

1964

# UWOMJ Volume 34

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# UWO MEDICAL JOURNAL

VOLUME 34, NUMBER 2

MAY, 1964

UNIVERSITY OF WESTERN ONTARIO

London, Canada

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# The Normal Physiology of Bone

JAMES A. SHARPE, '66

Bone is a variety of connective tissue. It appeared in the evolutionary chain in the subphylum *Vertebrata*, and occurs in all of the vertebrates with the exception of the *Chondrichthyes* (sharks, skates), and the lamprey eel. Bone functions to give strength, site of muscle attachment, and to store calcium salts for the animal. Its development has allowed terrestrial evolution of the vertebrates to occur. The active land vertebrate subjects his sturdy skeleton to much stress, giving rise to fractures. Fractures and metabolic diseases of bone attach much medical importance to this tissue.

This article is confined principally to the biochemical and metabolic features of bone, with an aim at providing a review as a basis for fuller understanding of the subsequent articles in this symposium.

## DEVELOPMENT OF BONE

Bone is derived from embryonic mesoderm of two sources. The sclerotomes, which separate from somites, give rise to the vertebral column, ribs, and the base of the skull. Condensations of mesenchyme give rise to the appendicular skeleton, branchial arches, and calvarium. The anlage of all the bones are present at the 12 mm. (seventh week) stage in the human embryo. Ossification begins during embryonic life and is not completed until early adulthood. Pathological ossification may also occur in the form of:

- 1) Heterotopic bone formation at sites of dense fibrous tissue, as in scars and organizing hematomas,
- 2) Myositis ossificans, and progressive multiple ossifying myositis.

Ossification proceeds by two methods. *Intramembranous ossification* occurs in the flat bones of the skull, the bulk of the mandible and in the clavicle. Membranous

bone is derived from areas of vascular connective tissue, wherein mesenchymal cells differentiate into osteoblasts amid already differentiated fibroblasts. Osteoblasts produce spicules of bone matrix which become calcified, enlarged, and fused with adjacent spicules to form trabeculae. These are arranged in a three dimensional network forming cancellous bone. The intertrabecular spaces become narrowed by proliferative osteoblastic activity to form compact bone. Cancellous bone remains to occupy the diploë of the membrane bones of the skull and the marrow ends of the other bones.

*Endochondral ossification* occurs in all other bones. This process involves the utilization and death of hyaline cartilage. The cartilage precursor enlarges by appositional growth of chondroblasts in the perichondrium, and by interstitial growth of chondrocytes in the lacunae of the cartilage matrix. Bone-forming cartilage becomes calcified and has a tropic effect on adjacent blood vessels. These invade the perichondrium and stimulate the differentiation of primitive mesenchymal cells into osteoblasts. Many investigators believe that mesenchymal cells in a compact environment with low oxygen tension produce chondroblasts whereas those present in compact tissue with a high oxygen tension form osteoblasts. Fibroblasts, on the other hand, are thought to be differentiated from mesenchymal cells in a high oxygen tension in less compact tissue where there is some physical tension in the tissue. Osteoblasts, together with capillaries, invade the calcified cartilage as periosteal buds establishing diaphyseal centers. Calcified cartilage is necrotic, since nutrients can no longer diffuse to the chondrocytes (cartilage is avascular). Trabeculae of bone are laid down on the calcified carti-



lage and replace it. Eventually compact bone is produced. Metaphyseal ossification centers are established at the ends of the bone.

Growth in the width of the bone is accomplished by appositional growth of osteoblasts in the periosteum. Interstitial growth does not occur. Growth in length of long bones is obtained by hyperplasia of the cartilagenous epiphyseal discs. Chondroblasts become hypertrophied and the matrix is calcified, possibly because of the increased content of alkaline phosphatase. Necrosis results, and endosteal buds of capillaries and osteoblasts invade this zone producing cancellous bone.

Normal bone growth requires concomitant bone resorption from within the medulla and from without at the metaphysis. Osteoblasts which resemble foreign body giant cells, possibly formed by the confluence of primitive osteoblasts, erode the organic matrix and are located in indentations of bared bone surface called Howship's lacunae.

The resultant compact bone structure is characterized by Haversian canals carrying blood vessels and communicating with the marrow cavity and periosteum by Volkmann's canals. These are surrounded by concentric lamellae (usually no more than six) between which are lacunae containing osteocytes. Processes extend from osteocytes in canaliculi toward adjacent osteocyte processes. Nutrients and wastes diffuse, through these canaliculi, between blood vessels and cells. Interstitial lamellae occur as the result of previous growth of bone. Endosteal and periosteal connective tissue cover the medullary and outer surfaces of the bones respectively.

