABLE III

Distribution of "Cryptic" Primary Sites.

		TOTAL: 10
A. Oropharynx	2	
Tonsillar fossa		1
Base of Tongue		1
B. Hypopharynx	2	
Post-cricoid		1
Piriform Sinus		1
C. Nasopharynx	3	
D. Thyroid	3	

Management of cryptic primary head and neck carcinoma metastatic to cervical lymph nodes

Regarding the management of patients presenting with metastatic squamous cell carcinoma involving the cervical lymph nodes and arising from cryptic primary sites in the head and neck region, the opinion is divided whether to apply surgery or radiotherapy as the primary modality of treatment. The overall prognosis in these cases is uniformly grave but the proponents of both schools of thought claim to have achieved equally good results with their form of therapy.

In our survey, eight of the ten patients reviewed received full course cobalt therapy both to the primary and metastatic lesion, in dosage ranging from 5500 to 6000 rads. Two of these eight patients subsequently underwent radical neck dissection for persistence of metastatic cervical mass and one of these 8 patients received methotrexate therapy for palliation because of recurrent disease following cobalt therapy.

One patient, out of the ten cited, was treated by surgery alone (total thyroidectomy and radical neck dissection) for metastatic papillary carcinoma of the thyroid gland. The remaining one patient, who was detected to have the primary lesion in the base of the tongue, was treated by chemotherapy alone, using Bleomycin initially, followed by Methotrexate which was continued until his death. (Table IV).

Results of Therapy: Comments

The results of therapy in our survey are summarized in Tables V and VI. Two of the ten patients survived for four years or longer. One of these had presented with metastatic neck mass from a primary lesion in the tonsillar fossa, treated primarily with full course cobalt therapy with good tumour response and subsequently using palliative Methotrexate therapy for recurrence. The second patient, who is still alive, arrived with a neck mass metastatic from a small primary focus in the piriform sinus. He was treated with full course cobalt therapy followed by radical neck dissection.

One patient, who was found to have the primary lesion in the posterior third of the tongue, was treated with chemotherapy alone (Bleomycin and Methotrexate). There was minimal tumour regression but the patient lived for 40 months since the initial appearance of the neck mass.

Two patients with metastatic neck masses from papillary carcinoma of the thyroid are still alive for over three years since initial presentation. One of them received radiation therapy alone, while the other was treated by total thyroidectomy and radical neck dissection.

The third patient with the primary site in the thyroid gland (anaplastic carcinoma) was treated with cobalt therapy alone. There was minimal tumour response and the patient died 27 months later of asphyxia and inanition.

TABLE IV

Treatment used in patients who initially presented with metastatic neck masses from cryptic primary carcinoma in the head and neck region.

Primary Site	Full Course Radiotherapy	Surgery alone	Full Course Radiotherapy & Surgery (Radical Neck Dissection)	Full Course Radiotherapy & Chemotherapy	Chemotherapy alone
Tonsilar Fossa				1	
Base of Tongue					1
Post-cricold	1				
Piriform Sinus			1		
Naspharynx	2		1		
Thyroid	2	1			

TABLE V

Results of Therapy

Duration of Survival	Radiotherapy alone	Surgery alone	Radiotherapy & Surgery	Radiotherapy & Chemo-therapy	Chemotherapy alone	Total No. of Survivals
4 yrs. or more			1*	1		2
3-4 years	1*	1*			1	3
2-3 years	1					1
1-2 years	2					2
Less than 1 year	1	1				2

*Patient alive at the time of the survey.

TABLE VI

Patient survival as related to the site of cryptic primary lesion.

Primary Site	Total no. of Cases	4 yrs. or more	3-4 years	2-3 years	1-2 years	Less than 1 year
Tonsillar fossa	1	1				
Base of Tongue	1		1			
Piriform Sinus	1	1*				
Post-cricoid	1				1	
Naso-pharynx	3				1	2
Thyroid	3		2*	1		

*Patients alive at the time of the survey

Two patients lived for 15 months each. One was detected to have the primary cancer in the nasopharynx and the other in the post-cricoid region. Both patients were treated with radiotherapy alone.

One patient with suspected primary lesion in the nasopharynx metastatic to the neck was started on radiotherapy but he died during the course of the treatment, having lived for two and a half months since the neck mass was first noted.

From our survey it is evident that excluding the two cases of papillary carcinoma of the thyroid gland metastatic to the cervical lympth nodes, which is known to be associated with long survival, three of our remaining eight patients have survived for more than three years, carrying a crude survival rate of 38%. Metastatic disease from the nasopharynx carried the worst prognosis in our review and only one patient out of three survived for 15 months.

In comparison Marchetta et al[1] reported a four year cure rate of 39% in 33 such cases, where radiation therapy alone was used.

Barrie et al[2], however, reviewed a series of 123 such patients and reported an absolute survival rate of 31% for 3 years, 25% for 5 five years, 16% for ten years and 13% for 15 years. In their series, the metastatic neck disease was always treated by surgery (radical neck dissection).

