THE NOVA SCOTIA MEDICAL BULLETIN

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A Happy New Year

This is the time of year when all of us seek to renew our hopes and ideals, and to put behind us all that is old and outworn. It is traditional to take stock, and to examine our faults and blessings, our failings and our virtues, so that we may firmly resolve to act in accordance with our principles.

Within The Medical Society of Nova Scotia, the Physicians Services Committee has been taking stock of the attitude of the Society towards Government intervention in Medical Services Insurance, collating the resolutions which have embodied the thinking of the members of the Society over the years into a most impressive series of memoranda on all aspects of this problem. Members of Council have all received copies of these collected thoughts in draft form at the Annual Meeting of the Society in Nova Scotia, and will have had the opportunity to examine the impressive logic and calm clear statements of each aspect of the relation of the physician to Government Insured Services. Each Branch Society has had an opportunity of reviewing these documents, and it is hoped that selected extracts or a summary will be published in the Bulletin once the final draft is approved.

Never before have the members of the Medical Society had such a clear statement of principles placed before them: never before have our members been in such need of a clear understanding of these principles. For in the coming year the final form and function of the Medical Insurance Act will become clear, and each and every one of us will have to ask ourselves whether we can live with this creature without compromising our fundamental principles, or whether we must reject it. We must ask ourselves whether the Government of Canada has asked the people of this country to accept a programme which will inevitably "supply the lowest acceptable rather than the highest possible standard of medicine"[1]. We must ask ourselves whether the programme is one which must inevitably be followed by a gradual deterioration in the quality of medical care instead of a continued advance. Is it wasteful and inefficient, or are the controls or restrictions imposed only those necessary for the maintenance of quality medical care?

At the time of going to press, we note with satisfaction the first sign of a willingness on the part of the Federal Government to introduce some element of flexibility into Bill C227, in allowing the Provinces some degree of choice on the supplementary benefits which may be included in provincial plans. As yet, there is no evidence of a change of heart in their attitude to universal compulsory coverage, and the suppression of non-profit organizations presently providing medical insurance at cost. Nor has there been any attempt to unravel the untidy mess of Federal schemes for the Veterans, the Indians, Sick Mariners and the Workmens Compensation Boards of the provinces, so that all medical services would be covered by the one Act. Bill C227 still excludes those services supplied by physicians under the Hospitals and Diagnostic Services Act such as radiology and pathology, perpetuating an unhealthy dichotomy within the profession.

All these anomalies point to the haste in which this bill was conceived, and to the lack of imagination and initiative of those who are currently attempting to foist it on the Canadian public. It is the responsibility of those members of the public who will be called upon to provide this service, and who, as taxpayers, will be called upon to provide a large portion of the funds required, to ensure that everything is done to transform bill C227 into an efficient workable plan for providing medical services. This means the use by everyone of us of all the available channels of communication: to our patients, to our local representatives, to representatives of other organisations, to the editors of news media, and to our members of parliament. Medical services insurance was our idea in the first place, and doctors have done more than any other body, party or group to make these services available to the largest possible number of Canadians. We cannot allow the public to accept a second class, inferior substitute.

Let us resolve to reaffirm our principles, the distillation of the wisdom of all the members of our society, and to make them known to all; only then can we, with clear conscience, wish ourselves, and all Canadians A HAPPY NEW YEAR. □

I.E.P.

References

1. Griffiths A. J. Presidential Address to Medical Society of Nova Scotia November 6616.

ERRATA

December 1966 issue of The Bulletin

Page 320 Fig. 5 renumber Fig. 7
Fig. 6 renumber Fig. 5
Fig. 7 renumber Fig. 6

Page 321 Table I second column should read:

Percentage Discharged Within two Weeks.

The Bulletin tenders its apology to Dr. Buhr for the scurvy treatment of his manuscript.

Ed.

Correspondence

Hearing and Speech Clinic

To the Editor:
Nova Scotia Medical Bulletin
Sir,

In December, 1966, I received a mimeographed announcement in the mail from W. D. Mills, Chairman, Board of Management, Hearing and Speech Clinic, Robie Street, Halifax.

This announcement stated that "the Clinic's services are continuing"; that the Clinic is doing "the auditory *screening* of adults and children over the age of three years. Infants and children under three years of age are being put on a waiting list."

I would like to bring to the attention of my fellow society members that since the untimely resignations from that Clinic of Adam Sortini, Ed.D. Audiology and Speech Pathology, as Administrator, and A. G. Shane, M.D., Medical Director and Consultant in Otolaryngology, the same high quality testing and diagnosing of hearing difficulties in all age groups is no longer availble there.

The board that circulated the above-mentioned announcement did so knowing that Dr. Sortini's services are still available at the Speech and Hearing Centre, Quinpool Road, Halifax. To suggest that doctors in this province put suspected hard of hearing children under the age of three on an indefinite waiting list instead of having them tested at an available clinic as soon as possible is preposterous.

No doubt Mr. Mills and his board are very concerned about the hard of hearing children of this province. However, it appears that they are prepared to put the "system" first and the welfare of patients second.

Could this be a sample of the type of bureaucratic interference in medical care we can expect under government controlled P.S.I? Unless we become cognizant of the facts of bureaucratic and political interference in medical practice and unless we are prepared to find some way to combat it, then the level of medical care in this province will surely deteriorate.

Yours very truly,

P. B. Jardine, M.D.

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Pulmonary Emphysema

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Patients with irreversible airway obstruction present in fact with a variety of overlapping respiratory disorders. Pulmonary emphysema is tightly locked into this constellation of airway obstruction and its unencumbered recognition at an early phase is of utmost importance.

Pulmonary emphysema is a world wide disease and appears to be more common in the Northern hemisphere where chronic bronchitis is endemic. It is also closely associated with chronic asthma, but is seldom seen in patients dying of acute status asthmaticus. Stemming from the shrewd observations of Laennec, the last 150 years continue to emphasize the close relationship of emphysema with chronic bronchitis. While such a relationship undoubtedly applies to some forms of pulmonary emphysema, clinical experience recognises irreversible airway obstruction without pre- or co-existing chronic bronchitis.

The pathogenesis of the more common form of pulmonary emphysema remains very largely theoretical, and the several highly artificial methods designed to reproduce emphysema alone produce results which have little in common with the naturally occuring disease. Recent patho-physiological observations have, however, provided a better understanding. Current pathological classifications are particularly useful, certainly preferable to the older terms of hypertrophic and atrophic emphysema, and they correlate fairly well with clinico-physiological observation.

Pathological classification of pulmonary emphysema

1) Regional dilatation of air-sacs.
   a) Compensatory emphysema
   b) Focal emphysema secondary to dust diseases and lobar bronchial obstruction
2) Destruction of the walls of the air-sacs
   a) Diffuse panacinar destruction of alveolar walls and lobar dilatation.
   b) Centrilobular emphysema with air-sac dilatation related to diffuse irreversible bronchiolar wall narrowing.
3) Regional destruction of air-sacs
   a) Giant bullous emphysema

This neat pathological classification does not preclude combinations of more than one type of emphysema. Nevertheless the major components of the common obstructive lung disorders are centered around the panacinar and centrilobular types outlined under (2). Fairly specific morphological detail concerning these two major types of emphysema emerges from electron microscopy.

Electron Microscopy

The alveolo-capillary membrane progressively disintegrates leading to fenestration of the alveolar walls. A system of trabeculae remains containing the residual bronchioles (irreversibly damaged in the centrilobular variety), pulmonary arterioles and venules as well as some lymph vessels. These trabeculae remain covered by an epithelium containing cells with short micro-villi and rare laminated bodies. The elastic fibres are truncated and thick in collagen and interlace at random within the trabeculae. Actual collapse of the alveolar connective tissue fibres around the broncho-vascular trabeculae coincides with the disappearance of a recognisable alveolo-capillary membrane and with free coalescence of the air-spaces.

