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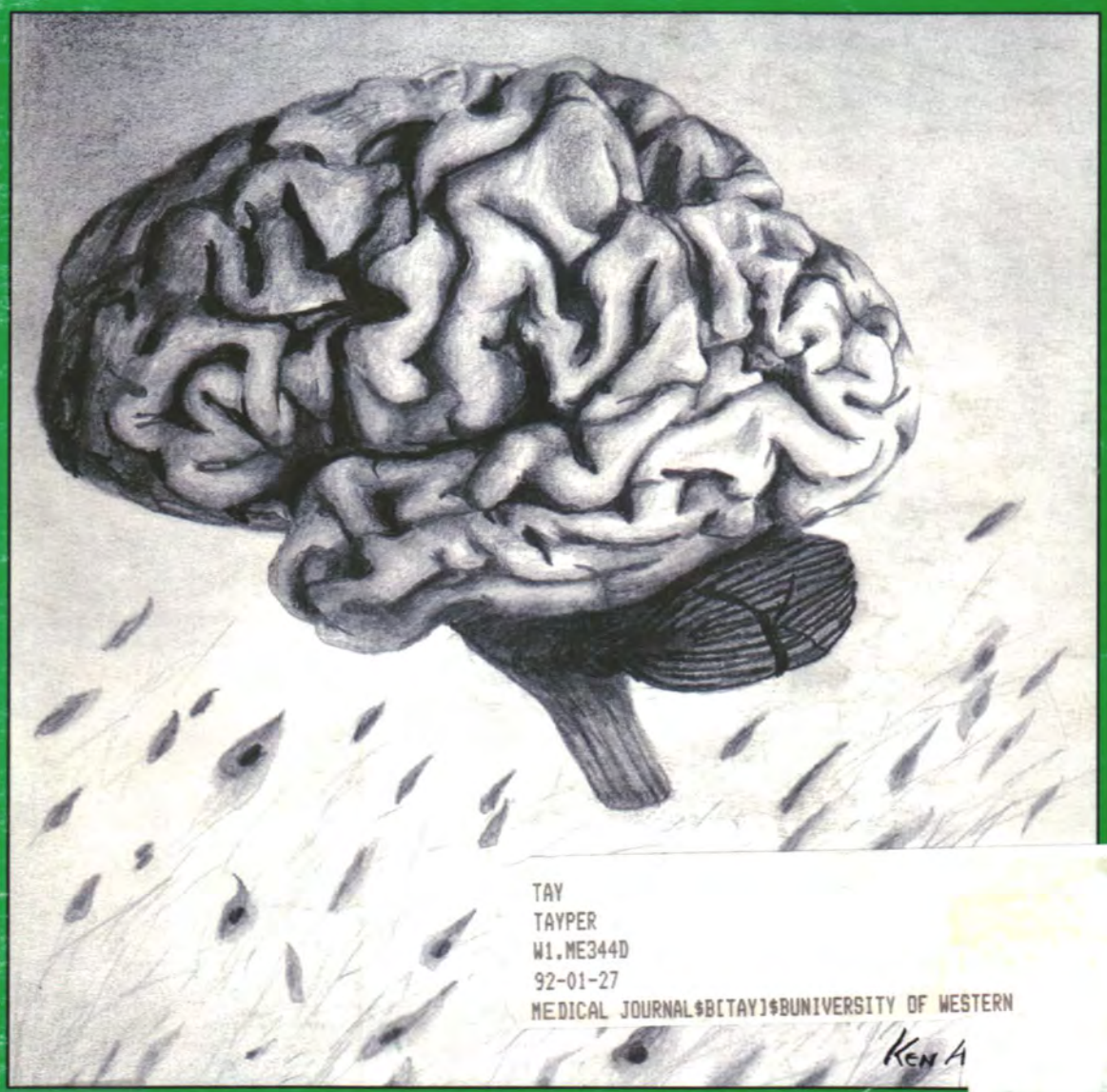
Western University

The UNIVERSITY *of* WESTERN ONTARIO

MEDICAL JOURNAL

Volume 61 Number 1 December 1991



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Guideline to Authors

The purpose of the UWO Medical Journal is to provide a single forum for original articles based on clinical or research medicine of topical or historic relevance. Since the readership of the Journal is interdisciplinary, articles published will attempt to reflect the wide range of medical disciplines. The Journal will consider empirical, theoretical, and research reviews. Book reviews will also be considered. The Journal reserves the right to refuse articles that do not comply with the Journal's publication criteria.

Manuscript Submission: Each submission should include two copies of the full manuscript a minimum of 20 days before the proposed Journal publication date. Authors are expected to submit the final revised version of the manuscript (usually with the two copies) on computer diskette. The preferred program is WordPerfect 5.1. All figures must be camera-ready and artwork must be black and white.

Manuscript Organization: Manuscripts submitted should be set with one inch margins and typed single-spaced. If necessary, the Journal will accept manuscripts not submitted on diskette that are typed with one inch margins, double-spaced, and single-sided on (8.5 x 11)" paper. Original research articles should have an abstract that clearly states the relevance of the article to the medical discipline being reported on. This dimension should be elaborated upon in the introduction. Experimental methods, results, and discussion section follow the introduction. Results and discussion sections may be combined if appropriate. Authors should rely on articles or information published in recognized journals and sources.

Authorship: All members of the Faculty of Medicine of UWO are invited to submit manuscripts for publication. Medical students are certainly encourage to collaborate with medical staff who specialize in the medical sub-discipline being reported on. Manuscripts will also be considered from medical faculty (including interns and residents) from universities other than UWO.

Modes of Communication: Authors should submit with their manuscripts a cover letter including a return address, telephone number, and fax number (where available). Two copies of the manuscript (as well as the final revised version on diskette) should be sent to:

The Editors
UWO Medical Journal
Health Sciences Building
Faculty of Medicine
University of Western Ontario
London, Ont. N6A-5C1

N.B. All material published in the UWO Medical Journal reflects solely the views and opinions of the authors of the material published and not necessarily the editorial staff of the Journal.

Next Deadline: February 20, 1992

On the Cover: The December 1991 edition of the U.W.O. Medical Journal features a special section on Dementia. The cover depicts a brain showing unusually severe, generalized, cortical atrophy seen in Alzheimer's disease. The leptomeninges have been stripped to show the narrowing of cortical gyri and widening of sulci. In the background neurofibrillary tangles are shown in a frozen section of the hippocampus. Adapted from Diagnostic Neuropathology: A practical manual (Esiri MM & Oppenheimer DR, Eds), Blackwell Scientific publications; Oxford. 1989. Artist: Ken Alanen, Meds '94 ■

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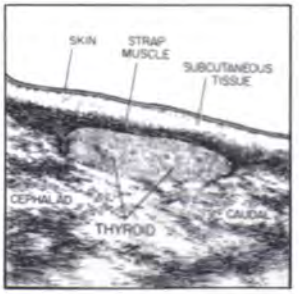

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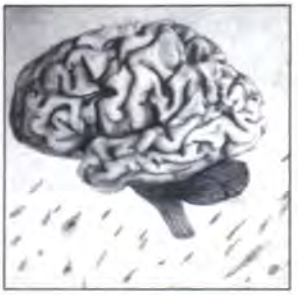

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Editorial Notes

A short while ago I laid me down to study,
to pray the Lord I wouldn't go nutty;
I hoped I could learn all that junk,
and if I couldn't I pray the Lord not to flunk;
And if I do don't pity me at all,
just lay my bones over my books in the study hall.
And now I lay me down to rest,
to pray the Lord I've passed all those tests;
Soon I'll fall into a deep deep sleep,
when I'll dream of malls and movies and two sunny weeks;
But if I die before I wake,
never again a test to take.

My verse may have neither the grace of T.S. Eliot nor the poignancy of Robert Graves, but it is the best my weary convolutions can muster. I am clearly happy that my first set of second year exams are over and I can echo the sentiments of one of my cohorts: "I'm still in medicine." During the first term I spent very little time in the classroom. In fact, except for clinical methods and the very odd ICC lecture or small group, all of my studying time was spent at home reading the appropriate text books. Because I was rarely seen by my fellow students all term, I have been recently asked by many people if avoiding lectures was of any value; now that the exams are over, I am certain that my study technique was effective and worthwhile. I should, however, qualify this statement. Although I avoided lectures, I studied constantly most of the term. I avoided classes because I didn't find lectures helpful or lecturers stimulating; this feeling may not apply to other students—and then again, it may. Furthermore, teaching departments shouldn't take these statements to mean that their departments aren't useful—up to this point, anyway, these departments just haven't been useful to me. Finally, my opinion is not the penultimate or ultimate word on the classroom setting—it is, nonetheless, my opinion, and I do feel somewhat disappointed by the fact that I am relegated to learning medicine on my own. The negative side to this is of course, gaining nothing from medicine at the level of the lecture. Notwithstanding this negative aspect, there is a postive side—a more effective management of time to deal with the voluminous course load.

The concept of time management leads me to another curious question—why there is such a robust work load in second year. Clearly, there must be some courses that needn't be taught in such intricate detail, only to forgotten ever so quickly—a medical fact lives such a fragile, transient existence in the mind of a medical student. For example, could it not be possible to combine neuroanatomy and anatomy in first year with the main issues strongly emphasized so that they might be encoded superiorly in a long term memory store. Perhaps pathology and microbiology could be moved to second year and biophysics moved back to first year, since the former subjects have more relevance to our impending clerkship than the latter subject—unless, of course, we're expected to carry a protractor, compass, and torque meter with us in order to measure to what extent someone's articular surface has worn down and what rotational force has caused such a limp. Furthermore, greater emphasis on a well-taught pharmacology course is clearly in order. All physicians will someday prescribe and administer drugs. I fear that thorough instruction in pharmacology has been supplanted by other courses that lack that all-encompassing importance this subject has.

I don't wish to be misinterpreted as suggesting that neuroanatomy, anatomy, biophysics, or any other subject is not interesting—all medical subjects have a particular appeal to me (and most medical students). I merely wish to be interpreted as suggesting that the medical curriculum should be carefully examined, with special attention paid to the need of the students and not as much paid to the people with tenure.

Well, now that that is off of my chest, I can say to the readers that I am very proud to be part of the editorial staff of the UWO Medical Journal. Language is an extremely valuable means of communication as well as an art form. Shirley and I are keenly aware of these aspects of language; we will ensure that these facets are reflected in everything published in the Journal. Furthermore, Shirley and I wish to maintain and advance a high standard of literary excellence expected in a journal publication. We have spent a great deal of time replanning and reorganizing the Journal and we hope that our readers find these changes useful. I will feel very content if after my four years of medicine I can leave the Journal better than its ever been, but not as good as it will become. Enjoy. ■

Jeffrey Politsky, Meds '94
Editor

At last, it's almost done. Having spent the last two weeks either attached to my computer terminal or phone chasing after advertisers and article submissions, I have been cranky to say the least. For those of you who have been faithful readers of the UWO Medical Journal, you will notice that there have been many changes made to the Journal this year. I hope that you enjoy its' New and Improved look. We've tried to place a greater emphasis on Basic Science articles, as well as Research and Clinical articles, with expanded coverage of events at the Undergraduate level -within the limits of non-slanderous material of course. This month features a special section on Neurology, and in particular, Dementia, an area we've all heard about but don't know much about! I hope that everyone learns something from the articles, which are meant to be entertaining and educational, and not boring. Our next issue will feature a special section on Cardiology -so for all you budding heart specialists, I expect to hear from you for our next issue. As well, I welcome material from faculty and UWO Medical graduates, updating us on what their classmates are now up to.