SUMMARY

Metastatic nodal deposits in the neck, from head and neck primary sites, are the commonest source of malignant neck masses. Eight per cent of these masses in our survey initially

presented with cryptic primary sites which were eventually detected to be residing in the oropharynx, hypopharynx, nasopharynx or the thyroid gland. Radiotherapy was used as the primary modality of treatment in majority of these cases, with surgery reserved for the residual cervical disease and chemotherapy for palliation. Excluding thyroid papillary carcinoma metastatic to the cervical lymph nodes, 38% of the cases in this series have survived for more than three years. When nasopharynx was the site of the primary cancer, the outlook was uniformly grave. □

Acknowledgement

We wish to thank all members of the Nova Scotia tumour clinic who made the patient records available to us for making this study possible.

References

1. **Marchetta, F. C.** et al: Carcinoma of the neck. *The American Journal of Surgery,* **106:**976, 1963.
2. **Barrie, J. R. et al:** Cervical nodal metastasis of unknown origin. *The American Journal of Surgery,* **120:** 466, 1970.

Physician Self-Assessment

Lea C. Steeves, M.D.,

Halifax, N.S.

The following questions have been submitted by the Division of Continuing Medical Education, Dalhousie University, and are reprinted from The American College of Physicians **Medical Knowledge Self-Assessment Test No. 1** with the permission of Dr. E. C. Rosenow, Executive Vice-President.

It is our hope that stimulated by these small samplings of self-assessment presented you will wish to purchase a full programme.

DIRECTIONS: Each of the questions or incomplete statements below is followed by five suggested answers or completions. Select the ONE that is BEST in each case.

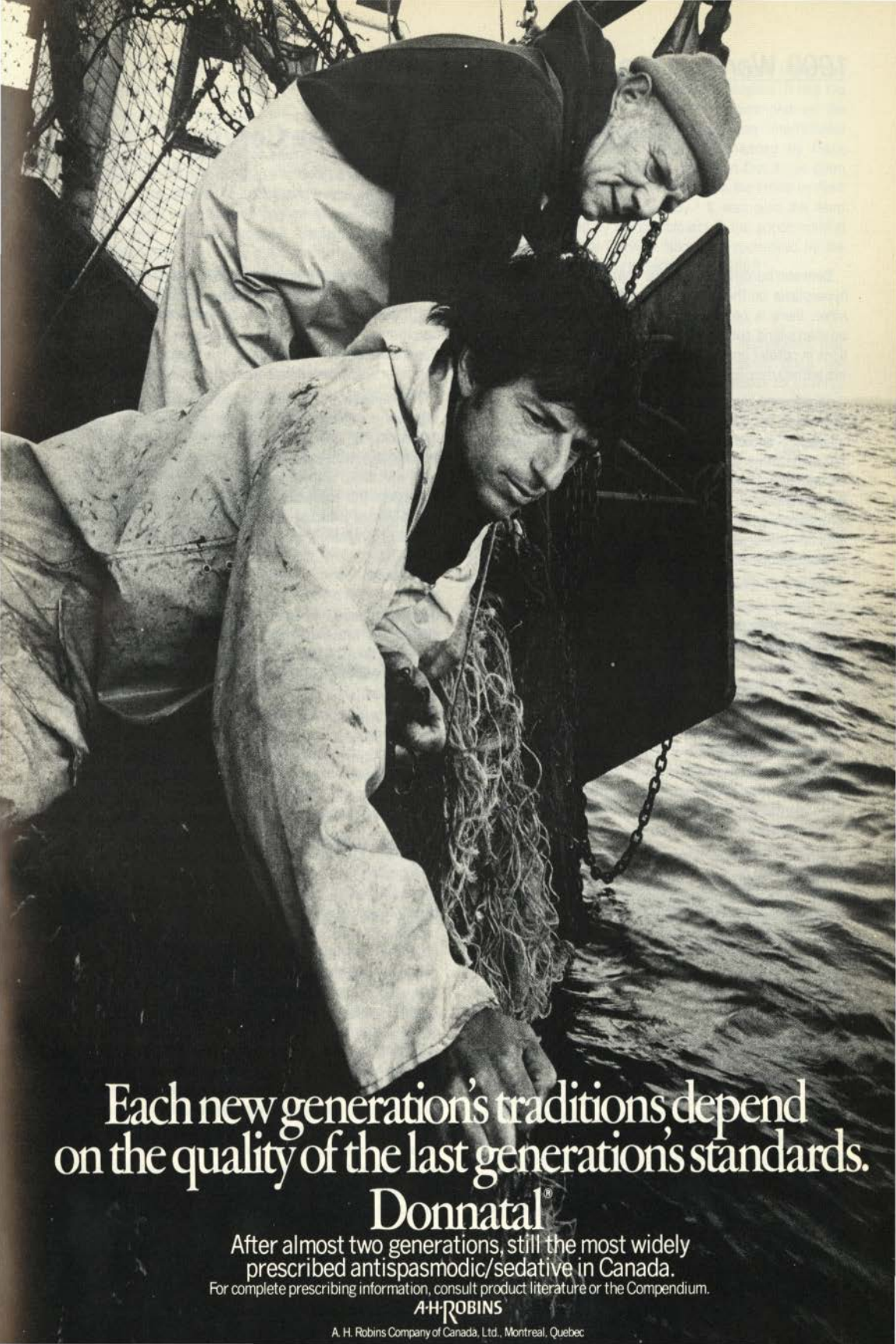
A 26-year-old Negro man complains of arthralgia and mild dyspnea on exertion. Physical examination shows hepatosplenomegaly, generalized lymphadenopathy, and bilateral iritis. Roentgenogram of the chest shows bilateral, symmetrical hilar adenopathy.