The Patho-Physiology of Pulmonary Emphysema

The distension of the emphysematous lung is readily revealed by an increased residual volume, and this is accompanied by a variable diminution in vital capacity. Alterations in static lung volumes are not, however, characteristic of emphysema and occur in other forms of obstructive lung disease. Obstruction to air flow in emphysema differs from that in asthma in that it follows expiratory collapse of the airways consequent upon loss of elastic recoil in the lungs. Expiration is normally passive from elastic recoil which drives the air up the airways and maintains the pressure above that of the intrapleural space. Any increase in intrapleural pressure from the use of the expiratory muscles by an emphysematous patient attempting to accelerate air-flow simply narrows the collapsed airways and traps gas in the lungs. Such trapping in normal

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subjects occurs at the end of the deepest exhalation. In emphysema the trapping occurs early in expiration and the airways resistance becomes very great indeed during attempts to increase minute volumes during exercise. Even at rest the airways resistance is usually increased, accounting for the well-known prolongation of expiration, which in itself is good evidence of an approaching positive pressure within the pleural space. The prolongation of the expiratory phase reduces the maximum breathing capacity, delays the delivery of the vital capacity beyond the normal three second limit and reduces the forced expiratory volume (FEV)[1] for one second to less than the 75 per cent of the vital capacity expected in a normal subject. In gross emphysema the work of breathing becomes so great that the oxygen consumption of the respiratory muscles becomes a high proportion of the total.

Emphysema has a patchy distribution so that the time constants for filling and emptying of different areas vary, leading to unequal distribution of the tidal volume. Uneven ventilation leads to an unequal use of the large lung interface for diffusion. Similarly the distribution of the pulmonary blood flow is uneven. If well ventilated areas of lung are not perfused, they act as dead space and waste portions of the tidal volume. Thus increase in physiological dead space is a cardinal abnormality of pulmonary emphysema.

If well perfused areas are poorly ventilated they act as a virtual right to left shunt and venous admixture takes place into the arterialized blood leaving the lung. In the absence of a major diffusion defect the oxygen tension in the arterial blood is solely determined by the integrated total of the oxygen tensions of each alveolar capillary. Maldistribution of the tidal volume constitutes the most common cause of arterial hypoxia in chest disease and may lead to obvious central cyanosis. Similarly the mean alveolar oxygen tension controls mean pulmonary artery pressure. If the total alveolar minute ventilation falls to less than 4.8 liters per minute, and this will occur with associated bronchospasm secondary to infection or oedema, the alveolar and arterial carbon dioxide tension will rise leading to respiratory failure. An elevation in the mean alveolar carbon dioxide tension produces a mandatory fall in the mean alveolar oxygen tension. This relationship emerges from the following:

$$P\,alv.O_2 = \frac{\text{Insp. } pO_2 - \text{art. } pCO_2}{\text{Respiratory Quotient}}$$

A reduction of the alveolar pO_2 to less than 100 mm Hg engenders pulmonary hypertension. A reduction of the mean arterial pO_2 frequently leads to secondary polycythaemia, yet this is not invariable. It is probable that intermittent reductions in arterial pH or an elevated HCO_3 level inhibits the secondary polycythaemia normally seen in central cyanosis of congenital heart disease.

Unlike, patients with simple bronchospasm from asthma or bronchitis the pulmonary diffusing capacity has been thought to be reduced in emphysema as a result of loss of surface area of alveoli. The interpretation of the low diffusing capacity is complex, and does not necessarily mean a reduced capillary bed. It may be markedly influenced by ventilatory inequality. The single breath technique is less affected by ventilatory inequality and a reduction in diffusing capacity found in this way denotes advanced emphysema mostly in those in whom the disease developed rapidly with little antecedent bronchitis.

The Clinical Features of Pulmonary Emphysema

Patients with obvious emphysema are usually in their fifties. Those with centrilobular emphysema are thin while those with the panacinar type may be obese and present with peripheral oedema. The inelegant designation of 'blue bloaters' and 'pink puffers' attempts a similar division in reverse.

The cardinal symptom of emphysema is dyspnoea which in the pure form in the young is insidious in onset and relentlessly progressive. Others relate their dyspnoea to effort or become episodically aware of it particularly in the Winter. Cough and sputum, if present, are the symptoms of bronchitis. Wheezing is usually the symptom of non-spasmodic asthma which may accompany the emphysema or bronchitis, particularly in the stage of airways collapse secondary to positive pressure during expiration.

A great deal of information can be derived from the study of the phases and patterns of respiration. Prolonged expiration with a descent of the trachea on inspiration points to marked airways resistance. The use of accessory muscles with intercostal indrawing indicates increased respiratory work with reduced lung compliance. Expiratory rise in the jugular venous pressure provides clear-cut evidence for a positive expiratory intrapleural pressure. The clinical recognition of central cyanosis from the mucous membrances implies an almost 50 per cent reduction of arterial pO_2 from gross ventilation/perfusion disturbance or alveolar hypoventilation or both.

The fixation of the thoracic cage in the inspiratory position with 'movement en bloc', lifting and angulation of the sternum, expansion of the anteroposterior chest diameters as well as the barrel-shaped chest are the classical physical signs of the far advanced disease and are by no means obligatory in the clinical diagnosis of moderately severe emphysema.

Early reduction in chest expansion with a diminished cardiac dullness to percussion with downward displacement of the upper limit of liver dullness are quite compatible with a normal appearing

chest configuration. Broncho-vesicular breathing with inequality in breath-sound intensity are valuable physical signs in the absence of expiratory rhonchi. In the presence of wheezing the quality of the breath sounds may be obscured, but diligent auscultation can still bring out the characteristics of broncho-vesicular breathing. Care is necessary in the auscultation of the heart sounds, often almost inaudible.

With the advent of respiratory failure and CO_2 retention the clinical examination of the cardiovascular system reveals the stigmata of a hyperdynamic circulation, i.e. full volume pulse, raised jugular venous pressure with a normally balanced 'a' and 'v' wave, later changing to a dominant 'a' wave, and warm, bluish vasodilated extremities. The ocular fundi may show papilloedema.

The cardiac impulse may now also be hyperdynamic. The second heart sound is loud as a result of the augmentation of the pulmonary component, and narrowly splits. Pulmonary and aortic ejection systolic murmurs are audible. If tricuspid incompetence from severe right ventricular hypertension ensues the normal 'x' descent in the jugular pulse disappears and the systolic murmur of functional tricuspid incompetence, loudest in inspiration, becomes audible.

Clubbing is not a feature of uncomplicated emphysema and its presence points to associated diseases such as bronchiectasis. Prolonged hypercapnia with gross bicarbonate retention leads to an expansion of the extra-cellular fluid and oedema. The full clinical syndrome of so-called *cor pulmonale* emerges at this stage and is much more common in patients with relatively moderate emphysema and gross airway obstruction.

The radiology of the lungs in emphysema reflects anatomical rather than functional changes and it is well-known that radiological changes may be quite slight in relation to severe disability. The exaggerated inspiratory thoracic posture with flattened diaphragms and retro-sternal lung hernias are such gross manifestations that they add little to the obvious physical signs. Disparity between attenuated vascular markings at the periphery, best brought out by tomography, compared with the often enlarged hilar vascular markings, are a more reliable radiological feature of emphysema *per se*, than radiological evaluation of lung inflation.

Careful clinical scrutiny and objective evaluation of the disordered physiology will usually establish the correct diagnosis.