#### CHEMISTRY OF BONE

Bone is composed of 20 to 25 percent water and 75 to 80 percent solid matter. About 40 percent of the solids are organic. The remainder consists of inorganic material, chiefly calcium salts.

Organic solids are mainly protein and a small amount of glycogen. The proteins

include: 1) collagen (ossein) arranged in longitudinal helices. Adjacent helices are twisted in opposite directions, giving bone its great tensile strength; 2) ossealbuminoid, which resembles elastin; 3) osseomucoid, a protein containing chondroitin sulphate as a prosthetic group. In addition, certain enzymes are present. These include proteinases, peptidases, phosphorylase, and alkaline phosphatase. This organic matrix is produced by osteoblasts preliminary to mineralization, and is termed osteoid. Ascorbic acid and vitamin A are necessary for its production.

About 60 percent of the bone solid is inorganic. The principal minerals are: calcium 26%, phosphorous 1 to 2%, and carbonate 3%. These occur in a hydroxyapatite crystal,  $(Ca_3(PO_4)_2)_3 Ca(OH)_2$ , or bone salt. These crystals are located in an orderly fashion in relation to the unit fibrils of collagen. Each crystal is surrounded by a hydration shell through which Sr, Ra, Pb, Ca, F,  $HPO_4$ , and OH ions may penetrate to exchange with Ca,  $HPO_4$ , and OH ions present in the crystal lattice. Some Ca,  $CO_3$  and  $HPO_4$  ion is adsorbed on the surface of the crystal. This is a labile component accounting for about 15 percent of the bone calcium. Pb, U, Mg, and Na ions may replace the adsorbed calcium. Other ions, including K and Cl, are dissolved in the hydration shell. Ions on the surface of crystals are in dynamic equilibrium with the extracellular fluid; approximately 100 sq.M. per gram of bone are in contact with extracellular fluid. Citrate may be an important factor in the mobilization of calcium from this surface, as it forms a soluble chelated calcium complex.

There is much dispute about the mechanism of mineralization of bone matrix. Blood is supersaturated with Ca and  $PO_4$  ions with respect to hydroxyapatite. Upon initiation of precipitation, by whatever mechanisms are involved, crystallization continues to completion as in the seeding of any supersaturated salt solution. It was thought that the increased activity of alkaline phosphatase raises the level of



PO<sub>4</sub> ion, initiating crystallization, but current opinion assigns it a role in the synthesis of osteoid. Osteoblastic cells and chondroblasts, in calcifying cartilage, contain much glycogen, ATP, phosphorylase, and lactic acid indicating high glycolytic activity. Glycolysis may provide a source of phosphoric ester substrate for phosphatase, or it may be more significant in providing energy for the mineralization of bone. There is evidence that collagen and cement substance mucopolysaccharide, which is a polyelectrolyte, serve as a template and have affinity for hydroxyapatite formation.

A bone may be demineralized by treatment with strong mineral acid, and in this state it is rubbery. In fact it may be tied in a knot.

#### **METABOLISM AND NORMAL HORMONAL CONTROL OF BONE**

Bone is not static tissue. Like other organs, the skeletal system is continually replenished with new constituents. The apatite crystal itself has a very slow turnover; however, the labile salts in the hydration shell of bone salt undergo rapid exchange with the body fluid. The half-life of bone protein has not been determined, but it is considerably longer than the total body protein half-life of 80 days in man. An adequate blood supply is essential for the life of the osteocyte and for the maintenance of bone.

The serum level of calcium and phosphate and the supply of vitamins is of prime importance for the health of bone tissue. These are regulated by diet, normal digestion and absorption, endocrine glands, and by healthy kidneys.

1. **Parathormone.** The parathyroid glands secrete parathormone in amounts regulated by the level of serum calcium ion. This hormone stimulates the activity of osteoblasts causing resorption of the organic matrix. There is evidence that it elevates citrate production by osteocytes, thereby rendering bone salt more soluble. Calcium ion is mobilized from the stable compon-

ent of bone salt at a slow rate. The associated rise of serum alkaline phosphatase in hyperparathyroidism is probably due to increased osteoblastic activity in an attempt to restore the bone, rather than to a direct effect of parathormone. This hormone also inhibits reabsorption of serum phosphate by the kidney (phosphaturic effect). The immediate response to a decrease of serum calcium is mobilization of the labile component of bone salt. This is not mediated by parathormone.

2. **Somatotrophin.** Growth hormone stimulates bone growth by inducing hyperplasia of cartilage in the epiphyseal plates. Hyperpituitarism in children results in gigantism. In adults acromegaly results. In addition, somatotrophin has a general protein anabolic effect necessary for bone growth and maintenance. Insulin is necessary for this effect.