4. Which of the following is the most likely diagnosis?
   (a) Rheumatic fever
   (b) Rheumatoid arthritis
   (c) Sarcoidosis
   (d) Tuberculosis
   (e) Hodgkin's disease

5. Which of the following abnormal laboratory findings is most likely to be present?
   (a) High serum calcium
   (b) Low serum calcium
   (c) High serum magnesium
   (d) High serum phosphorus
   (e) Low serum phosphorus

6. Which of the following tests would most likely be positive?
   (a) Tuberculin skin test (PPD No. 2)
   (b) Alcohol tolerance test
   (c) Latex fixation test
   (d) Elevated antistreptolysin O titer
   (e) Kveim test

(Please turn to page 31 for answers) □



Each new generation's traditions depend on the quality of the last generation's standards.

Donnatal®

After almost two generations, still the most widely prescribed antispasmodic/sedative in Canada.

For complete prescribing information, consult product literature or the Compendium.

A·H·ROBINS

A. H. Robins Company of Canada, Ltd., Montreal, Quebec

Dysplastic Lesions of the Uterine Cervix

Ian Maxwell,* M.B., Ch.B., FRCP(C),
Halifax, N.S.

Between benign physiological changes of *metaplasia* and *hyperplasia* on the one hand and frank malignancy on the other, there is no simple, sharp dividing line, but rather a no-man's-land composed of an infinite gradation of aberrations in cellular growth patterns. These cellular abnormalities are termed *dysplasias.*

At one end the cytopathologist may be able, with a fair degree of confidence, to say " . . . almost certainly not malignant" and at the other ". . . almost certainly malignant" but in between he must weigh up the odds of these two probabilities, 10:1, 8:5, 1:3, and so forth. If there is not to be a communications gap, he must be able to pass this information on to the clinician. This was the intent of the original numerical classification introduced by George Papanicolaou almost 30 years ago.

Since that time increased experience with the technique and greatly increased knowledge of the significance of the various criteria described by Papanicolaou have resulted in considerable modification of the usual numbering scheme. In a nationwide survey, which I conducted some three years ago, 75% of the laboratories no longer employed it.

In Nova Scotia the situation was particularly unfortunate. In one large centre, a high proportion of smears, almost 80%, were reported as Class II, that is "Benign changes, not suggestive of malignancy", which added not a whit to the diagnostic value of the test, and many of the remainder had been consigned to a grabbag, peculiar to Nova Scotia, known as "class deferred".

DEFER, according to the dictionary, means "to adjourn, stave off, to delay to act, retard, postpone, to waste time by delay, to put off, procrastinate,"[1] and that is hardly the response which would be helpful to the concerned clinican or even one to be expected from the usually omniscient pathologist. Clearly we in Nova Scotia were at variance with the rest of the world and changes were long overdue.

DYSKARYOSES

But what to recommend? Cellular abnormalities lying in that borderland of atypia which bridges the gap between truly benign and frankly malignant were given the name *dyskaryosis* by Papanicolaou, from *dys* — abnormal, or disordered and *karyos* — a nut or nucleus. A dyskaryotic cell, then by definition is one which has a disorderly nucleus. Papanicolaou recognized various gradations of this condition from early changes in which the nucleus was simply enlarged and rather hyperchromatic to late or advanced dyskaryosis in which the nuclear changes were those indistinguishable from carcinoma. By and large, however, according to Papanicolaou, the cytoplasm of the dyskaryotic cells was normal enabling their differentiation from true cancer cells.

The situation proved, however, to be not quite so simple. It was soon realized that various gradations of parallel immaturity of the cytoplasm could be recognized. To describe these Papanicolaou used a comparison based on the cell they resembled most closely. In squamous epithelium the most mature cells lie on the surface until desquamated whereas the least mature are situated in the depths. To indicate increasing degrees of immaturity, and so of malignant propensity, Papanicolaou spoke of *superficial* dyskaryotic cells, *intermediate* dyskaryotic cells, and *parabasal* dyskaryotic cells to indicate the cytoplasmic type i.e. hypermature, immature, etc. Unfortunately this nomenclature was widely misinterpreted as representing a source oriented classification so that a superficial dyskaryotic cell was automatically considered to have originated superficially and a parabasal one, deeply. Although this might well sometimes have been the case, the malignant potentials of the reverse, i.e. a deeply arising so-called "superficial" dyskaryotic cell or a superficially placed "parabasal" one were infinitely more ominous and the term *dyskeratosis,* or abnormal keratin production, was soon adopted to indicate cytoplasmic abnormalities.