The Management of Pulmonary Emphysema

The natural history is influenced by attacks of respiratory infection which profoundly exaggerate the physiological abnormalities. It is the episodic nature of symptoms which affords the physician his greatest opportunity. The scope of therapy covers: -

1 Correction of airway resistance
2 Correction of hypercapnia and arterial hypoxia by increasing alveolar ventilation
3 Correction of heart failure

Airways resistance is directly related to the diameter of the bronchial lumina. The muscle component should be maximally dilated at all times, even in the absence of audible wheezing, by the aminophylline group of drugs, and for routine purposes Choledyl has proved itself most effective. In the phase of acute bronchospasm recourse should be had to intra-venous aminophylline in adequate doses. Acute infection of the bronchial mucosa requires meticulous attention to the exact flora and sensitivity of the organisms. Cough plates are a much better method for obtaining this information than the conventional sputum sample. Wheezing will inevitably continue in the presence of maximum bronchodilator therapy, if the identity of such organisms as the aerobacter group, for instance, is missed. The ineffective bronchial arterial blood supply to the bronchial tree in emphysema renders the systemic route for chemotherapy inadequate and surprisingly gratifying results attend the administration of chemotherapy by the IPPB method.

Bronchial mucosal oedema not necessarily secondary to infection is best combated by such steroids as triamcinolone, particularly in patients who are constantly on the verge of respiratory failure.

In the presence of chronic respiratory failure bi-weekly diuresis using a powerful carbonic anhydrase inhibitor such as dichlophenamide is useful provided blood pH determinations are carried out at regular intervals. If such facilities are lacking then it is wiser to use intra-venous thiomerin. There is little point in the use of the chlorothiazide diuretics because of their effect on the chloride anions which are always low in bicarbonate retention and hypochloremic sodium depletion becomes inevitable.

The use of digitalis in patients in oedema secondary to carbon dioxide retention and alveolar hypoventilation is calculated to lead to increases in pulmonary hypertension and supra-ventricular arrhythmias, unless steps are taken at the same time to correct the alveolar hypoventilation.

The management of respiratory failure cannot be discussed in this brief review. It should be stated however, that respiratory failure is an ever present danger in patients with even minimal airways obstruction and its early recognition constitutes the cornerstone in the long term management of these patients. Their prognosis is now directly proportional to the efforts employed in guarding patients against respiratory failure.

No discussion of pulmonary emphysema can be complete without reference to social habits and environment. Obviously smoking restrictions and control of air pollution are a challenge to both physician and social enlightenment. □

Adrenergic Drugs

Factors Determining Specificity of Action and Clinical Usefulness*

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The current interest in autonomic drugs - particularly in adrenergic and adrenolytic agents - stems in part from their demand in the treatment of syndromes associated with the cardiovascular system and in part from the potential for development of agents with a variety of mechanisms of action. One is always a little suspicious when a variety of drugs are available in situations like this that no one of them is entirely satisfactory. It is this possibility that I propose to examine and, in doing so, I hope to show why this situation is likely to arise.

Specificity of drug action is a highly desirable characteristic but its attainment is inversely proportional to the complexity of the biological system in or upon which the drug acts. Let us therefore examine the biological system upon which drugs act to mimic or block sympathetic nervous activity.
Insert Footnotes

The chemical transmitter of nerve impulses at sympathetic (and parasympathetic) ganglia is acetylcholine, but at the peripheral end of the post-ganglionic sympathetic fiber the transmitter is nor-adrenaline. If our biological system were as simple as this, specificity of drug action might be easily attainable; but there are a number of complications that arise from the facts (a) that a close chemical relative, adrenaline, possesses some of the same physiological actions - both being catecholamines - and (b) that nor-adrenaline appears to play the role of a neurotransmitter in the central nervous system (CNS).

Nor-adrenaline – adrenaline Inter-relations

Many years ago it was observed that adrenaline, the hormone of the adrenal medulla, had quite opposite actions on morphologically similar tissues. It would, for example, induce contraction of the smooth muscle of some vascular beds and relaxation of others. These actions came to be known as the "excitatory" (E) and "inhibitory" (I) actions of adrenaline. Later, as a more sophisticated attitude toward problems of this nature developed, the onus for adrenaline's variable behaviour was placed upon the target organ which the hormone activated, and so the concept of α - and β - receptors was born. Support for the receptor theory was considerably strengthened by the finding that certain synthetic drugs that mimicked adrenaline's action on tissues did so in a way that was receptor-specific; in fact it was possible to classify receptors according to their reactions to these adrenergic agents.

Nor-adrenaline, as has already been pointed out, is a neuro-transmitter and probably as a result of its chemical similarity to adrenaline it mimics some of the actions of the hormone, but only some of them. Nor-adrenaline acts almost exclusively on α-receptors whereas adrenaline acts on both types. Thus, cutaneous blood vessels containing α-receptors react by constriction to both adrenaline and nor-adrenaline. Drugs that block α-receptors will therefore prevent both the hormone and the neurotransmitter from causing peripheral vaso constriction and, as a consequence, these blocking agents (Regitine, Priscoline, etc.) become clinically important in the treatment of certain types of vaso spasm.

The blood vessels of skeletal muscle contain β-receptors and adrenaline's action here is to induce vaso dilation. Nor-adrenaline does not act upon these β-receptors and this accounts for nor-adrenaline's lack of the biphasic pressor response that characterizes adrenaline's action.

Adrenaline induces cardiac muscle to contract more forcefully and at the same time increases the rate of contraction by stimulating the idioventricular pacemaker and by facilitating A-V conduction. The receptors upon which it acts, however, are of the β type. This statement should cause no confusion when it is pointed out that receptors are classified on the basis of their response to specific activating agents and not by the nature of the physiological response, i.e. as to whether it is excitatory or inhibitory. Confusion may arise, however, when one tries

*Based on a lecture given to the Resident Staff, St. John General and Lancaster Hospitals, St. John, N. B. September 21, 1966.

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to rationalize the facts that (a) the heart is endowed with β-receptors, (b) nor-adrenaline acts on α-receptors and (c) nor-adrenaline does act upon the heart, albeit in a manner somewhat different than that which characterizes adrenaline's action. (Pharmacologists caught in this type of a dilemma react somewhat differently. Some invent a third type of receptor and call it "gamma"; whereas others - unwilling to complicate the picture further - say "Well, you can't win them all - , so nor-adrenaline does act on *some* β-receptors"). Whatever the explanation, the fact remains that nor-adrenaline increases force of contraction and, if anything, slows the rate of contraction. Cardiac output, consequently, is little changed.

The identification of the cardiac receptors is of clinical importance because certain types of pathological and/or drug-induced arrhythmias appear to arise from the actions of catecholamines on the cardiac receptors. Correction of these abnormal rhythms can be achieved only with agents that block β-receptors; but these are not nearly so common as those that block α-receptors. The introduction of the drug Pronethalol promises to be an advance in the desired direction.

The mechanism by which adrenaline and nor-adrenaline are removed from the receptor sites is distinctly different from that which characterizes the removal of acetylcholine in the parasympathetic division. Although two enzymes, mono-amine-oxidase (MAO) and catechol-O-methyl transferase (COMT) have in the past been implicated in catecholamine inactivation, modern studies show them to play a very minor role. Current theory visualizes nor-adrenaline being stored in bound form within the axon, from which site a nerve impulse releases it. Having acted upon the receptor, an uptake mechanism transports the transmitter back into the area from which it was released (uptake step). Provided an excess of catecholamine is not present in the cytoplasm, the nor-adrenaline is then stored in bound form (storage step). It is important to distinguish these two steps in the inactivation process because drugs may exert selective effects upon them. Cocaine, for example, "sensitizes" adrenergically-innervated structures by inhibiting the primary uptake step. Nor-adrenaline, released as a result of adrenergic nerve activity, is thus not removed from the receptor surface, and this results in a prolonging and intensification of the actions of the transmitter, and adrenaline - either endogenous or exogenous in origin.