3. **Thyroxin.** Thyroxin hastens maturation of the skeleton. It affects the differentiation of epiphyseal ossification centers and their fusion to the diaphysis. However, excessive amounts of thyroid hormone have a protein catabolic effect resulting in the inhibition of osteogenesis.

4. **Adrenal Glucocorticoids.** These hormones inhibit the formation of osteoid because of their protein catabolic effect. Therapeutic administration of cortisone may impede fracture healing.

5. **Estrogens.** Estrogens favour retention and skeletal deposition of calcium. This action may be related to post-menopausal decalcification and post-menopausal osteoporosis (defective matrix formation).

6. **Androgens.** Androgens in the growing animal induce an increase in bone matrix. There is a general protein anabolic effect in bone. Closure of epiphyseal lines is retarded in prepubertal castrates.

7. **Vitamin D.** This vitamin is important in the maintenance of normal serum calcium and phosphate levels by promoting their absorption in the distal ileum. Moreover, it promotes mineralization of the



skeleton in both adult and growing animals independently of its effect upon absorption. Excessive amounts of Vitamin D promote mineralization of tissues other than bone.

8. **Vitamin A.** In addition to its requirement for general growth, vitamin A promotes the normal balance between bone formation and resorption, essential for normal bone structure. It is probably a factor in the control of activity of both osteoblasts and osteoclasts. In some species it has been demonstrated to stimulate endochondral bone formation. In puppies, deficiency causes a thickening of the skull and narrowing of the medulla in long bones.

9. **Vitamin C.** Ascorbic acid is necessary for production of collagen, and mucopolysaccharides of ground and cement substances by connective tissue cells. Osteoblasts require it to produce osteoid. Mineralization is not impaired by ascorbic acid deficiency.

10. **Intestinal Absorption.** In addition to adequate dietary sources of calcium and phosphate and a healthy intestinal mucosa, certain other factors must be balanced in the digestive phase in order to promote healthy bone maintenance.

a) *Intestinal PH.* Calcium salts, mainly phosphates and carbonates, are soluble at low pH. Their absorption is facilitated by gastric juice, lactic acid, and citric acid. Most absorption occurs in the duodenum before the pH rises greatly. In infants, lactobacilli in the gut may be significant in promoting absorption of calcium by producing lactic acid.

b) *Other Substances in Food.* Excesses of certain anions may precipitate calcium thereby inhibiting its absorption. Excesses of phosphates which occur in some patent medicines may be responsible. Excesses of fatty acids, as occur in biliary obstruction or sprue, form insoluble soaps with calcium.

Conversely prolonged excess of Cu, Fe, Pb, Mn, and Ca ions can cause rickets by forming insoluble phosphate salts and preventing absorption of  $PO_4$  ions.

c) *Vitamin D.* This vitamin promotes absorption of calcium in the distal ileum where it is otherwise poorly absorbed. It also lowers the pH in the ileum but the significance of this on calcium absorption is not known. Vitamin D also promotes phosphate absorption, possibly because it maintains an optimum Ca:  $PO_4$  ratio.

### The Physical Properties of Bone

Bone is a remarkably strong tissue. Its strength is comparable to that of cast iron but it is much more flexible and only one third the weight. Elasticity contributes much to this strength; bone is elastic up to about three quarters of its breaking strength. The tensile, compressive and shearing strength of bone may be measured by methods to determine the strength of structural engineering materials.

Tensile strength decreases with age and is greater in males than in females. Values of tensile strength along the lengths of fresh compact bone samples vary from 92,020 to 150,040 lbs./in<sup>2</sup>. The tensile strength of cancellous bone has not been determined.

Bone offers even more resistance to compressive stress. The strain is less when applied to the long axis than when applied at the ends of the bone. The compressive strength of wet compact bone approximates 18,000 lbs./in<sup>3</sup>.

Rauber determined that the shearing strength of bone loaded perpendicular to the long axis of its fibres is considerably less than its tensile or compressive strength. Samples of wet bone from the femur have an average shearing strength of 9800 lbs./in<sup>2</sup>.

Because of their orientation, the trabeculae of cancellous bone stimulated many engineers interested in bone structure to



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propose the trajectorial theory of bone architecture. The trabeculae in the ends of long bone were thought to be tension or compression resistant. However, they are probably concerned with holding the actual load carrying parts of compact bone apart, rather than offering resistance themselves. According to Wolff's law, published in 1892, every change in the form of function of a bone results in changes in its trabecular structure and external form in accordance with mathematical laws. There is controversy about the validity of this law. Considerable evidence has been presented that mechanical stimuli do not play the most important factor in the placement of osteons, although few investigators would deny that weight-bearing and tendon

forces on bone are important in determining bone structure by such mechanisms as the induction of traction epiphyses.