DYSKERATOSES

Regrettably, even the term dyskeratosis is fraught with problems. Not only, as with dyskaryosis, is it not part of the normal vocabulary of the clinician, and its import therefore possibly not quite clear to him, but also it has, quite properly from the semantic point of view, been applied to two completely different types of pathologic change. On one hand there are the *benign dyskeratoses* typified by the swollen, brightly eosinophilic cells of molluscum contagiosum or the *corps ronds* of Darier's disease, both of them packed with viral inclusion bodies; these conditions do not lead to any increased likelihood of subsequent carcinoma. The second group represent the *malignant* dyskeratoses seen for example in xeroderma pigmentosum, leukoplakia, solar keratosis, senile keratosis and the like, which may sometimes be indistinguishable from true carcinoma-in-situ and which unquestionably carry a greatly increased incidence of subsequent carcinoma developing in the same area. Some textbooks place erythroplasia of Queyrat and Bowen's

*Assistant Professor, Dept. of Pathology, Dalhousie University and Associate Director of Laboratories, Halifax Infirmary, Halifax, N.S.

disease in this category whereas others regard them as actual intraepithelial carcinomas.

Both varieties of dyskeratosis are represented in exfoliative cytology; the benign one in infections of various sorts, and the malignant variety, either arising *de novo,* preceding the development of carcinoma-in-situ by a variable period or deriving from the epithelium adjacent to in-situ or microinvasive carcinomas; representing prodromal evidence of the spread of the malignant process. Radiation changes in benign epithelium often show a similar picture. Nor is it by any means always possible to say where dyskaryosis and dyskeratosis end and *anaplasia,* that is reversion to a primitive undifferentiated state begins.

ANAPLASIAS

Even the word "anaplasia" is open to some misunderstanding. "The term anaplasia (distinct from anaplastic carcinoma) has no uniform interpretation. It is used by some to mean a primitive cell by others to indicate neoplastic character of the cell or lack of organization in a tumor. Popular usage has conferred a more specific meaning; that individual neoplastic cells . . . . have not replaced sufficient normal tissue to be regarded as an established progressive growth, a cancer."[2] Whether or not one agrees completely with this summation, any classification which is not able to discriminate, or even attempt to do so, between the various portions of the spectrum of atypias is really of little use. Furthermore, a classification based on nuclear or on cytoplasmic changes alone or one couched in technical jargon which is understood only by a cytopathologist would be of even less use.

Although some purists would prefer the precision and completeness provided by three or even five (mild, mild-to-moderate, moderate, moderate-to-severe, severe) divisions each of dyskaryosis and dyskeratosis and perhaps even of anaplasia (and there are indeed some laboratories which attempt something along these lines) to do so is to invite confusion in the mind of the referring physician who receives the report. Again, as indicated above, the really important feature is not so much the actual nuclear or cytoplasmic change *per se* although these are extremely important, but the combination of the two and, even more important still, the relationship of the individual abnormal cells to the neighboring cells in the tissue: in other words the degree of cellular disarray. Accordingly in Nova Scotia we have recommended the use of the more general term *dysplasia* i.e. abnormal formation, to include both nuclear and cytoplasmic changes and have proposed that three degrees of dysplasia be regularly catalogued, namely mild, moderate, and severe; though it is open to individual pathologists to further subdivide if they feel this is necessary to encompass as clearly as possible the various gradations referred to above.

DYSPLASIAS

The term dysplasia is not new to clinicians although perhaps more commonly encountered in other contexts, and it is preferable to the less specific word *atypia* which has been employed in the past by some cytologists. It has the paramount advantage that it was recommended as the preferred term for these changes by the international Committee for Histological Definitions headed by Hans Bettinger and James Reagan in 1961 and that it has been accepted ever since as the official term for the lesion by *Acta cytologica* since January 1, 1962.[3] It was also the term universally adopted by the participants in the epoch-making Conference on Early Cervical Neoplasia sponsored by the American Cancer Society in September, 1968.[4]

CLINICAL SIGNIFICANCE

For over 20 years pathologists have recognized that discovery of carcinoma-in-situ of the cervix does not necessarily indicate that the patient is about to develop invasive carcinoma and it is probably true that most clinicians now accept this fact. Even more so is it the case with dysplasia; in fact the natural history of mild dysplasia is almost invariably one of regression. This does not, however, hold true for either moderate or for severe dysplasia which not infrequently progress to intraepithelial carcinoma[5] or even direct to invasive carcinoma without ever passing through the stage of carcinoma-in-situ.[6] **Careful cytologic follow-up of all patients with any report of dysplasia particularly of moderate or severe degree is therefore mandatory.**

It is fairly generally agreed that a grading of **mild dysplasia** would imply *"Not malignant and probably not even pre-malignant. If there is infection, bring it under control and then send another smear. Check at least once a year unless you consistently receive normal reports in the future."*