Reserpine, on the other hand, does not interfere with the initial uptake step but does prevent the storage of nor-adrenaline in its bound form. Evidence suggests that as this non-bound nor-adrenaline accumulates in the cytoplasm it is acted upon by intracellular MAO and the products of oxidative deamination are returned to the circulation, and excreted. In this case, adrenergic nerve impulses continue to release nor-adrenaline from its storage sites - but in ever-decreasing amounts - because reserpine inhibits the replenishment of the nor-adrenaline storage sites. This depletion of stored nor-adrenaline results in decreased sympathetic tone - an action which underlies reserpine's use in the treatment of certain types of hypertension. This same action appears to be important in the CNS for reasons which will be dealt with later.

Many drugs which mimic the action of adrenaline and nor-adrenaline appear to do so partly by reacting with the adrenergic receptors and partly by inhibiting the uptake mechanism. Despite the theoretical mechanism of action, mono-amine oxidase inhibitors and other anti-depressant drugs exert a powerful inhibition on nor-adrenaline uptake.

CNS Actions of Nor-adrenaline

Histological studies have demonstrated the presence of nor-adrenaline in certain parts of the CNS where it appears to function as a neuro-transmitter. Its release from storage sites, and removal from post-synaptic structures is thought to be analogous to the situation described above for post-ganglionic sympathetic nerves. Also present in the CNS are amines, such as 5-hydroxy tryptamine (serotonin) and dopamine, both of which may play a role in the transmission of nerve impulses or are at least responsible for maintaining the "tone" of the CNS. As these three amines are potential substrates for MAO, inhibitors of MAO (tranylcypromine, etc.) might be expected to increase the local concentrations of these amines and thereby raise the level of CNS activity. The use of MAO inhibitors as anti-depressants would thus have a rational basis. However - as pointed out above - drugs of this type (and the non-MAO inhibitors such as Imipramine) appear to exert their actions by inhibiting the uptake of nor-adrenaline.

Because the same mechanisms of action may be involved in various tissues, specificity of action is difficult to achieve and unwanted side reactions appear frequently. When, for example, reserpine is used as a tranquillizer, postural hypotension (and the stuffy nose) occur as side reactions because nor-adrenaline stores in the CNS and peripheral adrenergic nerves are depleted. Anti-depressant drugs may in fact have their desired therapeutic action in the central nervous system but the patient may thereby become sensitized to his own adrenaline, so that hypertensive crises are not uncommon. Moreover, patients on this type of therapy must be careful not to eat certain types of well-aged cheese because these contain tyramine which not only blocks the uptake mechanism but, as some believe, induces a release of nor-adrenaline from its storage sites. This double-edged action leads to acute hypertensive episodes.

When one realizes the variety of tissues upon which adrenergic drugs can act - because the mechanisms of action and/or removal are a common feature - it is quite surprising that any specificity of action should appear at all. The drugs we have presently have been designed to permit them to enter into certain biochemical and physiological reactions that occur in cells. These molecular modifications result in "reaction specificity"; but from the nature of the biological system that has been described, it should be apparent that "organ specificity" would be a highly desirable objective. The fact that MAO inhibitors do appear to act more as anti-depressants than as hypertensive agents suggests that there may be some tissue selection involved in their distribution If so, then the important question becomes - why? Reserpine, on the other hand, seems to possess both central and peripheral pharmacological actions. Is this because there is no tissue selectivity? Clearly, a great deal has yet to be learned about the factors that confer organ specificity - relative as it may be - on molecules that are reaction specific. □

The Use and Abuse of Digitalis

References - continued from page 12

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FORTY YEARS AGO

From the Nova Scotia Medical *Bulletin* January, 1927.

THE CANADIAN MEDICAL ASSOCIATION

The Canadian Medical Association was founded in 1867, dating back to the year of Confederation. The organization signalized an attempt to develop a national esprit de corps among the medical men of the Dominion of Canada.

Since its inception, the Association has failed on two occasions only to hold annual meetings. These meetings have been moved about from East to West and from West to East throughout the past half-century, offering splendid opportunities to the profession in this very large country to become acquainted.

Sixteen years ago, the Association commenced publication of its own Journal. Before this venture had become firmly established, the great war was upon us. Then followed four lean years for the Canadian Medical Association, as the energies, efforts and interests of the profession were centred, naturally, upon the duty of the hour. Following the war and the return to practice of hundreds of our colleagues, the Association attempted to rehabilitate itself. The outlook was not too bright. During the war period, while the revenue was greatly diminished, printing and other costs continued to roll up a deficit. In 1921, we found ourselves at the cross roads, demanding a definite decision. We must either adopt an aggressive forward policy, or disband. At this time, we had a little over one thousand members paying an annual fee of $5.00. Our deficit was close upon $18,000. Our assets were practically nil.

At the Halifax meeting of that year, the Council decided that the Association would go forward; and the members present endorsed the sentiments by unanimously agreeing to double the annual fee and to raise, by bond subscription, a sufficient sum of money to liquidate our indebtedness. The year 1921, will be recorded in history, in so far as the Canadian Medical Association is concerned, as the mile-stone which marked the road toward a steady upward climb. During past five years, the membership has increased to a little over 3,000. A liability of $18,000 has been wiped out, leaving us a credit balance approximating $12,000. Our budget in 1921 did not exceed $20,000. Our budget in 1926 was just a little under $85,000.

The Use and Abuse of Digitalis

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Introduction

It was in 1775 that William Withering first discovered the therapeutic usefulness of digitalis. In 1785 he published his famous book, "An Account of the Foxglove and Some of its Medical Uses: With Practical Remarks on Dropsy and other Diseases". We have learned much about the use of digitalis and its mode of action since then. However, in many respects we have done little more than "tread water." As Withering said: - ". . . . . It is better the world should derive some instruction, however imperfect, from my experiences than the lives of men should be hazarded by its unguarded exhibition or that a medicine of so much efficacy should be condemned and rejected as dangerous and unmanageable."

Though Withering recognized the action of digitalis on the heart, we now recognize that the main value of digitalis lies in the management of congestive heart failure and certain cardiac arrhythmias.

Action

Digitalis increases the force of contraction of the failing myocardium, without increasing oxygen consumption (i.e. it increases efficiency). Until recently, this positive inotropic effect has been felt not to occur if the heart is non-failing. However, we now know that digitalis does have a positive inotropic effect even on the diseased or normal non-failing heart. Indeed, it has been shown experimentally that digitalis, via this effect, has prophylactic value in protecting the heart in stressful situations. However, the prophylactic use of digitalis usually has more disadvantages than clinical value.

Another important action of digitalis is that concerned with prolongation of the functional refractory period of the atrioventricular conduction system in the presence of intact sympathetic and parasympathetic innervation. It is this effect that is responsible for ventricular slowing in atrial fibrillation.

On the other hand, the refractory period of the ordinary myocardial cell is decreased thus rendering it more irritable. It is important to remember this latter effect when considering the use of digitalis in conditions in which the ventricle is already irritable or potentially so (e.g. ventricular arrhythmias, acute myocardial infarction.)

Digitalis also has a direct action on the renal tubule causing decreased sodium reabsorption. However, the diuresis seen following digitalization of patients in congestive failure is mainly due to improved renal hemodynamics.

Systemic venous and arterial tone are both increased by digitalis directly. In addition, digitalis has a direct central nervous system effect giving rise to several of the symptoms we usually associate with digitalis toxicity. (e.g. nausea, vomiting, visual disturbance. etc.).