In the relatively relaxed world of fourth year, it amazes me that we have finally reached the upper eschelons of undergraduate medical turf, i.e. being in FOURTH year. I can still remember how it felt to be in first year and watching the return of the fourth year students, thinking 'Wow, these guys are going to graduate'. All I can think now is 'Yikes! Scary stuff' - we still have so much to learn. Internship is uppermost in everyone's minds as we realize the seriousness of deciding what to do for the rest of our life and where we will live for the next couple of years. As well, each and every person's decisions seems to be made on completely different grounds. As one classmate put it, deciding where to be for internship is really 99% personal, and 1% medical. Considering that the Class of '92 is the last class graduating under the one year licensure clause, we are lucky in some ways -and unlucky in others. The changes in the LMCC Part I, as well as the additional need of writing the LMCC's Part II for portability, make for a great deal of uncertainty. Let's hope it's fair to those of us caught in this transition phase. But hey, if there was nothing else to be said about being in fourth year, it's good to see everyone again and be among the comradre of my fellow cohorts. Until next time..... ■

Shirley

Shirley Lee, Meds '92
Editor

Readers' Views

The following two letters are in response to an article on Alcoholism published in the November 1990 issue of the UWO Medical Journal.

Dear Editors:

Mr. Leslie Wright has to be congratulated for his excellent article when he discussed the subject of alcoholism. Not only is it refreshing to see a publication about a condition rarely discussed in medical school but that it led to further correspondence.

The articles and letters stimulate me to clarify some points. The main issue is that alcoholism can be considered a disease. The "Society for the Study of Inebriety" recognized in the late 1880's that alcoholism was more than a bad habit which was left to those who were morally bankrupt. Not until Jellinek, however, put forward his disease concept of alcoholism in the early 1960's did progress really take place. The American Psychiatric Association soon followed with an endorsement of such thinking. The significant characteristics that make alcoholism a disease are the loss of control and the inability to abstain. Furthermore there is the continuation of the behaviour despite significant negative consequences.

There is a danger in concentrating all our reserves on those persons addicted for then we would risk not dealing with people who simply abuse alcohol. Nevertheless, it is this second group of patients who probably are the ones most likely to irritate health professionals. What separates alcohol abuse from dependence is a thin imaginary line across which patients can vacillate. In practical terms there is the presence of tolerence and/or withdrawal symptoms in the dependent individual. When a patient consistently shows the criteria mentioned above there is unlikely, if ever, to be a return to controlled, nonabusive drinking. Equally compelling is the arguement that alcoholism is a social disorder or even a syndrome of variable severity. It is these flexible definitions that colour a physician's frustration in dealing with alcoholics. For the sake of simplicity why not use the World Health Organization's definition that an alcoholic is simply an individual who repetitively drinks excessively to the extent that it causes harm or damage in any area of their life. In other words, the damage is not limited to a physical disorder.

Alcoholism with its two component parts, alcohol abuse and alcohol dependence has now been defined. Definition is one of the criteria that enables it to be classified as a disease. The other criteria are as follows:

a) It has a definite course and progression.
b) It occurs independent of colour or race, creed, or culture.
c) It occurs independent of social deviance.
d) It is treatable.

Admittedly, treatment is only possible with patient compliance and motivation. If alcoholism is a disease why do we not therefore give alcoholic patients the same treatment as we would any other diseased individual? Nobody who picks up their first drink intends to become an alcoholic just as no one who smokes their first cigarette intends to have their first myocardial infarction. The incongruity of viewing alcoholics as patients less worthy of treatment is well inculcated into the physicians attitude and is influenced by many physicians coming from alcoholic backgrounds.

If an alcoholic can view himself as diseased it gives him or her hope, access to treatment, and resolves them of the unbearable guilt. It serves no purpose for a physician to criticize the patient. That only prevents the establishment of rapport and drives the patient deeper into denial which is a process whereby the alcoholic can make some sense of an untenable lifestyle.

Perhaps we can say that alcohol abuse is a risk behaviour that can lead to a dependence and patients should be advised accordingly. But then, are we not exercising preventive medicine which is really synonymous with primary treatment? It behoves all medical students and physicians to be effective in the management of alcoholics. There are at last some encouraging signs that the medical school curriculum at the University of Western Ontario will soon change to accomodate this need.

To be successful in dealing with alcoholics, health professionals must have a positive attitude, knowledge, and skills. A positive attitude is best enhanced by viewing alcoholism as a disease worthy of treatment. The skills include being able to effect intervention, to tolerate frustration, accept frequent relapses, recognize one's powerlessness over a patient and deal with the unpredictable. The knowledge required by a physician includes the ability to diagnose and to be aware of the appropriate treatment services available, be these detoxification centres, assessment clinics, counselling services, treatment programs, or self help groups. This author is not alone in viewing Alcoholics Anonymous as the single most helpful therapeutic tool in the treatment of alcoholism.

Remember that alcoholics may not tell the whole truth but what information they do divulge comes fairly close. I have learned more from patients than was ever taught to me by colleagues. Health professionals have much to gain from the lay man. So if medicine is to serve society we as doctors must work with our alcoholic patients and not appear contemptuous of them. Herbert Spencer said in 1912 "There is a principle which is a bar against all information which is proof against all arguements and which cannot fail to keep a man in everlasting ignorance -that principle is contempt prior to investigation." In eighty years practitioners have done little investigating. ■

Martyn Judson, M.B., Ch.B.,
D.R.C.O.G.,C.C.F.P., C.A.C.
Substance Abuse Treatment

Dear Editors:

A review of Dr. C.N. Ghent's measured response (April 1991) to Les Wright's fervency (November 1990) illustrates an unhealthy polarization within the medical profession. One extreme is clinical bigotry; the other, clinical conceit.

A curious dichotomy exists between opinions of eminent specialists which express the problem of alcohol abuse simply as a risk factor toward disease and the recent plethora of articles by family practitioners which, although appropriately dignifying alcoholism as a disease, insist that their authors and medical readers are well equipped to deal with it. Somewhere in the middle must lie the truth.

"Alcohol in excess" is certainly a risk factor. But, although it may be inherent to the definition of alcoholism, there are many alcohol abusers who are not alcoholics. Conversely, there are many alcoholics who haven't touched a drop for many years. The "simple" abusers should certainly be given, and may well heed, warnings to curtail their drinking. And, there is no excuse if they do not.

On the other hand, Alcoholism is a sometimes treatable but absolutely incurable disease entity. The result of some combination of genetic predisposition and exposure to a society which accepts and encourages the use of alcohol, it is marked by a powerlessness to stop drinking in spite of the exhibition of "controlled anger" by family, friends and doctors, and the obvious deterioration of their social, economic and physical well-being. An alcoholic simply cannot quit drinking: he/she may be able to stop temporarily on his/her own under threat but he/she simply cannot stay stopped without the invocation of a "power greater than themselves". The fact that this greater power may be non-medical should not constitute a threat but rather an enlightment to our profession.

Fundamentally, there are three components to the disease of alcoholism: physical, emotional and spiritual. The diagnostic criteria can be applied only by the individual afflicted. This evaluation may surely be expedited by the educated intervention of concerned family, friends and members of the helping professions. Only the individual can, however, complete the formulation. Naturally, the physical endpoint consequences, such as cirrhosis, should give him/her a hint, but denial is frequently strong enough to reject these. The insanity of the emotional component i.e. the restless, irritable discontent that knows no satisfaction, needs to be pointed out as abnormal. The alcoholic thinks it is "normal" to feel this way. The spiritual void must be filled: the great pointlessness of self-centered existence that leads alcoholics along the path of self-destruction.

Simply to shrug academically, dismissing the individual's problem as one of controlled personal choice, is as superficial and indefensible in its own way as the attitude of certain practitioners who feel that they are equipped to manage recovery of alcoholic patients on an exclusive one-on-one basis.

We are talking here not about a bad habit. Nor are we talking about an ingrown toenail. We are indeed talking about a disease -a complex, powerful, cunning and baffling one which unfortunately doesn't slip easily into some medical pigeon-hole. But, just because we cannot fully comprehend nor cure alcoholism doesn't strip it of its clinical identity. ■

James D.F. Harris, M.D.

Class Reports

Some Fooloscopy

by Will Marcoux, Meds '92

It is late November; there are snow flurries outside. I muse about my Meds '92 classmates spread across the globe: the Caribbean, Africa, the South Pacific, Europe. A leafless branch tossed by the wind taps at the window, and a pile of internship papers, interview letters waits to be completed. Ah, a perfect day for foolosophizing. Soon our Basic Sciences Selectives/Special Topics classroom block will begin and Meds '92 will be returning to the nest for one last fly by. I wonder what elective experiences we all will come back with in preparation for the final feather change from M4 to M.D.?

But how does the transformation really occur? Is it the moment the diploma is in one hand and the Dean's handshake in the other? Or is it more imperceptible? Is it complete in June or does it stretch into the post-graduate years and even beyond? It may be all of the above or none, but the reality of the change faces each of us as we enter the last stretch. The answer may be obvious or forever elusive depending on our definitions of M.D., and our expectations of ourselves as we enter the profession. Certainly, the sweat, tears and joys of the past four years did not focus on the initials as an end in itself, but only the means to an end.

Then, what is that end?! Each graduating class has had to reflect individually, and Meds '92 is no exception. Maybe some precious, valuable time needs to be squandered to attempt a cogitative answer. I am not so naive to think that all of our pre-med idealism remains intact, nor do I dispute that for many a comfortable lifestyle may be all sufficient. Whatever the framework we make for ourselves, to focus on the meaning of our lives, contemplate the goals toward which we move, and undertake a process of self-evaluation and values clarification will only do us good.

Perhaps here is where those of Meds '92 who involved themselves with Summer MedOutreach or organized oversea electives in the Third World have a broader base to attempt answers. Recently, the Meds Journal recieved a postcard from Zimbabwe, on the front was a Nyala, a beautiful antelope with exquisite markings, on the back was described "eye-opening experiences", one of which involved treating a hand grenade injury, encounters that change you from the inside. Purportedly, the wisest man of the East once said, "It is better to go to a house of mourning than to go to a house feasting, because that is the end of every man". May we not go through our careers viewing suffering as "an interesting case".

Only too soon our Alma Mater will kick us out of the nest for the last time. Undoubtedly we shall all fly, but where to? ■

Beep! Beep! Beep! Beep!

by Les Wright, Meds '93

Clerkship. It's a job, not an adventure.

Back in the old days (i.e. August), my heart would race at the siren song of The Beeper, and I would lurch to the nearest phone in anticipation of, just maybe, being able To Save A Life.

Now, under identical conditions, I fight the urge to roll over and go back to sleep.

Sound familiar? If so, then you are a seasoned veteran of Meds '93. Everywhere throughout the town, in the hospital corridors, the clinics, the ORs, and at Barney's, brave souls are discussing various and sundry tactics to survive the jungle warfare that is Life On Call.

So far, no casualties have been reported. Indeed those '93 warriors who took the nuptial plunge this summer seem to be doing just ducky. Many congrats to Gregg, Megan, Dave J., and

Dave H. for braving the marital minefields even before marching off to War On The Wards. An ultra-special commendation goes to Lisa and Jeff Fischer, whose pudgy progeny, Samantha Lee, graced our planet just at summer's end. Incidentally, the perennially statuesque Lisa informed your intrepid war correspondent at the "Friends of Fish" fiesta that, believe it or not, she had been pregnant. Looking good, Mom!

A few events that have seen committed, if somewhat piecemeal, attendance include the Grand Bend Bar-B-Q Beach Fest courtesy of Drs. Howard and Leriche (a zillion thanks!) and the aforementioned "Friends of Fish" Homecoming bash. Also, rumour has it that Meds '93 Dictator-for-Life Pete Chu and a rag-tag band of rebel clinical clerks descended upon the annual Fanshawe Picnic, deploying there a ribald flair that only seasoned Meds Warriors can. Then the usual Health Sciences Pub, occasional party and gathering, and, of course, evenings at Barney's have continued to provide the war-torn and weary with well-earned quality R and R.