On the other hand, a grading of **moderate dysplasia** would mean *"I do not think that this is malignant, but I could just possibly be mistaken particularly if this has been a poorly taken specimen or if I have been fooled into overrevaluating the part played by the infection which is also present in this slide. Anyway, infection or not, this patient is definitely a person at risk and she has at least a 50:50 chance of developing actual carcinoma-in-situ or invasive carcinoma within the next 10 years. Don't panic but you are strongly advised to clear up any infection and then send another slide, say in a month or two. If it clears up then an annual slide should suffice, but if you do not get a normal report then follow her every three to four months and if the condition does not improve, conization of the cervix should seriously be considered."*

A grading of **servere dysplasia** would imply, and I would so indicate myself within the constraints of the form, *"This is definitely a pre-malignant condition. I do not think it represents an actual carcinoma-in-situ but I regard it as the next stage to that condition. In the long run I would reckon that she stands an 80% chance of developing either intraepithelial or invasive carcinoma within the next five to ten years, perhaps sooner. On the other hand, the whole condition may clear up but I think this unlikely. If she wishes*

to have a family, she may want to carry on for awhile but if so watch her very closely indeed and carry out conization of the cervix before she becomes pregnant. Any infection present should be brought under control without delay and a repeat slide submitted. If you persistently get reports of this grade without any apparent remission wthin the next six months, then carry out a cone biopsy because there may be an occult carcinoma-in-situ close by."

This is a lot of mileage to expect from a simple, three category check-off form and a number of cytology laboratories eschew such forms and employ a free-style report on a blank page after the fashion of the usual tissue report. There are, however, many advantages to be gained by the use of a standardized layout and graded classification of changes, provided the meaning of the shorthand is understood both by the doctor issuing the report and by the one who receives it. Fortunately a telephone is always handy to clear up any misunderstanding. □

References

1. **Neilson, W.A.:** Webster's New International Dictionary. 2nd Ed. Springfield, Mass.: G & C Merriam Co., 1934.
2. Holland, J.F. and Frei, E: Cancer Medicine, Philadelphia: Lea & Febiger, 1973 pg. 115
3. **Editorial:** An International Agreement on Histological Terminology for the Lesions of the Uterine Cervix. *Acta cytol.* **6:** 235-6, 1962.
4. Proceedings of the Conference on Early Cervical Neoplasia. *Obstet. Gynec. Survey* **24:** 679-1048, 1969.
5. **Richart, R.M. and Barron, B.A.:** A Follow-up Study of Patients with Cervical Dysplasia *Am. J. Obstet. Gynec.* **105:** 386, 1969.
6. **Koss, L.G.:** Concept of Genesis and Development of Carcinoma of the *Cervix. Obstet. Gynec. Survey,* **24:** 850, 1969.

Retirement investment shouldn't be a shell game. Maritime Life lets you choose all three ways to security with one premium payment.

In today's financial climate your investment plans need to be flexible enough to adjust to changing conditions.

So what do you look for?

Well, first don't be taken in by a lot of smooth talk about tax savings and future security. Every registered retirement savings plan will give you that.

No, what you should look for is flexibility. Look for a plan that's flexible enough to meet your specific needs both today and in the future.

And that's where Maritime Life Assurance comes in. Of all the insurance companies Maritime Life doesn't lock you into a single investment format. In fact, our new Triflex Annuity Plan not only allows you your choice of three excellent investment vehicles, it also allows you to split your premium into the three funds in the proportions you choose.

So let's take a look at the three options.

Guaranteed Portion

Safe as the proverbial church. The percent of interest paid on your premium payment is fully guaranteed for five year terms. At the end of any term you can reinvest at the new guaranteed rate or move your money to another fund.

Property Fund

Premiums are invested in mortgages and property to provide a hedge against inflation while allowing you to benefit from the present real estate boom.

Growth Fund

An excellent investment in equities consisting of units of the Maritime Life Growth Fund. Although the exact results will depend entirely on the economy and the stock market, the investment policy of the fund is to achieve maximum long-term growth.

There are a lot of other big plusses with the Triflex Annuity Plan as well.

Like the fact that immediate cash values are available from the moment you enter the plan.

Like the flexible premium payment plans that don't tie you down to a contractual payment plan. Subject to minimums, payments can be made at any time.

Like the fact you can adjust your investment goals on any fifth policy anniversary and alter the proportions of your plan between the three funds.

If you're interested, just fill out the coupon below. We'll see that you receive full, detailed information on our new Triflex Annuity Plan.

The Maritime Life Assurance Company
P.O. Box 1030
Halifax, Nova Scotia B3J 2X5

Please send me more information on the new Triflex Annuity Plan.

Name

Address

City/Town

Province

Postal Code

TRIFLEX ANNUITY PLAN

A RETIREMENT ANNUITY PRODUCT OF

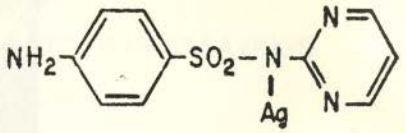
THE MARITIME LIFE ASSURANCE COMPANY

Head Office, Halifax, Nova Scotia

W.A. Parker,* Pharm.D.