In this paper, the mechanism of action of digitalis will not be described in detail. Considerable research is being done to elucidate this mechanism at a cellular level. This must of course be the ultimate goal. Suffice here to say that digitalis acts at the cellular level by affeting the exchange of ions in and out of the cell. The ions investigated have included sodium, potassium and calcium. The latter ion is presently receiving most attention. It is felt that digitalis acts by altering calcium exchange at the cellular level.

In addition, the glycoside responsiveness of the myocardium probably depends to some extent on the availability of endogenous cardiac catecholamines. This latter fact is of interest when one considers the common use we make of reserpine and guanethidine, both of which deplete the myocardium of catecholamines. Indeed, there is recent evidence that reserpine itself decreases the glycoside responsiveness of the myocardium.

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Perhaps here, certain factors which modify the action of digitalis on the myocardium can be reviewed.

Calcium enhances, whereas potassium antagonizes the action of digitalis. Thus the importance of low tissue and blood levels of potassium regarding digitalis intoxication. However, recent work has demonstrated that intravenous potassium chloride can depress the arrhythmia-producing ability of excesses of digitalis while allowing the positive inotropic effect to continue in a linear fashion.

The thyroid hormone is an antagonist. Thus, atrial fibrillation is harder to slow in hyperthyroidism, requiring large doses of digitalis. However, there is also more resistance to toxicity.

The administration of steroids, isoprotorenal (isuprel®) and epinephrine enhances digitalis potency, as does intravenous glucose with or without insulin.

Use

Most data available concerning the potency, absorption, metabolism and elimination of the various glycosides is inaccurate and misleading. Current research involving the use of radioactive glycosides will help to alleviate this inadequacy. However, certain facts are fairly well established. Digitoxin is completely absorbed orally whereas digoxin is about 80 per cent absorbed. Therefore, the oral and parenteral digitalizing doses of digitoxin should be the same. Digitoxin is bound to albumen, remains in the entero-hepatic circulation and is metabolized in the liver to be excreted more slowly by the kidney. Digoxin is excreted much more rapidly by the kidney and in the unaltered state. Therefore, the excretion of digoxin is significantly affected in renal insufficiency. With blood urea nitrogen (BUN) concentration of 20 - 50 mg per cent, one half the maintenance dose is required and with a BUN of over 50 mg per cent, onethird may be adequate.

From other studies, it has been shown that it is possible to digitalize a patient in 5 - 7 days by simply starting out with a maintenance dose of digoxin.

The indications for digitalis therapy will not be considered in detail. In choosing a preparation, there are no important differences in effect on the heart among the large variety of digitalis preparations, only differences in potency, absorption, time-action and elimination. Most people now use the pure glycosides rather than the crude leaf preparations. The only glycoside in the leaf that is significantly absorbed is digitoxin.

Digoxin acts more quickly than digitoxin and is more rapidly excreted. Digitoxin probably gives smoother, long-term control. However, in cases of toxicity, it is preferable to have a rapidly excreted preparation. Therefore, digoxin is preferred if there is a changing cardiovascular situation (e.g. during operative procedures) where intoxication is more likely to be a problem. (It is the writer's opinion that digoxin is the drug of choice in most patients). Lanatoside C and ouabain are more rapid in action than digoxin, but are rarely needed. Indeed, the intravenous route is only required when minutes count, in which case digoxin, 0.5 mg is given intravenously and repeated in 1 - 2 hours as required for full digitalization. Intramuscular digoxin is usually given in 0.5 mg injections every four to eight hours for a full digitalizing dose of 1.5 mg. The usual oral digitalizing dose for digoxin is 2 - 3 mg given over 24 - 48 hours. However, cautious observation of the patient and strict individualization of dosage must be stressed. Maintenance with digoxin is about 20 to 30 per cent of the initial dose or 0.25 to 0.75 mgm, and with digitoxin is about 10 per cent of the initial dose or 0.15 mgm daily.

It could be pointed out here that *too little attention is paid to maintenance.* This is a special pharmacologic problem. Serious over-digitalization is much commoner in maintenance than in initial digitalization.

Digitalis Intoxication

General

The immense value of the use of digitalis in clinical medicine is not to be undersold and is obvious. However, at present it unfortunately has become necessary to overshadow the usefulness of the cardiac glycosides with a plea for a better understanding of the magnitude of the problem of digitalis intoxication. Abuse of digitalis is assuming completely unacceptable proportions. Ignorance of the toxicity of digitalis and the frequency with which it goes undetected must be corrected.

Digitalis intoxication is a life-threatening situation. The morbidity in this situation is more common and even less well recognized. In this age of modern medicine, why has this situation been allowed to assume such prevalence? After all, it is basically an iatrogenic problem.

Firstly, one must recognize that now as in the days of Withering, the clinical use of digitalis is almost strictly empirical and intuitive. Medical science has offered little to guide the physician in his use of the drug. In the diabetic, the physician can measure blood sugar and serum insulin levels and control the use of insulin. Not so with digitalis.

For some reason, many physicians are either not aware of or forget that digitalis is a very potent drug. With usual full digitalizing doses of digitalis about 40 per cent of the lethal dose has been given and when toxicity develops about 60 per cent of the lethal dose has been given. Although the exact lethal dose is arbitrary, these figures are startling when one considers the marked individual variations in response to digitalis.

Undoubtedly, a major factor in the rising incidence of digitalis intoxication is the increasing use and abuse of newer more potent diuretics with attendant risks of hypokalemia. Recent work has pointed out the inability of some commonly used potassium supplements to repair this electrolyte disturbance completely.

Another factor is the increasing population of geriatric patients. These people are commonly candidates for digitalis therapy and are often more sensitive to the drug than are younger people. They are more likely to have renal insufficiency and its problems with respect to the excretion of digitalis.

Extra-cardiac symptoms of digitalis intoxication are not always the early features. Most series of hospitalized patients reveal that not only does one patient out of five develop toxicity, but that about 50 per cent of toxic patients are either undetected or their cardiac problems ascribed to the underlying disease. It is interesting to speculate as to just how many patients die at home from undetected digitalis toxicity.

Pathogenetic Factors

There are several factors which may modify the action of digitalis so to render a patient more prone to develop toxicity. The use of diuretics with resultant loss of potassium has been mentioned. Serum potassium levels do not help to assess the situation unless they are low. An intracellular deficit may increase digitalis sensitivity without altering serum levels.

Intravenous glucose and insulin may alter potassium metabolism so to sensitize a patient to digitalis. Likewise, the administration of calcium is at times dangerous. Steroids, isoproterenal, and epinephrine also create a situation which enhances digitalis potency.

In considering this problem it should be recognized that even before administering digitalis to a patient, there are several clinical conditions in which there is often increased sensitivity to the drug. Included in this category should be any patient who has an abnormal electrolyte status. (e.g. vomiting, diarrhea, diabetic acidosis, postoperative state, etc.) Also, patients with renal or hepato-bilary disease due to their inability to metabolize and/or excrete the drug normally. All elderly people should be considered as possible candidates for increased sensitivity. Caution should be exercised in treating the failure associated with cor pulmonale, myocarditis, cardiomyopathy, myocardial infarction and stenotic valvular disease. In these situations, since the failure is here resistant to digitalis, a dangerous tendency is to increase the dose of the drug. Toxic effects can be produced in this way. In muscular subaortic stenosis, the outflow tract obstruction may be increased by digitalis. It has recently been reported that digitalis intoxication can be precipitated following successful cardioversion of atrial fibrillation.

True drug idiosyncracy to digitalis can occur but fortunately is rare.