In the future, a Class Meeting concerning Electives/Selectives (and there is a difference) is to come in early December—if you are as confused as I am (which is beaucoup), BE THERE! And, of course, we have the Xmas semi-formal of December 18. Just think of it—hordes of outrageously tanked senior medical students in formal/quasi-formal attire grooving to the very latest funkified noise known to humanity. Future pillars of society, all!

Till then, take care—and remember, it is a jungle out there. ■

The JJ Report

by Jeffrey Politsky & Justin Amann, Meds '94

Justin: Well J, a new academic year has begun and its once again time to recall our journalistic skills. I must say J, it certainly is good to see you – a rare event these days. How are you? How's tricks? How's medical school by correspondence?

Jeff: One question at a time. You will see me again you know! I'm fine, things are fine, and its good to see you too. What's first on the agenda? Can we get silly right away?

Justin: One task we do have is to get people to laugh at themselves—too many hypersensitive people in our midst. But first, kudos to the Meds' 94 soccer team who won their championship. I also know that the Meds '94 hockey season has begun and the team is on the road to a second consecutive championship.

Jeff: That's right. Their season is off to a slow start, however, with a 2-3-1 record. Hey look J, isn't that Lesley?

Justin: So it is. Boy, doesn't her hair have a marvellous glow?

Jeff: Apparently she grinds up rose petals and adds them to her shampoo.

Lesley (moving very close, speaking in a soft tone): Hi J. Hi J.

J & J (cooing): Hi Lesley!

Jeff: Gosh, did you see the way her eyes were fixed on me?!

Justin: On You?? Not! Maybe just to see how red you turned. She was staring at me!!

Jeff: Oh, for sure J! Like, she needed some fashion advice or something!

Justin: Let's not fight J, Okay?? Anyways, speaking of eyes, what do you think of our neuro-case study classes? I think we should place little flags representing our ancestral countries on our oversized name plates.

Jeff: Kind of like a neurological model united nations for pre-schoolers...." My name is Politsky, I represent Poland, my answer is a lesion of the ascending right medial longitudinal fasciculus."

Justin: "I'm very sorry Poland, your response is incorrect. Dr Kiernan, would please launch the first missile head for Warsaw.' `Missile head launched, sir – Warsaw is now obliterated.' Bummer J, you should have waved your white flag.

Jeff: We should stress J, that our ridicule of any subject is of course just our way of poking fun – a mature defense mechanism, if you will, as our good friend Dr. Waldinger would say. Justin! Look over there! It's Debbie – she looks hurt – she's holding her gut.

Justin: Not quite J. She's laughing. Her she comes now.

Debbie (bent over in tumultuous fits of hysterical laughter): Hi guys!!

Jeff (perplexed): Hi Debbie, what's so funny?

Debbie (still laughing): I was just sitting in the Meds lounge talking to Anne and sewing a button onto my jacket, when I accidentally pricked my finger with the needle.

J & J (also laughing but very confused): So??

Debbie (out of control): All of a sudden I heard a thud – Anne was out cold on the floor. This is too funny to keep to myself, see ya.

Justin: I guess not everybody can stand the sight of blood, even if it's a teeny weeny itsy bitsy little dot from a needle prick.

Jeff: There's a couple of things I'd like to talk to you about – things that are beginning to grate my nerves.

Justin: What's the first one?

Jeff: There seem to be one to many monozygotic twin studies in psychiatry and I want to know what we can do about it.

Justin: Not too much J. Psychiatrists need a hobby too, you know. You might as well tell me the second item. Wait just a second. Isn't that our class president running toward us? Why it is. Hi Mark!

Mark (dyspneic): Guys, I'm glad I found you. I've got an announcement. Dr. Silcox is having a brown bag lunch talk today at noon on `What to do with your medical career when you realize that the specialty you chose was the wrong choice after all.'

Justin: That's great Mark, but it's now 4:00, this is the grad pub, and we're drinking and getting sloshed.

Mark: Four o'clock?!? Holy jumpin' Jesuit priests, I gotta go; I'm 15 minutes late for a meeting.

Jeff: There goes a nice guy that works too hard.

Justin: Awfully nice, indeed! Anyways, carry on my friend.

Jeff: Oh yes. I also wanted to talk about was this over-comprehensive connection between food and disease. With bread and butter pericarditis, cottage cheese discharge, chocolate ovarian cysts, and strawberry cervical spots, medical nomenclature has interfered with my aesthetic appreciation of breakfast and dessert. And before my concept of dinner is irrevocably changed, I want to fight back.

Justin: How?

Jeff: Let's make our own full course disease.

Justin: Oooooh! Sounds gross! But, okay. Are we calling it the JJ Syndrome?

Jeff: We may have to. Okay, starters: let's begin

with some red radish urticaria accompanied by feta cheese flaky dermatitis, progressing to honey-coloured crusty french bread impetigo with a cool ranch infiltrate.

Justin: But I like cool ranch!

Jeff: Okay, an oil and vinegar infiltrate.

Justin: Much better. May I interest you in something from the bar – some smoky coloured urine, perhaps, from our swollen glomerular vineyards.

Jeff: Good One J! Swollen glomeruli rapidly progress to a tomato basil fettucine in a chunky anti-basement membrane tomato sauce punctuated by grilled tiger shrimp shaped extra-capillary crescents.

Justin: We mustn't forget our associated finding of acute focal alveolar necrosis with hemosiderin-laden sweet black Perigueux truffle macrophages.

Jeff: Justin! Truffles?! That's sacrilege!

Justin: All's fair in plague and pestilence J. Can we have a happy ending to our meal?

Jeff: How about mocha cream sauce corticosteroid injections with a bottle of natural plasmaphoretic spring water.

Justin (licking his lips): Boy, am I full! What was the name of that restaurant anyway?

Jeff: Goodpasture's.

Justin: You know Jeff, it's Christmas time, and being the generous souls that we are, why don't we put together a gift list for our favourite professors? We can mail it to Santa himself.

Jeff: A splendid idea, simply splendid. We'll send it C.O.D.

"Dear Santa: We wish the following gifts for the following people:

Dr. Keirnan - A longer tie (gently ribbed?);

Dr. Roche - The Canadian Writer's Handbook and a big dictionary;

Dr. Hersey - The audiotape `Direct Communication made easy;'

Psychiatry Dept. - One professor with a number of personalities rather than a number of professors with the same personality;

Dr. Brown - Blinkers to keep his lectures on track (hee-hee!).

For everyone else, Santa, we wish a very Merry Christmas and a Happy New Year. Have a great break y'all. ■

Reflecting on the First Trimester

By Andrew Caruso, Meds '95

As I sat down to write this report, the date on the computer screen reminded me that it had been exactly three months since the day that the members of Meds '95 were first assembled as a group in University Hospital Auditorium A. Since that time numerous hours have been spent in lectures and labs, exams have been written, social gatherings have taken place, and most importantly, friendships have developed.

As I reflect upon what has transpired in this three month period, I cannot help but wonder what my classmates' initial assessments have been. I could send out an evaluation form -why not? It's done for everything else. Of course, if I did do that my classmates would probably lynch me for giving them another one of those things to fill out.

But if I did decide to have an evaluation, what kind of questions could I ask them? Of course there is always the standard, "What course/instructor have you enjoyed the most/least thus far?". But those are not very exciting questions, and anyways I already have a pretty good idea of what the responses would be. Maybe I could ask something like, "What has been the most memorable social outing you have been a part of thus far?" I guess for some it would be difficult to decide on just one, while others might have difficulty even remembering one. But I guess that would really all be irrelevant since all you have to do is attend class and pretty soon you hear all about what went on at a particular event -news sure travels fast in this class!

I could also ask, "With whom from this class do you tend to associate most with?" I know it's a lame question, but do I dare to be so bold as to ask, "Is there anyone in this class who you do not think too highly of?" Even if anyone feels that way about someone else in the class, I doubt if they would be in a great hurry to express it in an evaluation. Besides, being classmates for four years may just help to change a negative impression into a positive one -only time will tell.

Although there are probably many more questions like, "Did you choose Welch-Allen or Heine instruments?" or "What do you really think of the Meds jackets?", that I could use, I don't think that an evaluation would be such a great idea. After all, just because I wondered about my classmates' thoughts about the first trimester doesn't really mean that I have to know or even want to know. I just had to have something to write about. ■

Event Reports

The Homecoming Parade - When The Lights Went Out in London

by Harsh Hundal, Meds '95

"It looks better than I thought it would!"
- Jeff Spence, Meds '95

Those words echoed through my mind as the Meds'95 Homecoming float collided with Murphy's Law; or to be more precise, a traffic light at Cheapside and Richmond. The traffic light and half the float were demolished within seconds of contact.

On a flatbed truck provided by BIG V Pharmacies, we had constructed Gilligan's Island. An incredible wooden hut had been created, cardboard waves painted, and palm trees fabricated. Ross Mantle, armed with a skill saw, performed the Texas Chainsaw Massacre to the roof of the hut in order to meet the maximum height allowance. Life and limb were risked to accomplish this!!! Little did we know that it was to no avail.

11:50 p.m. -the night before the parade, after having slaved all night at creating our island paradise, it began to rain. Palm trees were toppled, and waves washed away. 6:00 a.m. -suffering from sleep deprivation, we re-painted and repaired. 9:00 a.m. -we were ready for our 3 hour tour! Then we met the traffic light...

It's fascinating just how many police officers can suddenly appear. I counted at least three. We feared the headlines of Monday's London Free Press would read:

MEDS DEMOLISHED CITY
- Heritage Site Destroyed or worse:

JAILBIRD MEDS
- Citizens Demand Lynching

However, after statements were taken, we were allowed to continue. While we patched together the remaining half of the float, St. John's Ambulance patched Gilligan (Wayne Hsieh) for a minor flesh wound.

The second law of thermodynamics states that the universe tends to randomness. Along the way, our examination table collapsed as Mr. Howell (Mike Lewell) was receiving CPR, the steering wheel of the Minnow snapped-off in the Skipper's hands (me), Ginger's (Britt Carlson) dress ripped, the parrot died, and Mary Anne (Tara Tingley) fell several times through a hole in the floor of the flatbed. By the time we reached the end of the parade, we and our float had collapsed into a state of exhausted entropy.

Yes, Jeff, once upon a time it did look great! However, in the words of Dr. McCoy," Damn it, Jim, I'm a doctor not a carpenter!" ■

Meds Car Rally '91 - Chrysler Cruisers Crush Imports

by Mohamed Moussa, Meds '95

Through the hard work of organizers, Lea Babcock Meds '93 and Al Furman Meds '92, the annual Meds Car Rally was a success with over 62 lbs of non-perishable items being collected for the London area Food Bank.

Over twenty cars were entered in the rally, with a rookie team, The Cruisers, coming out on top in the end. The Cruisers, consisting of a hardy crew from Meds '95, made it to the finish line with lightening-speed in a mere one hour and eight minutes, defeating the two-time reigning champions, The Babymakers. The new champions cruised to victory in a Chrysler Minivan, beating out many imports including Hondas, Acuras, Volkwagens, and Toyotas. Lee Iococca would have been proud of The Cruisers on this day for leading a practical Chrysler family vehicle to the winner's circle.

The cars in the rally traced a route through London and its surrounding area, trying to solve riddles by looking for clues along this route. Points were awarded for correct answers and the drivers were encouraged not to speed, as more points could be gained through correctly answering the riddles than for finishing the rally in the fastest time. All teams managed to finish safely in under three hours. With the exception of a flat tire, and a couple of teams with a bad sense of direction, no problems were encountered throughout the day.