SILVER SULFADIAZINE

(Flamazine® - Smith & Nephew Ltd)



Approved Indications

Topical therapy for the adjunctive treatment and prevention of infection in severe burns.

Pharmacology/Mechanism of Action

Silver sulfadiazine is a broad-spectrum antibacterial agent. It appears to inhibit DNA, RNA, and protein synthesis by binding to bacterial cell membranes and, to a lesser extent, the bacterial cell wall.[1] The silver has also been shown to bind to the bacterial DNA.[2] Unlike other sulfonamides, the action is bactericidal and is not inactivated by wound exudate or para-aminobenzoic acid.[3]

Biopharmaceutics

Relatively insoluble, silver sulfadiazine acts as a drug depot in the epithelium. The silver reacts extremely slowly with chloride, sulfhydryl compounds and protein in the wound to liberate sulfadiazine.[4] The silver remains in the exudate while the sulfadiazine is absorbed, usually below 10%, yielding blood levels in the 3-5 mg% range.[5] About 50% protein bound, the absorbed drug is rapidly cleared by the kidneys (15-40% inactive acetylated metabolite, 60-85% unchanged), and is actively reabsorbed (70%) by the renal tubules.[6] Impaired hepatic and/or renal function may result in increased systemic blood levels, especially following prolonged treatment of extensive burns. Sulfadiazine crosses the placenta and appears in the milk.

Toxicology

Topically applied, silver sulfadiazine has shown little evidence of toxicity following acute and chronic applications. Over-dosage, either topically or orally, has not been reported. Animal and human studies have failed to demonstrate teratogenic effects.

Summary of Clinical Trial Results

Clinically attainable concentrations of silver sulfadiazine have been show to inhibit the growth of various strains of *Enterobacter, Klebsiella, Escherichia coli, Proteus, Pseudomonas, Staphylococcus, Streptococcus,* and some strains of *Candida albicans.* The development of bacterial resistance and/or superinfection has been very low. Studies[5,7,8] have shown silver sulfadiazine to be as effective as silver nitrate or mafenide, but without the complications of staining, painful application, or electrolyte and acid-base disturbances. Because of decreased eschar autolysis, treatment should be combined with daily hydrotherapy and debridement.

Side Effects/Adverse Drug Reactions (ADR)

This compound is generally well tolerated. Less than 3% of patients experience local reactions, such as rash, pruritus, or a burning sensation. Sensitization has been reported at less than 0.25%, although cross-sensitivity with other sulfonamides is a possibility. Since significant amounts of the drug may be absorbed following prolonged treatment of extensive burns, all the adverse reactions attributable to systemic sulfonamide therapy are possible.

Drug Interactions/Laboratory Modifications

No consistent, clinically significant interactions have been reported.

Evaluation of Therapy

In favorable cases, epithelialization of second-degree burns is apparent after about 10 days.[1] Treatment should be continued until satisfactory healing has occured or until the burned site is ready for grafting.

Dosage/Administration

Following cleansing and debriding of the wound, the drug should be applied topically with a sterile gloved hand or spatula once or twice daily to a 1-5 mm thickness. More frequent applications may be made if required, and the wound may be dressed or left open. Concomitant daily hydrotherapy and debridement are recommended.

Application is **not** recommended to pregnant women at term nor to premature/newborn infants.

How Supplied/Drug Identification

Available for **hospital use only.** 1% w/w micronized silver sulfadiazine in a topical, water-miscible cream base.

Cost: $20.00 per 500 Gm wholesale. □

References*

1. **Ballin, J. C.:** Evaluation of a new topical agent for burn therapy —Silver sulfadiazine (Silvadene) *JAMA* **230-8:** 1184-85, 1974

*Detailed bibliography available from Dr. W. A. Parker, Dalhousie University College of Pharmacy, Halifax, N.S.

*Assistant Professor of Pharmacy, Dalhousie University, Halifax, N.S.

2. **Fox, C. L.:** Silver chelates of nitrogenous bases and effect on structure and function of microbial DNA. *Fed Proc* **28:** 362, 1969

3. **Fox, C. L. et al:** Antibacterial action of silver sulfadiazine and DNA binding, 133-38 International Congress on Research in Burns, Prague, 1970. Huber, Bern 1971

4. **Moncrief, J. A.:** Burns *N Engl J Med* **288:** 444-454, 1973

5. **Baxter, C. R.:** Topical use of 1.0% silver sulfadiazine 217-25 Contemporary Burn Management, Polk, h. C. et al Little Brown and Company, Boston, 1971

6. **Goodman, L. S. et al:** The Pharmacological Basis of Therapeutics, 1186-87, Collier-MacMillan, Toronto 1970

7. **Stanford, W. et al:** Clinical experience with silver sulfadiazine, a new topical agent for control of *Pseudomonas* infections in Burns *J. Trauma* **9:** 377-88 1969

8. **Fox, C. L.:** Silver sulfadiazine-a new topical therapy for *pseudomonas* in burns *Arch Surg* **96:** 184-88 1968

NO SMOKING

Once again there is a tip-in which may be easily removed for use as a poster in a place of your choice.