Symptoms and Signs

The symptoms and signs of digitalis intoxication should be well known and understood by every physician. Most are aware of the gastrointestinal symptoms which include nausea, vomiting and diarrhea. Perhaps even more common is simple anorexia or loss of appetite. These symptoms can be produced by any digitalis preparation, the mechanism being central nervous system stimulation. Other CNS symptoms include headache, personality disorders, other psychiatric problems, focal neurologic lesions, somnolence and visual disturbances. The latter run the gamut from blurring of vision, through green and yellow vision to complete blindness. A general sense of ill health is perhaps a common complaint.

Cardiac arrhythmias are common. The commonest is nodal tachycardia or simple nodal rhythm and probably the most specific is paroxysmal atrial tachycardia with block. Ventricular bigeminy is also very common. Conduction disturbances of any degree can occur and almost any other arrhythmia may be produced, sometimes several in one patient. A regular rhythm which becomes irregular (or vice versa) should alert the physician as to the development of toxicity. Another common situation, which if unrecognized can be fatal, is the development of increasing congestive failure after a patient has previously benefited from the drug.

All of these situations, symptoms, and signs are often overlooked in the face of the patient's overall problem.

Management

The first step in the management will be dictated by the clinical status of the patient. The old adage that "an ounce of prevention is worth a pound of cure" certainly pertains here. The initial move will be to discontinue digitalis therapy until toxicity is gone. In addition any of the previously mentioned drugs capable of increasing sensitivity to digitalis should be stopped. This latter group includes diuretics which may have caused excess potassium loss.

Reduced activity or bed rest either in or out of hospital must always be part of management. The degree of restriction of activity and the question of hospitalization will be considered in the light of the clinical status of the patient. It should be re-emphasized that any degree of intoxication is associated with a varying risk of serious cardiac arrhythmia and sudden death.

The next step in management is the administration of potassium chloride. The relationship between this substance and digitalis has been well demonstrated. It has been shown that the administration of potassium will decrease myocardial irritability in certain arrhythmias not induced by digitalis as well as those that are. It has recently been shown that the chloride ion as well is essential in correcting this type of electrolyte disturbance.

The route of administration will depend on the severity of the situation. Usually oral potassium is sufficient and certainly less dangerous than by intravenous injection. It is given in the form of either effervescent potassium plus a source of chloride or elixir of potassium chloride in juice or other vehicle to promote less gastric irritation. Intravenous potassium chloride is given over a period of one to two hours (20 to 40 mEq KCl in 500 to 1000 ml. 5 percent glucose in water.) This may be repeated. Electrocardiographic monitoring is essential and is a much better indication of therapeutic effect than serum potassium levels, though the latter must be watched.

In most patients, the foregoing outline of management will be all that is required for the acute phase. After treatment of this phase, reassessment of the underlying disease is indicated with subsequent consideration of the cautious reinstitution of digitalis therapy with appropriate modifications including close follow-up.

Certain patients will be relatively resistant to the above therapy or will have serious arrhythmias requiring additional treatment. In these cases, the available armamentarium is limited but growing.

For the treatment of serious arrhythmias, procaine amide has a place in management. It may be given by any route in the usual dosage depending on the clinical status of the patient.

Relatively recently, diphenylhydantoin (Dilantin®) has been shown to be particularly effective in treating supraventricular and ventricular arrhythmias associated with digitalis intoxication. A dose of 100-300 mg diluted in 5 to 10 ml. of saline is given intravenously over one to three minutes with electrocardiographic monitoring. If there is no response to this, no further drug is given. If the arrhythmia reverts toward normal, a maintenance dose of 100 mg three to four times daily is given either intravenously or orally. If the arrhythmia recurs, the intravenous dose can be repeated. Note should be made of the potential danger of producing irreversible cerebellar damage with this drug when it is given parenterally.

The use of synchronized direct current electrical discharge (cardioversion) can be used as a last resort but is dangerous in the presence of digitalis.

The use of beta-adrenergic blocking drugs (e.g. pronethalol) had been shown to be effective in this situation but reports of clinical trials have cast serious doubt on their usefulness. Intravenous local anesthetics (e.g. Xylocaine) have been used to reduce myocardial irritability but their value is questionable. Recent work has shown that paired electrical pacing may possibly add something further to treatment of the emergency in the future.

Finally, mention is made of the use of the "provocative" digitalis test. This test involves giving small amounts of acetyl strophanthidin to patients in whom serious doubt exists as to whether the situation involves excess or insufficient digitalis. If the condition worsens then digitalis is stopped. This test is dangerous and should only be used by experienced physicians.

Conclusion

It is concluded that a better knowledge of this potent, efficient drug should be sought by most physicians. This will be the first step in stopping the rising incidence of toxicity. A high index of suspicion is paramount. Until we can become more scientific in the use of digitalis, extreme caution is urged. □

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(continued on page 8)

Genetics and the Physician

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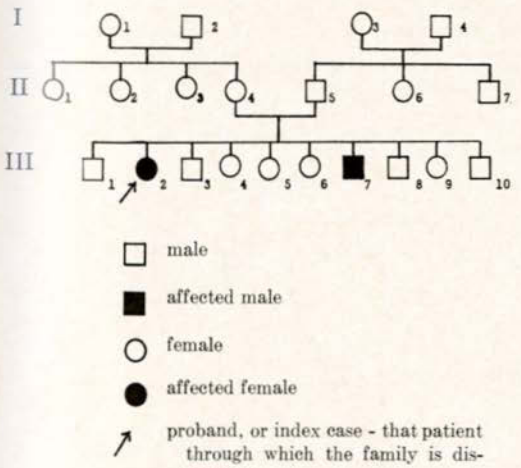
PART VI

A Congenital Defect and its Recurrence in the same Sibship

Information is now becoming readily available for giving the recurrence rate of a given congenital defect in a succeeding pregnancy. Such a risk figure can follow simple *Mendelian* laws if the defect is inherited in a simple Mendelian way, or can be calculated from the observation of recurrences in a large number of families if the defect is inherited in a more complex manner: these are *empiric* risk figures.

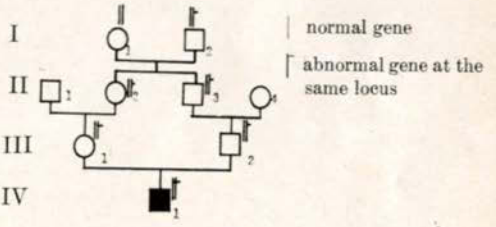
Mendelian ratios are very easy to understand. We can be dealing with: -

A an autosomal recessive condition: a family tree can easily be constructed from a detailed family history. It may look like Figure I. Notice that both sexes can be involved, that usually the case is sporadic, i.e. other branches and other generations of the family are not involved. The recurrence rate is one in four. Occasionally both parents are first cousins as in figure II. The chance of an offspring of a first cousin marriage carrying a pair of bad genes at the same locus is one in 64, and everyone of us carries six or seven bad genes.



I - III generation.