An array of prizes donated by local merchants were awarded consisting of restaurant vouchers, memberships to video rental stores, t-shirts and baseball caps. Without a doubt, their support was greatly appreciated by all medical students participating in this most worthwhile event. Thanks again to all those who got involved and helped support the London Food Banks. ■

MedOutreach and International Healthcare -Why Should We Care?

by Debbie Penava & Ian Hosein, Meds '94

MedOutreach comprises a group of students from the Faculties of Nursing and Medicine who endeavour to gain an understanding of the concept of Primary Health Care (PHC) by learning about and participating in PHC field programs. Presently, we aim toward this through health education and promotion. One way that we promote health and education is through the implemention of a specific PHC project in a developing community. In addition to this, one of the fundamental objectives of MedOutreach is to raise awareness of our activities and experiences. The intent of this article is to share our knowledge and our experiences from our most recent program this summer in Nigeria and to present an account of the state of health care in the region.

Since the inception of MedOutreach in 1986, this organization has progressed from an idea of a few medical students to a strong committment to learn about and participate in primary health care through the association of developing communities. For the past four years, MedOutreach has been sending group members to Nigeria. Our efforts have been concentrated in the two communities of Michika and Calabar. Here we have worked toward development of the concept of "HEALTHY PEOPLE, HEALTHY COMMUNITIES", hoping that one day the philosophy will be a reality.

Before sharing our experiences, it is necessary to present some background information about Nigeria and its health status, as a representative developing nation. Further, our discussion will also focus on the role of health in international development since health care does not exist in a vacuum. That is, it must be examined in an appropriate context. By the year 2000, four-fifths of the world's population will live in developing countries (6). Of these, 80% will lack the basic human requirements for living: adequate housing, employment, food, access to safe water, and elementary health services. Unless conditions improve, the poor health status of this population (approximated by measurements by life expectancy at birth, population mortality rates and infant mortality rates) will only worsen. In the developing world, the average life expectancy at birth is only 54 years, compared with greater than 76 years in the developed world (6). Infant mortality rates range from 100-200 per 1000 live births in the poorest regions of the world, such as the sub-Saharan Africa (eg. Michika, Nigeria). The World Bank has estimated that half of all these infants die within their first year of life (6, 8). In the population of the developed world, there are less than 20 deaths per 1000 in the first year of life. Under the age of five, mortality rates in the developing world average about 150 per 1000, (6). In comparison, this rate is about 11 per 1000 in most of the industrialized world.

The validity of these statistics as accurate representations of standardized levels of health may be questioned, but it cannot be denied that they provide evidence that levels of health in the developing world can be improved. Since "...everyone has the right to a standard of living adequate for the health and well-being of himself and of his family, including food, clothing, housing, medical care and necessary social services..." (United Nations, 1948), this prevailing poor status of health in the developing world should raise our concern. Accordingly, the World Health Organization has declared that there should be "an attainment by all citizens of the world by the year 2000 of a level of health that will permit them to lead a socially and economically productive life" (7). These declarations guarantee health as a internationally recognized right and not simply a privilege of developed society.

Health care professionals are trained to have a thorough knowledge of the human body, its pathophysiology and treatment of disease. Such knowledge, however, is not sufficient to solve the health care problems faced by communities of the developing world. This is because health care status is determined by a variety of factors including education, economic conditions and political climate. As such, medical knowledge alone is unlikely to change the poor health care climate existing in developing communities: health care needs to be addressed as a national priority. This would raise awareness of health as a political issue and allow for a greater allocation of economic resources. Resources could be then be utilized to develop programs for accessible and

equitable health care for the population. In the short-term, allocation of resources into health programs will improve the health status of the majority of the population, as well as improve the quality of their lives. In the long-term, health status should improve and infant mortality rates should decline; it is proposed that rates of fertility would then begin to fall (2). Over time, these combined factors would result in decreased rates of growth of populations. With slower growth of the population and an improved national health status, resources could then be re-allocated to national priorities aimed at sustaining and improving national development. Integration of the various factors involved in achieving acceptable levels of health throughout the world were first examined at a WHO conference in Alma-Ata in 1977. The concept of Primary Health Care (PHC) was developed, providing a theoretical framework designed to initiate change and improvement in the status of health in the developing world. PHC was the main focus of MedOutreach programs and activities this past summer. Our orientation included lectures on PHC theory, but stressed practical application of theory through various PHC programs in operation in Nigeria. PHC comprises five main principles: (1) health care is accessible and equitably distributed (2) health care involves participation at both the individual and community level (3) health care should focus on prevention rather than cure (4) the provision of health care should involve the use of appropriate technology for the community and (5) maintenance of health and good health care involves the integration of many factors, eg. education and agriculture.

Following from these five main principles, nine essential lements of primary health care have been established: education about health, an adequate supply of safe water and sanitation, maternal and child health, family planning, nutrition, communicable disease control, immunization, environmental improvement and the treatment of injuries.

We have provided basic information on the current state of health in developing communities and its important role in international development; it is now possible to integrate MedOutreach's practical experience into the framework. This practical experience is vital to the understanding of the state of health care in the developing world. We discovered early in our experience that the theory and practice of primary health care did not always correlate. For example, when working with the people in our respective communities near Michika and Calabar, we discovered that not all PHC programs were well-received; that is, some of the nine "essential" elements of PHC were more essential than others. Compliance of a community with PHC programs was dependent on the existence or provision of two basic necessities -a safe supply of water and adequate amounts of food. Mothers simply would not bring their children for programs such as growth monitoring or immunization if there were inadequate supplies of food and water. To mothers, the benefits of immunization did not outweigh the risk that their babies could die because of inadequate supplies of food or water.

Recent figures indicate that 40,000 children in the world die each day (6). The diseases that kill children in the developing world are diarrhoea, tetanus toxin, measles virus, pertussis toxin, diphtheria toxin and pneumonia. For each child that dies, 10 survive in a mild to severe malnourished state (6). Diseases resulting from infection and malnutrition are the main causes of mortality and morbidity in the developing world. High levels of morbidity result from the chronicity of most of these illnesses, decreasing labour productivity and income of families, gradually resulting in poorer and inadequate living conditions (3). These diseases are preventable, having been largely eradicated from the developed world. All that is required is provision and integration of the basic human requirements for life: education, sanitation, water management, nutrition, employment and adequate living conditions. The concept of PHC lays the foundation for working toward prevention and attainment of adequate levels of health.PHC programs focus on achieving particular factors toward this goal. MedOutreach has identified an active role that we can play in this process.

We participated in many PHC programs this summer in the villages around Michika and Calabar. Each experience was unique and reflected differences in health care facilities, epidemiological profiles, and living conditions of the regions. We worked in various facilities including maternity clinics, village dispensaries and general hospitals, where we learned about different approaches to health care. These approaches were generally dependent upon the availability of qualified personnel. For example, only three physicians work in Michika, an area with an estimated population of 500,000. As a result, nurses and health care attendants are responsible for much of the health care of the population. This lends a strong sense of a community-orientation toward health; prevention of disease is emphasized through education and

screening programs. However many people still cannot get adequate care due to dispensaries not being accessible from their own village. Some dispensary attendants compensate for this inaccessibility by travelling home-to-home with their equipment—educating the community, immunizing children and mothers and monitoring infant and child growth. Outreach trips to such villages were certainly valuable experiences for us, underscoring the true meaning of health care.

Outreach to remote villages was a large part of our program. Involvement in health education, however, was also a focus for the MedOutreach team. We participated in teaching rounds at hospitals, and various centres concerned with physical rehabilitation or care of patients suffering from leprosy, tuberculosis or vesico-vaginal fistulas (VVF). We visited secondary schools to participate in Child-to-Child programs, teaching students about health. For example, during our stay in Michika, the population was suffering from an epidemic of dysentery (now known to be cholera); thus, teaching about the transmission and treatment of faecal-oral disease was stressed. We also taught in many clinics about the management of locally endemic diseases such as Schistosomiasis, Guinea Worm, and Malaria. Specifically, women were taught about nutrition, family planning, and antenatal care. Unfortunately, language barriers sometimes prevented us from teaching with different modalities such as drama and song, a method in which Nigerians are very fond of for learning. At such times, we simply observed the teaching methods of local health care workers and learned much about identifying with and teaching at a community level.

We were involved with education at many levels, both teaching and learning, and look forward to incorporating it further into future MedOutreach programs. We believe that education in all forms, not solely about health, is an important component in working towards the attainment of adequate levels of health. Education broadens the mind and assists in the development of analytical skills which are applicable to various health issues: diet and nutrition, the development of consistent habits for water management and sanitation, early recognition of disease and appropriate choice of treatment. Traditionally, most of these responsibilities in a family are left with women. In the majority of developing countries the education of females is of low priority (Sivard, 1990). Fertility rates and mortality rates (both measures of health) have been associated specifically with the percentage of females in the population who are literate (1, 4). Such findings have great potential for determining directions to be pursued in the attainment of adequate levels of health in the developing world: educating females could be one of the best investments for the future health of a nation.

The role of females in the attainment of health in the developing world is signficant and the importance of their health status cannot be undermined. Women face a wide range of medical difficulties over and above those affecting the rest of the population, including venereal disease, repeated pregnancies, post partum complications, rape and domestic violence. These difficulties can result in decreased capability to function effectively at home, or even premature death. Such loss to a household would have devastating effects, leaving children and infants without a primary caregiver. As mentioned earlier, such children would then be placed at risk for malnutrition and diseases resulting from it, increasing infant and under-five mortality rates. Thus the cycle of unacceptable levels of healthcare continues.

With these considerations in mind, the MedOutreach team decided to initiate a project focussing on maternal and child health care in Nigeria. We believe that this area deserves special emphasis in the development of sustained levels of adequate community health. Our project was implemented at the Ekori Health Centre in southern Nigeria and involved education about nutrition as well as growth monitoring of both infants and children, with a a special focus on education during the weaning period, when many infants fail to thrive due to lack of proper nutrition and feeding practices.

Our project on maternal and child health care will continue to be supported by MedOutreach, enabling us to work with the community on the logistics of funding, implementation, and evaluation of a project concerned with primary health care. We look forward to following this project through a successful course, knowing that we have worked together with a developing community to help the people help themselves.

The MedOutreach team returned to Canada with a new understanding of health care in the developing world, in theory and in practice, as well as the potential role for health in the international development of such countries. We learned about health conditions and facilities available in a developing country and have identified some ways in which MedOutreach can play an active role in improving the state of health of the people of two Nigerian regions. We believe that we have made a

MedOutreach con't

difference. We wish to continue working toward this difference by sharing our experiences with peers, university colleagues and fellow Londoners through various media and slide presentations, future seminars and fundraising events (such as a reception to be held on January 15 with speakers to be announced). We also hope to provide individuals on a future team with the opportunity to work in the field to gain valuable experience and insight into these issues.

We welcome any contribution to MedOutreach through our newly-formed club, whose members are working together toward a better understanding of some of the issues raised here. We believe in the value of our contribution to the improvement of the state of health care in the developing world, through educating ourselves about the issues or actually working with a developing community toward the realization of international community health. There is much to be done to improve the present state of health care in the developing world. As MedOutreach, we are helping people in a few developing communities to help themselves in an effort to achieve 'Health for All by the Year 2000'. ■

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1991 Dr. L. DeWitt Wilcox Award in Medical Research: Limited Usefulness of Ultrasonography in Diffuse Thyroid Disease

by Joan Lipa, Meds '92
In Association with: Dr. W.C. Vezina, Dr. L. Hutton, Dr. R. Rankin, Dr. T.J. McDonald, R.J. Vanderwerf, R.T.N.M.