The Society's Drug and Alcohol Abuse Committee appreciates your co-operation in the Medical Profession's anti-smoking campaign.

Correspondence

To the Editor:

As a regular reader of the publications of the provincial Divisions of the C.M.A., I nominate the Nova Scotia Medical Bulletin as the best. Although long delayed in the mail, your August-October issue 1975 is a case in point. The writings of the late Jim Reid set the tone and one does not have to be a Senior Citizen to appreciate the merits of the symposium on geriatrics.

Back injuries, medical women, smallpox, obituaries, Around the Willow Tree, gardening — I read them all with interest. Without offence to Dr. McQueen, a metric illiterate must confess that the S.I. Units was difficult to comprehend and I'll reserve for future perusal the Constitution and By-Laws of the Society.

Permit me to congratulate you on the excellence of your Bulletin.

Yours,

A.D. Kelly, O.C., M.B., D.Sc., L L.D.
5 Edmund Gate
Toronto, Canada
M4V 2M1 □

NEW MEMBERS

The Physicians listed below have joined The Medical Society of Nova Scotia between November 1, 1975 and January 31, 1976. A most cordial welcome is extended by the Society.

Dr. Ian H. Anderson	Digby, N.S.
Dr. John M. Archibald	Sydney, N.S.
Dr. L. William Caines	Halifax, N.S.
Dr. Allan D. Cohen	Halifax, N.S.
Dr. Ivan A. A. DeCoutere	Dartmouth, N.S.
Dr. Roland J. Genge	Baddeck, N.S.
Dr. J. David Gordon	Digby, N.S.
Dr. John A. Hynes	Kentville, N.S.
Dr. Peter H. Jeffrey	Shelburne, N.S.
Dr. Kamla Kishan	New Minas, N.S.
Dr. Liam L. McKeough	Sydney, N.S.
Dr. Christopher B. MacNamara	Cheticamp, N.S.
Dr. Annada Pandey	Sydney, N.S.
Dr. P. Michael Reardon	Halifax, N.S.
Dr. Michael D. Riding	Halifax, N.S.
Dr. Thomas W. Shaw	Kentville, N.S.
Dr. Wing-Hei Tam	Truro, N.S.
Dr. Robert J. Wedel	Halifax, N.S.
Dr. Peter R. White	Sydney, N.S.

Personal Interest Notes

NEW APPOINTMENTS AND SERVICES*

Izaak Walton Killam Hospital for Children

Early in 1976 a new service to family physicians will be inaugurated as part of the Regional Pediatric Services of the Izaak Walton Killam Hospital for Children. This will consist of a monthly newsletter which will be mailed without charge to every family physician in the province. The newsletter is designed to be of immediate practical value to all physicians who care for infants and children. The entire publication will be readable in a matter of minutes, and will include such features as:

1) Practical guides to appropriate uses of medication in children.
2) Common misconceptions in pediatric care.
3) Advances in pediatrics that are of practical value to the family physician.
4) A "Question and Answer" section in which questions from community physicians on pediatric topics will be answered.
5) News and announcements: Information concerning new services available to children, new appointments, etc., with emphasis on services available outside the Halifax-Dartmouth area.

Regional Pediatric Care Program

This unique, provincially-sponsored program is designed to improve both preventive and therapeutic health care of children throughout Nova Scotia within their own communities. Coordinator of the program is **Sister Nuala Kenny, M.D.,** and the project has received the enthusiastic endorsement of The Medical Society of Nova Scotia, as well as that of the Nova Scotia College of Family Practice and the Nova Scotia Council of Health.

The program permits a highly-trained pediatrician (Dr. Kenny) to visit any community or region of the province that officially requests her services, either through the local branch of the Society or the community hospital. Dr. Kenny will spend significant periods of time, e.g. one month or longer, working with health care professionals to improve the quality of care for infants and children in the community.

Several features of the program deserve emphasis: First, participation is only at the request of the physicians and/or hospital of the community. Second, there is no charge for any of the services. Third, it is considered essential that the program should help strengthen or establish only those services that can continue to be sustained by the community itself.

Services offered include audits of pediatric hospital practices; assessment of pediatric needs of the community; working with physicians and public health nurses to improve immunization practices and other preventive services such as pre-school screening for vision and hearing defects; pediatric consultation with individual physicians in their offices or in hospital; substitution for local pediatricians who wish to spend brief periods in post-graduate study; the improvement of care for children with complex or chronic illness within their own communities; and improvement of liaison and collaboration with the staff and services of the Izaak Walton Killam Hospital for Children. A major objective is to reduce unnecessary travel by patient to Halifax, and thereby to cut financial and emotional costs to many families.

Ultimately, it is hoped that the program will encourage highly qualified pediatric consultants to settle in the many areas of the province which currently offer no such consultant personnel, but where the population base is more than adequate to support such services.