FIGURE 1: **A Pedigree demonstrating a condition inherited recessively.**



The Chances of

	II_2	inheriting the bad gene is 1/2
	II_3	" " " " " 1/2
II_2 &	II_3	" " " " 1/4
	III_1	" " " " " 1/4
	III_2	" " " " " 1/4
III_1 &	III_2	" " " " " 1/16

IV_1 inheriting a pair of bad genes at the same locus is 1/64

FIGURE 2: **Pedigree demonstrating a first-cousin marriage.**

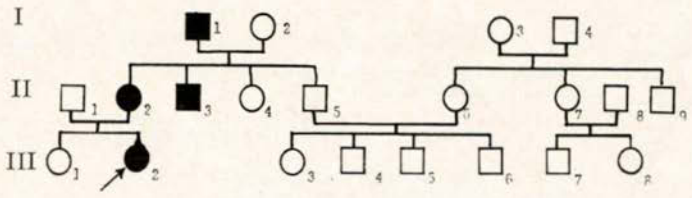
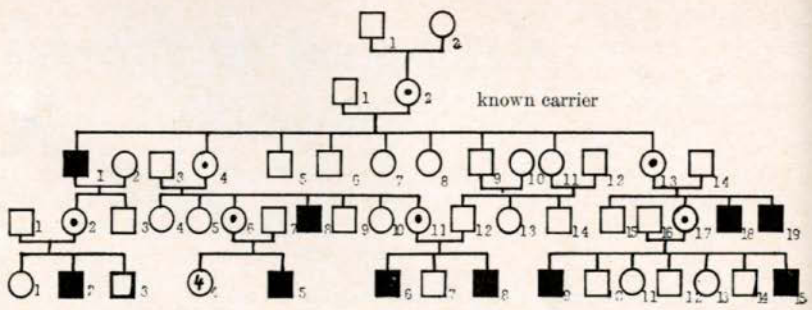


FIGURE 3: **Pedigree illustrating a condition inherited as an autosomal dominant.**

B an autosomal dominant condition. Males or females can be affected. The condition is usually passed on from generation to generation, as in Figure III. The chance of a succeeding pregnancy of 2 being affected is one in two.

C a sex-linked recessive condition. Only men are affected here; the condition is carried by females who do not normally manifest the disease, as in Figure IV. Here, the chance of a further boy being affected is one in two, and the chance of a daughter being a carrier also one in two.



Present Royal Family

I_1 Edward, Duke of Kent (1767-1820)
II_2 Queen Victoria
III_1 Leopold, Duke of Albany (1853-1884)
III_4 Alice (1843-1878)
III_9 Edward VII (1841-1910)
III_{13} Beatrice (1857-1944)
IV_2 Alice (1883-)
IV_6 Alix, Czarina of Russia (1872-1918)
IV_8 Frederick (1870-1873)
IV_{11} Irene (1866-1953)
IV_{17} Victoria, Queen of Spain (1887-)
IV_{18} Leopold (1889-1922)
IV_{19} Maurice (1891-1896)
V_2 Rupert (1907-1928)
V_5 Alexis (1904-1918)
V_6 Waldemar (1889-1945)
V_8 Henry (1900-1904)
V_9 Alfonso (1907-1938)
V_{15} Gonzalo (1914-1934)

FIGURE 4: Haemophilia in Queen Victoria's family.

NOTE: 1) IV_{11} and IV_{12} are first cousins

2) Some females in generation V may be carriers: many married and only had daughters and grand-daughters.

Empiric risk figures are now available for many defects. Some conditions inherited in a Mendelian way are listed in Table I, and some empiric risks given in Table II.

The Sporadic Case

What advice should a physician give parents of a child with a congenital defect? Frequently, a good family history fails to reveal the occurrence of any other similar case. With an exact diagnosis, for instance cystic fibrosis, one may be able to determine the inheritance pattern, and risk figures for succeeding pregnancies can be given. However, in many cases the exact inheritance pattern is not known. Let us consider for instance a sporadic case of congenital deafness: this could be:

TABLE I:

SOME CONDITIONS INHERITED IN A MENDELIAN WAY –

The Figures are approximate – incidence per 100,000.

	Incidence	Carrier rate	Mutation rate /100.000 gametes.	Fitness
AUTOSOMAL				
RECESSIVE				
Cystic Fibrosis	40	4.000		0
Phenylketonuria	5	1.300		0
Albinism	10	2.000		1
DOMINANT				
Huntington's chorea	1		.2	1
Achondroplasia	15		6	.2
Neurofibromatosis	30		10	.66
Retinoblastoma	1–2		.5	
Marfan's disease	1–2		.5	
SEX-LINKED				
Hemophilia	10		3	
Muscular dystrophy	8		5	0
Colour-blindness	9000			1

TABLE II:

EMPIRIC RISKS FOR SOME CONGENITAL DEFECTS:

incidence per thousand – 1st degree relatives include sibs and children.

	INCIDENCE	SEX RATIO MALE:FEMALE	recurrence rate for 1st degree relatives	
Congenital Heart Defects	6	1	18	(x3)
Hare-lip (with or without cleft palate)	1	1.8	35	(x35)
Pyloric Stenosis	3	5.0	40–220	(x13–70)**
Congenital dislocation of the hip	1	.17	40	(x40)

** according to sex.

a inherited recessively. Both parents would be carriers. The chance that the outcome of a succeeding pregnancy would be affected is then one in four.

b inherited as a dominant, with low penetrance and/or low expressivity of the condition in one of the parents (cfr. Genetics and the Physician I). It is most important to rule out this possibility by a very careful and detailed family history, and by careful examination of the parents.

c acquired as a dominant mutation. This would have occurred during meiosis in the sperm or the egg. The recurrence rate is then practically nil. A higher mutation rate is associated with increasing paternal age: according to Lenz, a mutation at a given locus can occur twenty times as often in the formation of sperms in males over the age of forty than at the age of twenty.

d acquired as a sex-linked recessive mutation. This would have occurred in the X sex chromosome of the sperm or the egg of the maternal grandparents. This is probably what accounted for the hemophilia that developed in Queen Victoria's offspring. It is interesting to note that her father Edward, Duke of Kent, was 52 years old when she was born. The reccurrence rate is then one in two for boys. One daughter in two will be a carrier.

If the affected child is a boy, it is frequently impossible to differentiate between possibilities c and d. It is important however to try to do so: carriers can sometimes be detected, as occasionally in hemophilia for instance by blood studies.

e acquired later in development: viral or bacterial infections, anoxia or other trauma in utero or at or after birth, is then responsible. A positive history is frequently present, and the recurrence rate is low.

One can see immediately that in the case of sporadic deafness it may be very difficult to give an exact figure for the outcome of a future pregnancy. One has then to advise the parents that the risk is slightly increased: whereas the outcome of any pregnancy carries the risk of a congenital defect in one in 40, in this particular instance the risk figure could be one in 25. This figure does indicate the risk of an anomaly is increased; it is not too frightening a figure, and it is more realistic than the advice so frequently given 'not to worry' or 'one in 1000' etc. . . It means that the chance of having a child with a congenital defect is increased. If the child has a defect, it will more likely be deafness than any of the others.

In these few lines, I have tried to describe some principles of genetic counselling. In future issues I hope to cover the genetics of certain conditions associated with a particular system, i.e. cardiovascular system, gastrointestinal system etc. . . □

The High Risk Patient

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Obstetrics has made great strides in the past fifty years, but in spite of this we still lose mothers and babies. We ask ourselves - why? It soon becomes obvious that more attention to *problems* in the antenatal period might have avoided many of the mortalities and morbidities occurring in later pregnancy and delivery. Because of this belief, a concept has developed in obstetrical practise which may be defined as a selection of high risk patients who, in effect, contribute the major portion of maternal and perinatal deaths.

This new concept has been developed in other centres and only recently have we, in this area, organized such a service. We have set aside in our obstetrical wing of the Grace Maternity Hospital an area to which are admitted all problems of obstetrics in the antenatal period. This area is run by well-trained personnel with special facilities directed towards the early diagnosis and early treatment of complications of pregnancy. No one will deny that the earlier we pick up the complications, the more we study the problem, the better will the ultimate outcome be. Daily rounds are made in this area, so that problems are openly discussed and consultations frequently held.

As time goes on, it is hoped that newer concepts will arise in the treatment of these complications and that more and more mothers will end their pregnancies with healthy bodies and healthy babies.