ABSTRACT

Ultrasonographic texture analysis has recently been promoted, particularly in the paediatric literature, as a substitute for radioisotope scanning in the differentiation of diffuse thyroid disease (DTD). This study was initiated because it was thought that ultrasound (US) echopatterns would be nonspecific; thus, a single-blind, controlled, prospective study was carried out to assess the clinical usefulness of US as a diagnostic test for DTD. 334 cases from a database (systematically acquired through a battery of thyroid investigations, including thyroid US, performed on all patients referred to Nuclear Medicine over a 5-year period for a I-123 thyroid uptake and scan) were found to have diagnoses relevant to this study. Blinded interpretation of real-time B-scan and static B-scan US images included grading gland texture: homogeneous (A), inhomogeneous-hyperechoic (B), or inhomogeneous-hypoechoic (C). 94 of these US images were interpreted by a second observer. Gradation of US echogenicity yielded the following results: **Normal Controls (n=113): A=96 (85%), B=17 (15%), C=O. Graves' Disease with thyroid autoantibody titres 1:6400 or less** (n=94): A=36 (38.3%), B=58 (61.7%), C=O. **Graves' Disease with thyroid autoantibody 1:25 600 or greater** (n=10): A=2 (20%), B=7 (70%), C=1 (10%). **Hashimoto's Thyroiditis** (n=96): A=17 (17.7%), B=70 (72.9%), C=9 (9.4%). **Silent Thyroiditis** (n=21): A=7 (33.3%), B=9 (42.9%), C=5 (23.8%). The kappa value for interobserver agreement of gland texture-homogeneous vs. inhomogeneous was 0.52. Hypoechogenicity vs. other gland textures gave a kappa value of 0.15. **CONCLUSION:** The large overlap in the distribution of the three basic echopatterns (A, B, and C) among the five diagnostic categories suggests that US is nonspecific; no echopattern is diagnostic of a specific disease. Interobserver agreement in the detection of US abnormality is good; it is poor in the detection of specific US echopatterns. Thus, US cannot replace radioiodine uptake and scanning for the differentiation of diffuse thyroid disease.

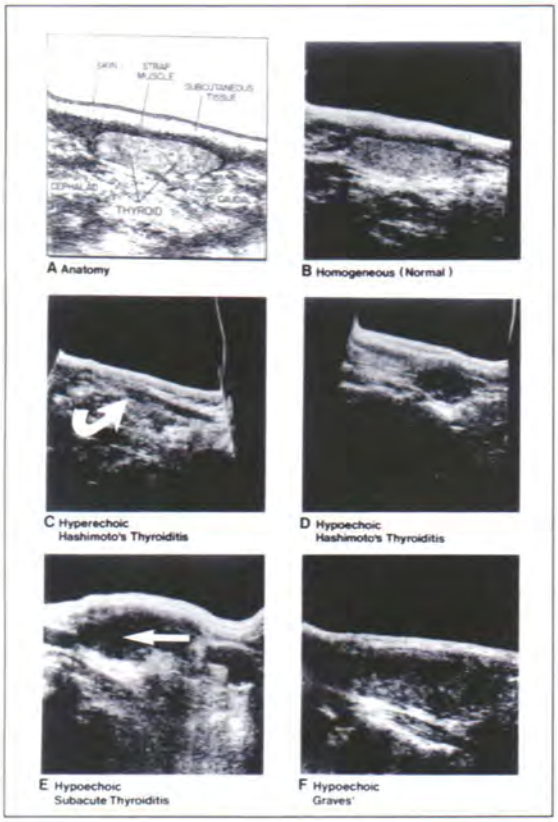

Fig. 1. **Thyroid gland anatomy and texture. A.** Normal anatomy of sagittal section of neck (artistic recreation) showing thyroid gland, strap muscles, subcutaneous tissue, and skin. B. Normal anatomy of sagittal section of neck as seen on thyroid ultrasound. C. Demonstration of an inhomogeneous, relatively hyperechoic gland typical of Hashimoto's Thyroidits. D. Demonstration of an inhomogeneous, predominantly hypoechoic gland, also seen in Hashimoto's Thyroiditis. E. Demonstration of an inhomogeneous, predominantly hypoechoic gland, seen in the acute phase of silent thyroiditis. F. Demonstration of an inhomogeneous, predominantly hypoechoic gland, seen in Graves' Disease with high antibody titres.
Straight arrows - areas of decreased echogenicity.
Curved arrows - areas of increased echogenicity.

INTRODUCTION

Radioisotope thyroid scanning has been a widely used tool for the evaluation of thyroid disease. Overall alterations in gland function give dramatic pictures of either an increase or decrease in

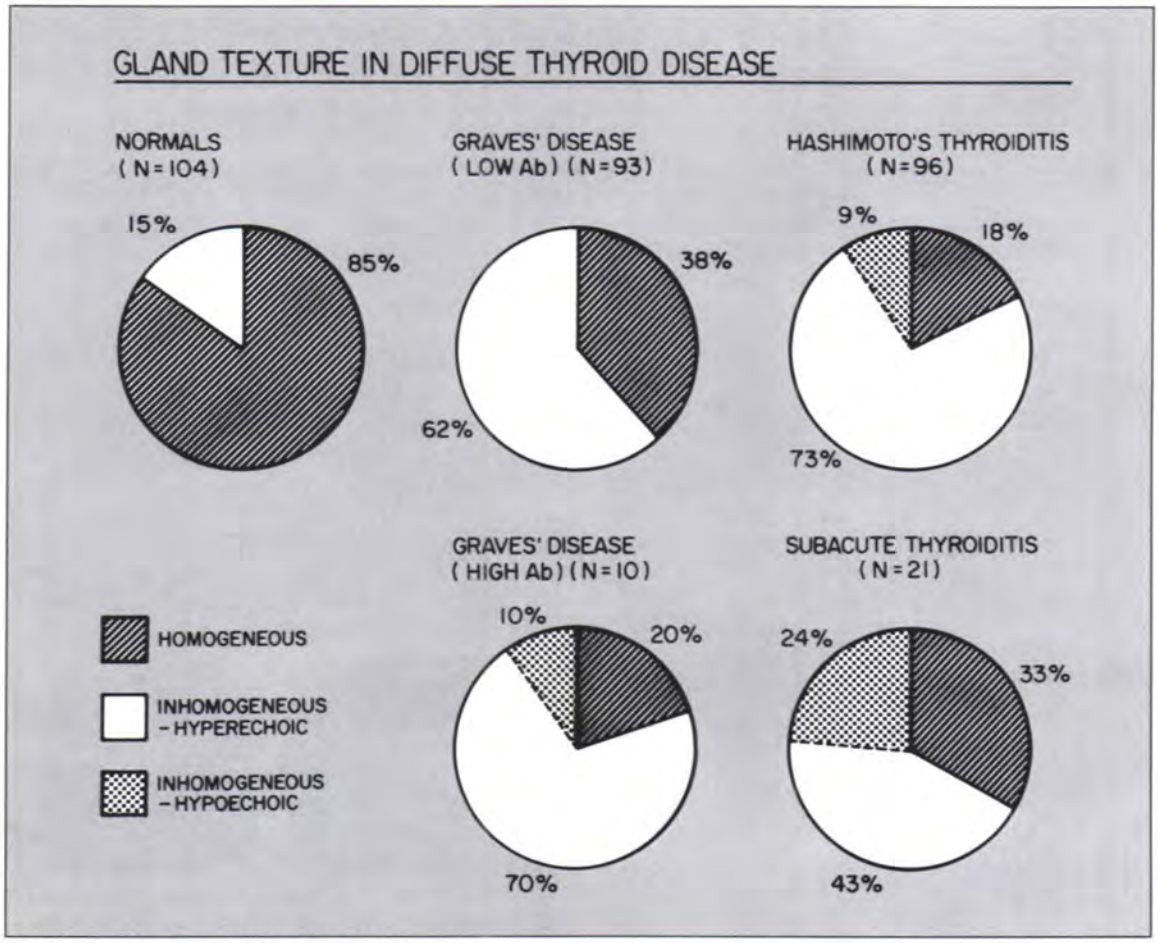

Fig. 2 - Gland Texture in Diffuse Thyroid Disease

radioiodine uptake; this is a characteristic of disorders that tend to affect the entire gland – diffuse thyroid disease (DTD). While ultrasound (US) imaging has been considered the gold standard for the evaluation of anatomic, focal lesions (1), it recently has been proposed, particularly in paediatric literature, that the role of radioisotope scanning in the differentiation of DTD can be replaced by ultrasonographic texture analysis (2,3,4). This study was initiated because it was thought that the US echopattern would be nonspecific; that is, that no one gland texture pattern is diagnostic of a particular DTD. Although the proposed role of US has been challenged previously (5), there is a need to determine the clinical usefulness of US as a diagnostic test for DTD in a single-blind, controlled, prospective study.

METHODS

The study was conducted at University Hospital in London, Ontario, Canada using a systematically acquired database. All patients referred to the Nuclear Medicine Department over a five-year period for a I-123 thyroid uptake and scan were subjected to an investigative routine. Information obtained included: a patient history guided by a standardized questionnaire; palpation of the thyroid gland by a Nuclear Medicine physician; results of total T4, total T3, T3 uptake, and TSH; antithyroglobulin and antithyroid microsomal antibody titres obtained by hemagglutination assays; real-time B-scan US images obtained with a 10 MHz Diasonics Wideview and later with a Diasonics 400 or Diasonics 1000 using a 7.5 MHz transducer and static B-scan US images obtained using a Picker Echoview system 80-L with a 5.0 MHz transducer; and a thyroid uptake and 3-view scans using a gamma camera and pinhole collimator to obtain images 24 hours following ingestion of I-123 NaI, 100 microcuries.

334 patients (mean age = 45.6 years; range = 9-89 years; 263 female, 71 male) were found to have probable diagnoses of either DTD or a normal study based on all available database information, excluding the US findings, as compared to established diagnostic criteria (Table 1). Graves' Disease, Hashimoto's Thyroiditis, and Silent Thyroiditis were chosen since these DTDs could

TABLE 1. DIAGNOSTIC CRITERIA

Disorder	Clinical Presentation	Laboratory Presentation
Normal	Palpation of gland within normal limits Clinically euthyroid	Euthyroid/normal thyroid indices
Graves' Disease	Thyrotoxicosis Infiltrative ophthalmopathy Infiltrative dermopathy	Elevated I-123 uptake Elevated T_3, T_4, and FTI Low TSH
Low Antibodies		Autoantibody titres 1:6400 or less
High Antibodies		Autoantibody titres 1:25600 or greater
Hashimoto's Thyroiditis	Indurated goitre or Nonpalpable gland ± Clinical hypothyroidism	Normal/slightly elevated I-123 uptake Overt or compensated hypothyroidism Autoantibody titre 1:2000 or greater
Silent Thyroiditis Variants: - de Quervain's - painless - postpartum	Painful thyroid gland Systemic manifestations Temporal relationship with upper respiratory infection or pregnancy	Elevated ESR Trends: - low (less than 2%) uptake at first, then elevated, then normal - thyroid indices show thyrotoxicosis, then transient euthyroid state, then hypothyroidism, and finally recovery

Abbreviations: T_4 - total tetraiodothyronine; T_3 - total triiodothyronine; ESR - erythrocyte sedimentation rate; FTI - free thyroxine index.

potentially be confused with one another, either by their clinical or laboratory presentation, depending on the stage of the disease. Since they all have different treatments and prognoses, it is necessary to be able to differentiate these disorders. Normal studies (patients that had been referred because of vocal cord paralysis, a neck mass, fatigue, anxiety, weight changes, or to search for a primary site of cancer in a patient with metastatic disease) were used as controls in the study. Two radiologists, both having greater than 15 years postresidency experience in academic staff positions, each interpreting 50% of the hospital's US images (L.H. is a diagnostic radiologist with a major interest in chest radiology and a subinterest in ultrasonography and R.R. is an interventional radiologist also with a subinterest in ultrasonography) were asked to blindly interpret the real-time B-scan and static B-scan US images and to comment on the gland texture. The texture was recorded as one of homogeneous, inhomogeneous-relatively hyperechoic, or inhomogeneous-predominantly hypoechoic. A homogeneous echopattern is characteristic of normal thyroid gland parenchyma: it has a smooth echorich pattern of stronger echogenicity than the surrounding strap muscles of the neck (2). Inhomogeneous echopatterns have areas of increased and decreased echogenicity within a single gland. These glands were subdivided into "relatively hyperechoic" or "predominantly hypoechoic" based on their overall appearance. Representative echopatterns are illustrated in Fig. 1, A-D.