Although the program has only begun, the response of physicians and hospitals throughout the province has been overwhelmingly enthusiastic. Already, Dr. Kenny has been invited to visit Bridgewater, Liverpool, Digby, the Annapolis Valley, Yarmouth and New Glasgow and has made preliminary visits to several of these communities. She will spend the month of November in the New Glasgow area.

New Appointments

Dr. Barry J. Bergen has been appointed Lecturer in the Department of Pediatrics and a member of the full-time Active Medical Staff of the Izaak Walton Killam Hospital for Children.

A Manitoban by birth, Dr. Bergen is a pediatric neurologist who graduated in Medicine from the University of Manitoba in 1967. Following internship and pediatric residency in Minnesota (Mayo Clinic) and the Childrens Hospital in Winnipeg, he spent the period 1972-75 training in pediatric neurology at the University of Minnesota. In addition to his experience in pediatric neurology, Dr. Bergen is also trained in electroencephalography and electromyography.

Dr. Bergen's appointment represents part of a program to strengthen both teaching and service in pediatric neurology in the Maritime region. Until his appointment, Dr. John Tibbles had been the sole pediatric neurologist in the three Maritime provinces.

In January, 1976, Drs. Tibbles and Bergen will be joined by another new appointee in pediatric neurology, **Dr. Jean Gibson.** Dr. Gibson is a Dalhousie graduate, fully trained in both pediatrics and neurology through both the Dalhousie and McGill programs. Under her guidance it is planned to establish a new Child Development Clinic at the Izaak Walton Killam Hospital for Children. The purpose of this Clinic is to institute a highly efficient system for the rapid investigation of

*From the Department of Pediatrics, Dalhousie University, Halifax, N.S.

children with developmental delays, leading to a comprehensive management plan which can be carried on as much as possible within the child's own community. The clinic will bring together specialists in pediatrics, neurology, genetics, psychology, education, physio- and occupational therapy, so that families will have the opportunity of meeting all the appropriate consultants at one time and so that a system of comprehensive management and follow-up of such children can be maintained.

Dr. Maurice A. Nanton, a pediatric cardiologist, has joined the Department of Pediatrics and the full-time staff of the Izaak Walton Killam Hospital for Children. Dr. Nanton is a 1964 medical graduate of Leeds University. His early training in England was chiefly in Internal Medicine and Cardiology. He came to Canada in 1973 and became a Research Fellow in Cardiology at the Hospital for Sick Children, Toronto, a post he held for two years until moving to Halifax.

Dr. Nanton joins Dr. Douglas L. Roy in the Department of Cardiology at the Izaak Walton Killam Hospital for Children, and brings with him an extensive experience in clinical cardiology, cardiac catheterization and echocardiography.

Dr. Sonia Salisbury joined the Department of Pediatrics with the rank of Assistant Professor in October, 1975, as pediatric endocrinologist at the Izaak Walton Killam Hospital for Children. She holds a joint appointment in the Department of Medicine.

Dr. Salisbury grauated in medicine from McGill in 1959 with a distinguished academic record. She held a Medical Research Council Fellowship from 1964-67 and did graduate training in endocrinology at The Middlesex Hospital, London; and New England Medical Center Hospitals, Boston; The Beth Israel Hospital, Boston; and the Royal Victoria Hospital in Montreal. She is a Canadian authority in the field of thyroid disease, and has authored numerous publications on this subject.

In addition to her undergraduate and postgraduate teaching responsibilities in endocrinology, Dr. Salisbury will be supervising the Endocrine Clinic and the Clinical Investigation Unit at the I.W.K. Hospital for Children. She will also be investigating the feasability of establishing a newborn screening program for congenital hypothyroidism for all infants born in the province.

The J. J. Carroll House for Senior Citizens has been opened in Antigonish, N.S. It has been named to honor **Dr. James J. Carroll** (Dal./24). He has practised in Antigonish since 1930. Dr. Carroll has also been honored by his fellow practitioners in 1972 with an Honorary membership in The Medical Society of Nova Scotia. He was awarded an honorary doctorate of laws by St. Francis Xavier University in 1973 and was named the Senior Doctor of the Year in Nova Scotia by the Canadian Medical Association in 1973.

Tribute was paid to **Dr. Arthur Hines** on the occasion of his 84th birthday on Nov. 1, 1975 by the community of Cheverie, N.S., and his former patients. As well as his dedicated service in medicine he took an active interest in community affairs. According to his many friends, he made the term "Country Doctor" come alive with true meaning.*

Dr. R. Wayne Putman (Dal./69) has been named Assistant Director of the Division of Continuing Medical Education, Faculty of Medicine, Dalhousie University. A native of Truro, N.S., he practiced in Fredericton, N.B., for six years before accepting this post and a lectureship with the Division of Family Medicine. □

**As this issue goes to press, we have learned that Dr. Hines passed away on January 27, 1976. Our sympathy is extended to his family.*

Physician Self-Assessment

Question No. 4	Correct Answer C
Question No. 5	Correct Answer A
Question No. 6	Correct Answer E

ADVERTISERS' INDEX