A good example of the type of case treated on such a floor would be a diabetic who is difficult to control. We all know that this is a dangerous situation in the pregnant mother, but we also know that the incidence is increasing, as diabetics live longer and are treated better. Consequently, we are able to admit a pregnant mother with diabetes to this area, to help control her diabetes, and carry the mother as close to term as possible. We also now have available means of determining the state of the baby in utero, so that while the mother is in hospital we are able to follow the health of the mother and of the baby and are better able to determine when to induce this mother, and get a live baby rather than a still-born, which is the frequent outcome in a diabetic mother. This then, is an example of a high-risk patient who can be handled in a situation where personnel are well-trained, and properly equipped to handle this type of patient.

Toxaemia of pregnancy is probably one of the biggest problems that we have to face in the care of the obstetrical mother. We know that it can lead sometimes to the death of the mother and baby, but more often the mother survives the pregnancy, but is left with some residual damage to her renal vascular system. With early, proper care, this can be avoided. We also know that the care is difficult to carry out at home. Very often the mother is not able to follow the instructions given by the doctor. Therefore, it is essential that such a mother, who fails to respond to the early treatment initiated by the doctor, be admitted to the hospital. Here we are able to avoid most of the complications connected with toxaemia *if* they are properly treated in a proper environment. We feel that the High Risk Floor is the proper place for such a person to be cared for, because the personnel on this floor are taught to understand the problems associated with this condition and do their best to alleviate all the symptoms.

Vomiting of pregnancy in its mild form usually requires little treatment. However, when this condition gets to the point where the patient is not able to keep anything in her stomach, and is vomiting continuously, very quickly she gets into a situation that requires hospitalization. Treatment of such a patient is rather special and demands considerable understanding of the situation. To place such an individual in the usual atmosphere of hospital beds does not, as a rule, bring good results. We have found that if we can provide the special facilities and well-trained personnel who understand the situation, that the condition very quickly corrects itself. Here again, then, is a situation in which the High Risk Floor plays an important part.

The cardiac patient, who all too often shortens her life because her pregnancy was not handled adequately, is more easily treated and observed in an area such as this. Here she can receive rest, which is so important to the cardiac patient. She can be exposed to specialist's care with con-

sultations as required, where personnel are trained to understand her special needs and care, and who try to create an atmosphere that will be conducive to a happy frame of mind for the patient who must be under rather trying circumstances for the remainder of her pregnancy. Admittedly we have for some time accepted the above conditions as requiring special care. It is only recently that attention has been focused on what used to be considered as minor conditions of pregnancy. We now know that these conditions may contribute to the morbidity and mortality of the pregnant woman. Some of these can be adequately treated on an outpatient basis *but many* require extensive investigation and treatment available only in hospital. Such conditions as suspected premature rupture of membranes, urinary tract infections, excessive weight gain and anaemias unresponsive to the usual treatments, are but a few of the so-called minor conditions faced daily by those engaged in caring for pregnant women.

These, then, are but a few examples of the type of patient that can be handled in such a high risk area. Any problems in the ante-natal period can become serious, but if adequately treated they can be either averted, or at least the serious results can be minimized. We feel that an area such as this High Risk Floor can do much to achieve these results.

The High Risk Floor in the Grace Maternity Hospital is available to all doctors in the Halifax area for the care of their ante-natal problems. It is also available to any doctor in Nova Scotia who wishes to refer an ante-natal problem to this floor. We would hope that doctors will make use of this floor in order to reduce the morbidity and mortality that can result as a consequence of complications of pregnancy. We are also hoping that the hospitals in other parts of Nova Scotia would develop similar areas in their obstetrical units for use of the doctors in their area. There is no doubt in our minds that the full development of the above concept will do much to guarantee safer pregnancies for mothers and healthier babies in Nova Scotia. □

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Appreciation

Ian Mackenzie

Ian Mackenzie was born in Scotland in 1910, and spent his childhood on the Island of St. Kilda where his widowed mother was government nurse, in charge of the welfare of the small community. Here, Mrs. Mackenzie was a much beloved and admired personality for her devotion to the families of sick crofters.

In company with his younger brother, who was later destined to be killed on active service; the family lived amid the lonely grandeur of St. Kilda, to the accompaniment of the sounds of the cry of the sea birds, the roar of the breakers, and the howling Atlantic gales that thundered against the face of the rugged cliffs of the island.

Many of the islanders were avid readers and both the Bible and the classics were their constant companions. Thus, Ian Mackenzie's love for the Bible was acpuired at an early age, and it came as no surprise one day, when as a medical student at Edinburgh University, he won a prize for biblical knowledge in open competition against Divinity students, much to their astonishment.

Having received his high school education at Inverness, he proceeded to enter the Faculty of Medicine at Edinburgh University and duly graduated M.B., Ch.B. in 1933 with first class honors in many subjects.

He subsequently became a surgical resident at the Royal Infirmary, Edinburgh, during the halcyon days of surgical teaching at Edinburgh under the expert guidance of that magnetic personality, the late Sir John Fraser. Thereafter he underwent post graduate training at the University Departments of Pathology and Bacteriology, and later joined the Wilkie Surgical Research Laboratories, under the direction of the late Sir David Wilkie. At this stage of his career he showed indications of interest in the aetiology of malignant disease and the same malady which ultimately claimed his life. Having done research for some years on the aetiology of Hodgkin's disease, he took the FRCS(E) examination, passed with distinction, and was successful in obtaining a Commonwealth Research Fellowship tenable at the Rockefeller Institute for Medical Research, New York, in 1939. Here, he entered the laboratories of Dr. Peyton Rous and Dr. Huggins, recent co-recipients of the Nobel Prize for cancer research, and immersed himself in their classical studies, on the then obscure and much doubted virus theory of cancer.

In 1939, he voluntarily relinquished his period of post graduate training at the Rockefeller Institute, and returned to join his unit in London and was promptly posted overseas with the ill fated British Expeditionary Force to France.

It would be too easy to narrate to the reader a dramatic account of his war time exploits. His string of British and Foreign decorations. His repeated acts of gallantry and devotion to the care of the wounded, as a surgeon on the field of battle. Likewise, his service with British and French and Yugoslav troops as a Parachute Unit surgeon, engaged behind enemy lines.

However, those interested in the grim fighting in Yugoslavia, should read the classic account of Brig. Fitzroy MacLean (Winston Churchill's personal representative to the H.Q. of Tito) titled "Eastern Approaches". Efforts to discover the rôle Mackenzie played with British Paratroops serving with the French Maquis underground, prior to the Allied landing on D Day, evoked the following interesting answer from The Military Attaché to the French Embassy in London. "Major I. Mackenzie, R.A.M.C. was mentioned in depatches of the Corps d'Armée and was awarded Croix de Guerre avec étoile de Vermil by order No. 20, dated March 23rd, 1948."

After the cessation of hostilities he returned to Edinburgh. The old place had changed; he felt the loss of his brother; Sir David Wilkie had passed on, and the familiar blue Delage coupé car was no longer at the door of the surgical research laboratories. Sir John Fraser had retired from surgery, to become Principal of Edinburgh University. Ruefully, Mackenzie accepted a position in the Department of Surgery at Durham University, Newcastle on Tyne, and thereafter was appointed at Cumberland district as Senior Surgical Consultant under the British National Health Services scheme. Wishing to return to academic life, he applied for and received the Chair of Surgery at Dalhousie University.

As he had doubtless anticipated himself, Mackenzie's debut in Halifax received a frosty reception. However, the job presented a challenge to him, and after some preliminary skirmishes, good sense prevailed and everybody got on with the dual tasks of trying to find enough time to earn a living on the one hand and to teach surgery to medical students on the other. Mackenzie put everything he had into trying to make a success of the job and stuck to his duties up to the end. Mackenzie made many good friends throughout Nova Scotia and Canada, and among various interests was Chairman of the Maritime School of Riding for children and adults at Dartmouth.

C.E.V.R.

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