A retrospective review of the cases designated as "silent thyroiditis" was carried out by longitudinal follow-up with referring physicians. All cases for the study were reviewed by an endocrinologist with a special interest in thyroid disease to verify that a spectrum of disease was present (mild and severe; treated and untreated) and to ensure that a definitive diagnosis had been made without the results of the US findings. As well, normal studies, being used as controls, were analysed to ensure that they did, in fact, represent a cross-section of normal glands in a true, random sample. This was done by comparison of the rate of occurrence of the incidental US abnormalities (such as nonpalpable cysts and micronodules that result in an inhomogeneous texture) in our group (39%) versus that in the literature (36%) (6).

Finally, a subset of each diagnostic category was set aside to have their ultrasounds interpreted a second time by the radiologist that had not yet seen the US images. Interobserver agreement could then be measured. The numbers available for the subset were limited by several factors. These included the relatively small number of cases of diseases with low prevalence in our community and the proportion at which the "normal" cases would appear in our US review so that the case selection would be neither weighted toward normal studies nor uncommon diseases. Eventually, 21 cases of each of Normals, Graves' disease with low autoantibody titres, Hashimoto's Thyroiditis, and Silent Thyroiditis and 10 cases of Graves' Disease with high autoantibody

titres were chosen. The resulting normal rate of 22.3% was a compromise between the rate of normal studies performed in tertiary care centres and "cottage-hospital" settings in our community. These 94 cases were delivered to the appropriate radiologist for review after having been randomized by a lottery system.

RESULTS

The occurrence of each echopattern in the 334 cases (homogeneous, inhomogeneous hyperechoic, and inhomogeneous hypoechoic) was calculated as a proportion for each diagnostic category (Fig. 2). A condensation of this information is shown in Table 2, where hyperechoic and hypoechoic glands are grouped together as "inhomogeneous". Interobserver agreement for the assessment of US gland texture in the subgroup of 94 cases was measured by the kappa statistic, which is an estimate of chance-corrected agreement used on categorical data. The kappa value was calculated for each category, and overall, considering (A) a division in gland texture description into homogeneous and inhomogeneous, and (B) a division in gland texture description into inhomogeneous-hypoechoic and normal/hyperechoic. These results are shown in Table 3.

DISCUSSION

The sensitive, noninvasive, high-resolution imaging modality of US is currently used to differentiate solid from cystic masses, solitary from multiple nodules, intrathyroidal from extrathyroidal lesions, and to assess gland size. If it could, as well, be used to differentiate diffuse thyroid diseases from one another, it would be useful in cases where radioiodine uptake and scanning could not be used. These situations would include pregnancy, childhood, adversity of radioisotope scanning, exogeneous thyroid hormone administration, and administration of iodine-containing medications or preparations. As well, the cost of a single US study is less than that of a single nuclear medicine study.

The echogenicity of the thyroid gland can be affected by an adjustment of the gain by the US technologist obtaining the images. However, in our favour for acquiring highly reproducible images is the fact that the thyroid gland is a superficial organ and is not a deep (in antero-posterior dimension) organ. There is, therefore, little need to manipulate the gain which could otherwise create an artificial gradient in a thick organ. A factor causing increased echogenicity in the gland is the degree of fibrosis and calcification; a factor causing decreased echogenicity in the gland is the degree of lymphocytic infiltration and edema (7,8,9,10). Thus, the pattern of echogenicity can be considered to represent such changes taking place in the gland parenchyma and these patterns can potentially be specific for certain diseases.

However, the results of this study show large overlaps in the distribution of the three basic echopatterns among the five diagnostic categories, suggesting that US is nonspecific. This is further illustrated in Fig. 1D-1F, which shows thyroid glands of three different diagnostic categories (Hashimoto's Thyroiditis, Silent Thyroiditis, and Graves' Disease with high autoantibodies) each having remarkably similar hypoechoic appearances. No echopattern can be considered diagnostic of a specific disease. It is possible, however, that very severe cases of a specific disease, as opposed to the entire spectrum of severity used in this study, may yield distinctive echopatterns. This could explain some of the dramatic results obtained in previous studies.

TABLE 2. GLAND TEXTURE IN DIFFUSE THYROID DISEASE

		GRAVES' DISEASE				
	NORMALS†	GRAVES (ALL PATIENTS)	GRAVES (LOW Ab)*	GRAVES (HIGH Ab)**	HASHIMOTO'S THYROIDITIS	SUBACUTE THYROIDITIS
•HOMOGENEOUS						
	85%	35%	38%	20%	18%	33%
	(87)	(36)	(34)	(2)	(17)	(7)
•INHOMOGENEOUS						
	15%	85%	62%	80%	82%	67%
	(17)	(67)	(59)	(8)	(79)	(14)
TOTAL	100%	100%	100%	100%	100%	100%
	(104)	(103)	(93)	(10)	(96)	(21)

Absolute number of patients in each group are shown in parentheses.

† Inhomogeneity mainly due to non palpable micronodules with otherwise normal gland texture.
* Both antimicrosomal and antithyroglobulin antibodies < 6,400 (normal <400)
** Either antimicrosomal or antithyroglobulin antibody >25,600 (normal <400)

Measurement of interobserver agreement allows a study to be translocatable to any centre with similar equipment and radiologists of similar experience and training. The kappa value of 0.52 (homogeneous vs. inhomogeneous, for all categories) shows good agreement (11) as opposed to the kappa value of 0.15 (hypoechoic vs. all other gland textures, for all categories). This implies that US is good for the detection of US abnormalities (such as inhomogeneity) which radiologists can recognize quite readily, but is not as useful for the detection of specific echopatterns (such as hypoechogenicity), which is less likely to be agreed upon.

Thus, in our study we found that US cannot replace radioiodine uptake and scanning for the differentiation of diffuse thyroid disease. ■

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TABLE 3. INTEROBSERVER AGREEMENT

Diagnostic Category	n	Kappa Statistic* (Homogeneous vs. Inhomogeneous)	Kappa Statistic* (Hypoechoic vs. Normal/Hyperechoic)
Combined/All Categories	94	.522	.149
Normal	21	.487	-.044
Graves' Disease (Low Ab)	21	.125	.244
Graves' Disease (High Ab)	10	0	.703
Hashimoto's Thyroiditis	21	.237	-.021
Silent (Subacute) Thyroiditis	21	.612	.308

* K < .40 - Poor agreement beyond chance
.40 < K < .75 - Good agreement beyond chance
.75 < K - Excellent agreement beyond chance[11]

Overview of Dementia of Alzheimer's Type

Current Neuropathological Mechanisms and Clinical Approach

by Ruth Dippel, Meds '95
Shirley Lee, Meds '92

Dementia is a clinical syndrome prevalent amongst our elderly population. Because dementia can be the result of a variety of causes and mechanisms, it is essential to differentiate it from potentially correctable causes. Dementia is a progressive syndrome which eventually affects all facets of a person's being -intellect, memory and personality (7). Too often, elderly persons are assumed to be "demented" or "slow" in thinking because of their age. Benign senescent forgetfulness, i.e. the mild degree of forgetfulness that accompanies aging, is markedly different from dementia, as it does not significantly interfere with work or usual social activities and relationships with others (3,7).

Dementia typically involves global or multifocal impairment of cognitive function. Diagnostic criteria for dementia include impairment in short and long term memory (the most prominent symptom initially), associated with impairment in abstract thinking, judgement, other disturbances of higher cortical function, and changes in personality and behaviour, in the absence of unconsciousness (3,7). The **incidence** of dementia increases exponentially with age, affecting approximately 2% of the population between 65 to 70, and 20% above the age of 80. It has been estimated that 12% of persons with serious dementia die of causes secondary to severe dementia (6).

The leading cause of dementia in 70% of cases is **Alzheimer's disease.** Approximately 15% are caused by **strokes,** with occasional involvement of multiple small infarcts (1). The remaining 15% of dementias are due to other neurodegenerative diseases, eg. Huntington's disease and Parkinson's disease, or treatable conditions. Secondary causes of dementia are numerous and are listed in Table 1 (1,2,3).

ALZHEIMER'S DISEASE

Alzheimer's disease is a difficult disease to diagnose in that most subtypes have no known etiology. As well, no effective treatment or cure presently exists. Unfortunately, the diagnosis of Alzheimer's can only be established with absolute certainty upon post-mortem examination of the brain. Alzheimer's is a **cortical** disease affecting mainly the frontal and temporal lobes. Typically, the ventricles are enlarged with increased spaces between the gyri (7). The neuropathologic hallmark of Alzheimer's disease is the presence of **senile amyloid plaques** and **intracellular neurofibrillary tangles.** At this time it is not known what role these pathological changes play in the process of Alzheimer's, although there are a number of ongoing theories (2,9). Profound **neurotransmitter deficits** have also been found in Alzheimer patients involving mainly choline acetyltransferase in the cerebral cortex and hippocampus, with involvement of other neurotransmitters as well (3,6,7). Reduced activity of neurotransmitters in turn are associated with reductions in cerebral blood flow and decreased oxygen and glucose metabolism in the brain (4,7). Increased concentrations of aluminum deposits have also been found in the brains of Alzheimer patients (11). At this time, ongoing research seems to indicate that it is an important risk factor in the pathogenesis of Alzheimer's, although its exact mechanism is not known (11).

Genetic transmission of Alzheimer's has been documented in some cases of familial Alzheimer's. Genetic predisposition appears to play a greater role in cases of early-age onset of Alzheimer's, i.e. in those diagnosed in the 40-50 age group (2). In these families, an autosomal dominant pattern may be found. The risk of Alzheimer's disease hase been found to be 7 times greater if a first degree relative has the disease (6). A correlation between Down's syndrome (trisomy 21) and Alzheimer's disease has also been found, with the majority of people with Down's syndrome developing brain lesions typical of Alzheimer's after 35 years of age (2,5,8). In most patients diagnosed with Alzheimer's disease, the lifespan is 2 to 15 years (average 8 years) after the onset of symptoms (7).

VASCULAR DEMENTIA

This section will only cover Vascular dementia briefly, in order to acquaint the reader with basic concepts, as a more extensive coverage of Vascular dementia has been provided in the following article, courtesy of Dr. V.C. Hachinski.

Vascular dementia, or Multi-infarct dementia (MID), results from the occurrence of multiple discrete lesions occurring at different times, involving both large and small cortico-subcortical infarcts, lacunar infarcts, and widepread white matter ischemic changes (3,4).

The diagnosis of Vascular dementia is characterized by a sudden onset, reinforced by a history of previous stroke (7). Vascular dementia is differentiated from Alzheimer's disease in that patients diagnosed with the former disorder typically experience a stepwise deterioration and a "patchy" distribution of deficits suggestive of **focal** ischemic brain lesions. In comparison, Alzheimer's disease has a tendency toward progressive decline with no periods of improvement. A previous history of cerebrovascular disease i.e. hypertension, coronary heart disease, thromboembolic disorders, cardiac arrythmias, previous myocardial infarct, and systemic hypotension are often associated with Vascular dementia and not with Alzheimer's disease (3,4). Evidence of focal neurologic signs and symptoms i.e. increased deep tendon reflexes, extensor plantar response, pseudobulbar palsy, ataxia, and extremity weakness, also increase ones suspicion of MID (3). Primarily, the most common cause of MID is recurrent bilateral cerebral embolism from the heart and/or carotid arteries (3,4).

The dementia seen in Binswanger's disease (i.e. subcortical atherosclerotic encephalopathy) involves a substantial loss of subcortical white matter and ventricular enlargement secondary to hypertension and atherosclerotic disease involving vessels supplying the white matter area (7).

TABLE 1 – Secondary Causes of Dementia

1. **Chronic CNS infections**
   - tertiary neurosyphilis
   - tuberculous and fungal meningitis
   - viral encephalitis
   - HIV & HIV-related disorders
2. **Brain trauma** - chronic subdural hematoma
3. **Toxic-metabolic disturbances**
   - pernicious anemia (Vitamin B12 deficiency)
   - folate deficiency
   - hypothyroidism
   - bromide toxins
4. **Brain tumors**
   - slow growing, CSF-obstructing intraventricular tumors
   - subfrontal meningiomas
5. **Normal pressure hydrocephalus**
6. **Postanoxic and posthypoglycemic states**

(N.B. This list is by no means complete, but is provided to give the reader examples of the main areas of secondary dementia causes).

CLINICAL PRESENTATION

Typically dementia has an insidious onset over several months with progression of symptoms. **Memory impairment** is often the most prevalent sign, affecting both short and longterm memory. In mild cases of dementia, patients forget telephone numbers, directions, and have difficulty in recalling the day's events. In more severe cases, names of close relatives as well as birthdays are forgotten, with the patient no longer being able to carry out activities of daily living. Inappropriate behavior, impaired judgement, and mood changes (characteristic of depression, apathy, and agitation) are often seen. Disturbances of higher cortical function is seen in more severe cases of dementia, affecting areas such as language (rambling, repetitious, aphasia, dysarthria), and perception (hallucinations, illusions). There is often an impairment of abstract thinking as well, where patients are unable to find similarities and differences between related words. As the dementia progresses, physical deterioration occurs with decreased food intake secondary to depression, and an inability to maintain personal hygiene (1,3).

In the work-up of dementia, certain lab tests are essential to rule out reversible causes. They include CBC,ESR, blood glucose, electrolytes, calcium, liver function tests, thyroid function tests, serum B12 and folate, chest x-ray, EEG, and CT/MRI (7).

N.B. For a more elaborate discussion of specific physical examination findings and lab investigations employed to confirm the diagnosis of a certain dementias, the reader is referred to Harrison's Textbook of Internal Medicine, 12th Ed. pp183-193).

MANAGEMENT

Using the above work up, approximately 10% of dementias are found to be treatable neurologic disorders or systemic illnesses. Another 10% are found to be pseudodementias, which are due to treatable psychiatric illnesses. In another 10% of cases, a modifiable factor is usually found, such as alcoholism or hypertension. The remaining cases of dementia are usually irreversible (7). At this time, there is no known treatment or cure for dementia. Various therapies have been experimented with, using a variety of methods, eg. vasodilators, vitamins, and hyperbaric oxygen. In the early stages, psychotropic drugs can be of some use to treat associated depression, anxiety, insomnia, and psychotic symptoms. However, it should be noted that these medications can sometimes exacerbate symptoms instead of improving them, especially in the elderly. At this time the therapeutic approach toward irreversible dementia consist of mainly supportive measures for both the patient and the families involved. As patients with Alzheimer's tend to do better at home, every effort is made to assist families, through the use of VON's and support groups. We can only hope that ongoing research can someday help us better understand and treat this common clinical syndrome which affects so many of our elderly. ■

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Towards a New Understanding of Vascular Dementia

by Vladimir C. Hachinski, MD, DSc. (Med)
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Once it was thought that our mind was as old as our brain arteries, their slow narrowing by atherosclerosis leading to cerebral ischemia and neuronal death. Cerebral blood flow and metabolism studies discredited this view and established that chronic ischemia does not occur in the brain. When vascular disease is responsible for cognitive changes, it is through the agency of multiple cerebral infarcts (multi-infarct dementia). With increasing recognition of Alzheimer's disease as the leading cause of dementia in the Western world, multi-infarct dementia came to be considered rare, although world-wide the leading cause of mental impairment in the elderly are vascular (5). Moreover, multiple cerebral infarcts often coexist or complicate Alzheimer's disease.

THE MATTER OF WHITE MATTER

The advent of sensitive brain imaging techniques in the mid 1970's began revealing brain white matter changes in the elderly, particularly those with dementia. The hitherto obscure entity of "Binswanger's disease" began increasingly to be invoked as an explanation for these white matter changes. "Binswanger's disease" is neither Binswanger's nor a disease (3), and the white matter changes seen on computer tomography (CT) and magnetic resonance imaging (MRI) scanning of the brain are almost certainly heterogeneous (4). The causes range from increased fluid (vacuolation) in the brain to small infarctions and enlargement of perivascular spaces (7). The most intriguing etiologic possibilities occur in Alzheimer's disease. About one-third of Alzheimer's patients will show white matter changes (leukoaraiosis) on CT scan and an even higher proportion on MRI imaging of the brain. This finding correlates with the severity of the dementia and the rate of progression of the disease (6, 2). The etiology of these vascular changes remains unknown, but it may be related to a very extensive deposition of amyloid in the blood vessels of patients with Alzheimer's disease. Moreover, there is some evidence that the blood vessels of Alzheimer's patients are denuded of the normally rich network of nervous innervation (9), probably leading to impaired cerebral blood flow autoregulation. Patients with leuk-araiosis may have not only a decrease in the cerebral blood flow to the white matter, but they may display an impairment in autoregulation (1). This impaired autoregulation could result in repeated fluctuations in brain perfusion following changes in systemic blood pressure which would imperil the survival of oligodendroglia, the most sensitive cells in the brain to ischemia, leading to demylination and white matter change.

PROBLEMS AND SOLUTIONS

In the past neurology has been characterized by anatomic exactness and etiologic uncertainty. A classification that includes a definition, a description of clinical manifestations and the usual course when applied to an entity such as Alzheimer's disease are appropriate. When applied to the syndrome vascular dementia, such a classification does not make sense. Vascular dementia is the end result of a number of processes, as diverse as the causes of stroke itself. And yet, most textbooks deal with vascular dementia as if it were a single entity. Attempts at subclassification of vascular dementia usually have been in terms of the end result, i.e. cortical versus subcortical dementia, for example, and not in terms of etiology, such as atherosclerotic extracranial disease, hypertensive small vessel disease, or cardiac embolism. From the therapeutic viewpoint, it is the etiology that matters since so much of stroke is now treatable and preventable.

A further conceptual obstacle to progress is the definition of dementia itself. To some it implies reversibility, to others it has no such implications;in some people's minds it means a global cognitive impairment, others look at dementia as being a multi-focal but not necessarily a global process. A more serious problem is that by

TABLE I

TREATMENT AND PREVENTION OF VASCULAR DEMENTIA

I. Brain at Risk Stage

- The Aged
- Hypertensives
- Smokers
- Diabetics
- Blacks
- Hispanics
- Orientals
- Atrial fibrillators
- Cardiac patients

II. Pre-Dementia Stage

- Patients with transient ischemic attack
- Patients with stroke
- Patients with subtle cognitive impairment
- Patients with silent cerebral infarctions

III. Dementia Stage

- Cardiac embolism
- Atherosclerosis
- Other

TABLE II

POTENTIAL THERAPIES OF VASCULAR DEMENTIA

I. Brain at Risk Stage

- Smoking cessation
- Exercise (prevention and management of diabetes)
- Diet (control of diabetes, hyperlipidemias, obesity)
- K+ supplementation (vascular protective effect)
- Antihypertensives (ACE inhibitors and Ca++ channel blockers may be particularly suitable)
- Lipid lowering agents
- Anticoagulants (for atrial fibrillation)
- Aspirin (for selected patients at high risk)

II. Pre-Dementia Stage

- Carotid endarterectomy (symptomatic patients with carotid stenosis of 70-99%)
- Anticoagulants
- Aspirin
- Ticlopidine
- Agents that interfere with amyloid deposition in vessels
- Ca++ channel blockers (pretreatment to attenuate effect of infarcts)

III. Dementia Stage

- Antidepressants
- Antihypertensives
- Cholinergics
- Aspirin
- Ticlopidine

the time that a patient has satisfied a conventional definition of dementia, it is often too late to treat the condition or prevent further damage. In view of the major advances in stroke prevention that have occurred recently (8), it makes more sense to consider treatment and prevention of vascular dementia as occurring in different stages.

A number of potential treatment and preventive measures have become both larger and based on every increasing higher standards of proof.

CONCLUSION

The vascular dementias are as diverse as the causes of stroke itself. A number of measures of stroke prevention have proven effective in the recent past, but very few of them have been applied to the prevention and treatment of vascular dementia. This is an area where there are many tools, and very few doing the job. ■

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The Role of $InsP_3$ Receptors and Excitatory Amino Acids in the Pathophysiology of Neurodegenerative Disorders

by Jeffrey Politsky, Meds '94

INTRODUCTION

It is now known that the production of intracellular (IC) second messengers and the subsequent activation of associated protein kinases mediates the physiological effect of many CNS neurotransmitters[3,26,27]. The molecular components of such signal transduction systems include specific receptor recognition sites, a complement of guanine-nucleotide binding proteins (G-proteins), and second messenger-generated enzymes. The G-proteins provide functional coupling between receptors and their effector enzymes[17].

One classical type of signalling system involves the stimulation of cyclic adenosine monophosphate (cAMP) formation due to receptor mediated activation of adenylate cyclase. A second more recently discovered receptor-linked signal transduction system involves hydrolysis of inositol-containing membrane phospholipids by phospholipase C (PLC). The hydrolysis of membrane polyphospho-inositide (PPI), primarily phosphatidylinositol-4,5-biphosphate ($PtdInsP_2$), produces two second messengers: inositol-1,4,5-triphosphate ($InsP_3$) and diacylglycerol (DAG). Of particular significance, these second messengers closely regulate either directly or indirectly, IC calcium (Ca^{++}) levels; this regulation is important for the maintenance of neuronal function[4].

The cellular effects of many CNS neurotransmitters (including acetylcholine (ACh), dopamine (DA), norepinephrine (NE), serotonin (5-HT), and glutamate (Glu)) are linked through the inositol phospholipid (IPL) signalling pathway to the mobilization of IC Ca^{++}. It is now recognized that the impairment of the regulation of IC Ca^{++} homeostasis contributes to the pathogenic process of certain neurodegenerative disorders [21]. Given that a disturbance in IC Ca^{++} flux may aid the development of certain neuropathological conditions and that certain neurotransmitters are coupled to IC Ca^{++} flux through PPI-generated second messengers, it is possible that both these neurotransmitters implicated and their associated IC second messengers are involved in specific neuropathogenic processes. Indeed, each of ACh, DA, NE, 5-HT, and Glu have been implicated in the etiopathogenesis of certain neuropsychiatric disorders[10,13,33]. Furthermore, recent findings suggest that IPL turnover may also be altered in certain disease states[14,38,47].

Excitatory amino acid (EAA) receptors are among the most abundant type in the mammalian CNS[45]; Glu, aspartic acid (Asp), and perhaps other EAAs mediate synaptic transmission at the majority of excitatory synapses in the brain[46]. Furthermore, glutamatergic transmission occurs through receptor subtypes which activate either ion channels (ionotropic) or IC metabolic (metabotropic) responses, such as second messenger formation. EAA receptor activation is a field of study undergoing intensive examination and rapidly changing concepts. Nonetheless, Table 1 lists the current classification of EAA receptors[8,16,37]. Brain regions with the highest density of EAA receptors include the hippocampus, striatum, and cerebellum[19,22,46]. There is much evidence to indicate that where as NMDA, KA and AMPA preferentially activate ionotropic receptors, Quis and Ibo stimulate both ionotropic and metabotropic receptors[45]. The metabotropic receptors activated by Glu are coupled to PLC and lead to $PtdInsP_2$ breakdown[24,25,37].

There has been much sustained interest in the proposal that Glu receptor activation may cause neuronal injury[2,18,28,34]. The progression toward Glu-mediated neuronal injury involves two stages[18,34]: an immediate, reversible component of cell swelling; and a secondary component of delayed cell degeneration. The first phase is dependent upon Na^+, Cl^-, and H_2O influx. The second phase, which may be irreversible, is dependent upon sustained Ca^{++}-dependent depolarization in response to extracellular Ca^{++} influx to intracellular Ca^{++} concentrations and to $InsP_3$[30]. The most likely mechanism underlying

TABLE 1: CLASSIFICATION OF EXCITATORY AMINO ACID RECEPTORS

Receptor Subtype	Receptor Function	Ionic Properties
NMDA	Ionotropic	Na+-dep.; Ca^{++}/Cl^{-} – dep.
KA	Ionotropic	Ca^{++}/Cl^{-} – indep.
AMPA	Ionotropic	Ca^{++}/Cl^{-} – indep.
$Quis_p$	Metabotropic	Ca^{++}/Cl^{-} – dep.
Ibo_p	Metabotropic	Ca^{++}/Cl^{-} – dep.
L-AP4	Autoreceptor	??

ABBREVIATIONS: AMPA, a-amino-3-hydroxy-5-methylisoxazole-4-proprionic acid; L-AP4, L-2-amino-4-kphosphonobutyrate; Asp- Aspartic acid, Glu, Glutamic adid; Ibo_p, Ibotenic acid (receptor subtype associated with PPI hydrolysis); KA, Kainic adic, NMDA, N-methyl-D-asparatic acid, Quis, Quisqualic acid (receptor subtype associated with PPI hydrolysis), dep., dependent; indep., independent; ??, unknown.

the toxic Ca^{++} influx appears to be NMDA receptor activation, which opens channels permeable to Na+ and Ca^{++}[8,22,45]. Furthermore, a number of observations indicate a putative role for PtdIns breakdown products in sustaining the Ca^{++} - dependent depolarization during the delayed phase of excitotoxic damage[18,40].

NEUROPATHOLOGICAL PROCESSES, EXCITOTOXICITY, AND $InsP_3$ RECEPTORS

Dementia of Alzheimer's Type

Senile dementia of Alzheimer's type (DAT) is a neuro-degenerative disorder that becomes clinically apparent between 50 and 65 years of age, although signs of the disease may manifest earlier[9]. There is some tendency, albeit sporadic, to familial occurrence[9]. One subtype of the disease has an apparent genetic localization to chromosome 21q21 – the etiopathology of the majority of subtypes is unknown[20]. Cognitively, severe language, memory, and thought disturbances characterize this disorder[6]. The distinguishing morphological alterations in DAT include neurofibrillary tangles associated mostly with the hippocampus and senile plaques seen predominantly in the neocortex[48]. A major neurochemical defect in DAT is the loss of cholinergic neurons innervating the hippocampus, cortex, and nucleus accumbens[23].

Recent findings suggest that the pathogenesis of DAT also involves alterations in PPI turnover. For example, Stokes et al identified significantly reduced levels in the anterior temporal cortex of DAT brain[38] – unfortunately, no other brain regions were examined. In another study, Young L. et al observed a 50-70% reduction in the binding of $[^3H]$-$InsP_3$ in the parietal and hippocampal cortices of DAT brain[47]. These changes in $InsP_3$ binding reflected changes in receptor binding density (B_{max}; i.e. the maximum number of binding sites available), but not the receptor binding affinity (K_D). Although more than one cortical region is usually affected in DAT, Young L. et al did not find significant changes in $InsP_3$ binding in any other cortical region of diseased brain[47]. Additionally, no significant changes in binding were observed in the amygdala or caudate, two regions not primarily affected in DAT; this result, however, may have reflected the small sample sizes used for these brain areas[47]. The authors suggested as one possibility that this deficit in $InsP_3$ binding was related to cell loss.

Olivopontocerebellar Atrophy

Olivopontocerebellar atrophy (OPCA) is an autosomal dominant disorder[32] characterized by the development of cerbellar ataxia and extensive destruction of Purkinje cells. Whereas minimal changes occur within the cerebellar granule cell layer, marked gliosis occurs in the Purkinje cell and molecular cell layers[14].

Two excitatory inputs to Purkinje cells are the climbing fibers from the inferior olives of the brainstem and parallel fibers from the granule cells[5]. Aspartate, which increases Ca^{++} permeability through inotropic receptors, is the neurotransmitter of the climbing fibers[43]. Glu is the neurotransmitter of the parallel fibers[35]. In Purkinje cells, Quis is 30 x more potent than Glu at

maximally augmenting [^{3}H]-InsP_3 formation, suggesting the presence of a Quis$_p$ receptor subtype in these cells[5].

Results from a recent study examining InsP_3 binding in OPCA are consistent with the possibility that alterations in PPI-generated second messengers are associated with the pathogenesis of OPCA[14]. For instance, Kish et al. observed significant reductions (61%) in [^{3}H]-InsP_3 binding in cerebellum, but not in frontal or occipital cortices of OPCA brain compared with control brain[14]. Due to limited tissue supply, these investigators did not perform competition assays on diseased tissue; thus it was not possible to attribute the decreased binding to changes in K_D, B_{max}, or both. The reduction of InsP_3 binding supports the localization of such sites to Purkinje cells, specifically to the dendritic zones which are greatly reduced in OPCA[14].

Cerebrovascular Accident

Cerbrovascular accident, or stroke, refers to the acute onset of a focal neurologic deficit, such as hemiparesis, and is caused by a disutrbance in cerebral circulation[9]. Vascular events which cause stroke may be progressive, complete (maximal upon onset), or associated with transient ischemic attacks. Ischemic episodes may develop suddenly, lasting from seconds to hours, with the exact neurologic features indicating the brain region involved[1]. Several lines of evidence support a potential role for the IPL signal pathway in ischemia. For example, after hypoxic ischemia-induced neuronal cell death, enhanced agonist-stimulated PPI hydrolysis was observed in CA1 hippocampal and striatal cells[36]. As well, Onodera and Kogure found that post-anoxic reperfusion after induction of transient forebrain ischemia in CA1 hippocampal cells caused a significant (23%) in InsP_3 receptor sites only three hours after ischemia and prior to any morphological alterations[29].

Huntington's Disease

Huntington's disease (HD) is a progressive neurodegenerative disorder with autosomal dominant inheritance. The gene for HD maps to chromosome 4p16.3 using a G8 probe[20]. The gene is completely penetrant with initial signs of the disorder, motor or mental, manifesting between the third and fifth decade of life and lasting approximately 16 years before death[7]. Choreoathetosis and slow, dysarthric, nonaphasic speech chanracterize the progressive motor impairment of HD; mental disturbances present as nonamnesic forgetfulness, slowed cognition, apathy, and depression[6].

In HD brain, the most prominent morphological changes are nuclear membrane displacement, bleb formation, perinuclear space enlargement, and bilateral, nonspecific, gray and white matter atrophy[15]. Degenerative changes are most marked in striatum, moderate in frontal and occipital cortices, and mild in thalamic and hypothalamic nuclei[15]. Neuronal loss in the dorsal striatum may reach 70-85%[41], and with accompanying astrocytic proliferation and may produce a neuron to glial ratio of 1:2-3.5 in early stage HD and a ratio of 1:>30 by late stage HD[41].

The levels of sundry neurotransmitters, hormones, and cell specific proteins have been measured in HD. Primarily, deficits in these substances occur in the striatum, and include reductions in glutamic acid decarboxylase, GABA-transaminase, chloine acetyltransferase, ACh, DA D_1 and D_2 receptors, substance P, Glu, NMDA, KA, and Asp[7,11-13,31,46]. For a more detailed discusssion of this list, the reader is encouraged to examine these references.

The ability of EAA's to produce pathological changes in animal brain similar to those seen in HD brain suggests that EAA-induced neurotoxicity may play a role in this disorder. These animal models of HD involve intrastriatal injections of quinolinic acid (a Glu agonist)[2,44].

Experimental evidence exists which suggests that InsP_3 receptor function, formation, or both, might be affected in HD striatum compared with non-neurologic controls. Recent experiments of [^{3}H]-InsP_3 binding in HD brain showed significant reductions in B_{max} in the caudate (-71%) and putamen (-75%), but not in the frontal or occipital cortices of post-mortem brain tissue from HD patients compared with controls[42]. Furthermore, further binding analysis performed on caudate nucleus showed reductions in both binding density (-57%) and affinity (-50%) in HD brain compared with controls. The authors offered a number of plausible expalnations to account for the concomitant changes in both B_{max} and K_D including increased inhibition of InsP_3 receptor binding by a Ca^{++}-sensitive protein associated with the InsP_3 receptor complex [42]. Other explanations also included alterations in glucose metabolism, alterations in cytoskeletal architecture, or over-activation of NMDA - or Quis$_p$-sensitive Glu receptors leading to elevated IC Ca^{++} levels and consequent cell destruction.

The findings related to alterations in PPI hydrolysis in the disease states discussed, suggest a potential role for InsP_3 receptor formation and function in the mechanisms of neuronal injury

associaed with DAT, OPCA, CVA, and HD. This role may be linked to EAA receptor over-activation. In each disease (with the possible exception of DAT), the alterations of $InsP_3$ binding tended to reflect the brain regional specificity of the respective disease states. In DAT, OPCA, and CVA, changes in $InsP_3$ binding may simply be a reflection of general cell loss. In HD, alterations in $InsP_3$ binding suggested these changes may be associated with mechanisms beyond those reflecting the loss of cells.

None of the experimental evidence implicating alterations in PPI hydrolysis in neuronal injury suggested when in the course of disease changes in $InsP_3$ binding may occur. For example, in HD, findings revealing that alterations in $InsP_3$ are as marked in early-stage HD as they are in late-stage HD would provide strong support that these receptors are associated with the pathophysiology of HD. Thus, time course studies of $InsP_3$ binding at various stages of pathology may be useful.

IMPLICATIONS

In summary, compromise of IC Ca^{++} homeostasis leading to sustained elevations of IC Ca^{++} levels is an obligate step in the development of cytotoxicity. Furthermore, neuronal cell death, the hallmark of neurodegenerative disease, occurs in association with sustained elevations of intraneuronal Ca^{++} levels subsequent to Glu-induced excitotoxicity.

Several lines of evidence suggest that enhanced $InsP_3$ formation and stimulation of Ca^{++} release from the endoplasmic reticulum might participate in or be affected by the pathophysiological processes leading to neuronal cell death in a number of neuropsychiatric illnesses. Whatever the exact mechanism(s) that underlie the changes in $InsP_3$ receptor binding observed in various neurodegenerative diseases, the findings of altered $InsP_3$ binding indicate that the neuropathophysiological processes leading to these disease states involve alterations in $InsP_3$ receptors. To this extent, it may be appropriate to reconsider the therapeutic strategies for these neurologic illnesses as current therapeutic approaches (which do not prevent the progression of disease) for these disorders involve drugs which act at the cell surface and not distal to it. ■

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