The author expresses his gratitude to Dr. R. C. Buck for his help in the preparation of this paper.

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## Neoplasms of Bone

M. C. HICKEY, '65

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Many advances have been made in bone pathology in recent years. Consequently, new names had to be coined such as benign chondroblastoma, chondromyxoid fibroma, non-osteogenic fibroma, and aneurysmal cyst. Lesions, both neoplastic and non-neoplastic, have been found to be distinct clinical and pathological entities. The majority of tumors are fascinating and the diagnosis is often a difficult one to make. Many bone tumors are not really tumors at all but are malformations in bone structure.

Anyone concerned with tumors of bone should have a triple view of them with a clinical, radiographical, and pathological

approach. Emphasis in this discussion will be placed on diagnosis as a basis for appropriate and effective treatment. Accordingly the diagnosis is arrived at with care and the treatment is carefully planned and carried out.

#### CLASSIFICATION

No classification is entirely satisfactory until the obscurities of nature and origin of all the tumors have been clarified. The following classification used by Lichtenstein<sup>6</sup> is useful because it classifies bone tumors according to the probable tissue of origin.



## —Neoplasms of Bone—

TISSUE OF ORIGIN	BENIGN	MALIGNANT
1) Osteoblastic	Osteoma Osteoid osteoma	Osteogenic sarcoma
2) Cartilaginous	Osteblastoma Chondroma (enchondroma, osteochondroma) Chondroblastoma Chondromyxoid fibroma	Chondrosarcoma
3) Non-osteoblastic connective tissue	Non-osteogenic fibroma Benign giant cell tumor	Fibrosarcoma Malignant giant cell tumor
4) Mesenchymal connective tissue		Ewing's sarcoma
5) Hematopoietic		Multiple myeloma Malignant lymphoma Acute leukemias Chronic myeloid leukemia
6) Nerve	Neurofibroma Neurilemmoma	
7) Vascular	Hemangioma Hemangiopericytoma	Hemangioendothelioma
8) Fat cell	Lipoma	Liposarcoma
9) Notochord		Chordoma
10) Metastatic tumors (from prostate, breast, kidney, lung, gastro- intestinal tract, geni- talia, thyroid)		

### Method of Spread of Malignant Tumors:

a) Spread of primary tumors is by the blood stream mainly to the lungs, by direct spread to adjacent bones or soft tissue, and by lymphogenous routes.

b) Spread of secondary tumors is mainly by the blood stream (venous or arterial). The Batson pathway or the vertebral venous system accounts for the distribution of metastases. This is a network of veins around the spinal dura mater and the vertebrae. The venous pool is connected to veins in the cranium and body wall. It is also connected to the caval, portal, azygos and pulmonary vein systems, providing by-passes of metastatic spread for them.

### GENERAL CONSIDERATIONS

Bone is a specialized type of connective tissue containing cells with long branching processes. The cells are embedded in a matrix consisting of bundles of collagenous fibers in an amorphous ground substance containing calcium phosphate complexes.

Grossly, bone consists of periosteum, compact bone, cancellous bone, and bone marrow. There is an increase in length of a growing long bone which occurs at each end in a specialized cartilage structure, the epiphyseal plate. The periosteum is made up of two layers of fibrous tissue and osteoblasts. The deep layer of cells cause

an increase in the width of bone. The bone itself contains adult bone cells, osteoblasts, osteoclasts, and matrix. The marrow contains marrow cells and reticuloendothelial cells.

## CLINICAL MANIFESTATIONS

Bone tumors generally present clinically in two ways. Swelling and/or deformity are often seen first. Local pain is also a presenting symptom and may be associated with swelling and pathological fracture. Pain and swelling are frequently preceded by a history of trauma although they are not directly caused by trauma.

### 1. Benign Tumors

Benign tumors are often quite large when diagnosed. They are usually slow growing and generally produce no severe symptoms and signs for a long time. Frequently pain is a principal complaint following a pathological fracture. A fracture may occur in any tumor but is seen most often in a bone cyst.

### 2. Malignant Tumors

Malignant tumors show a variable picture. They generally grow more rapidly and are more often painful. If there are metastases, then there is often loss of weight and anemia. Some malignant tumors present with no symptoms for months or several years. Vertebral collapse frequently occurs causing local pain, tingling, and weakness related to nerve trunk involvement. In Hodgkin's disease and Ewing's sarcoma there is often pyrexia of the so-called Pel-Ebstein variety with elevations to about 101°F.

## DIFFERENTIAL DIAGNOSIS -

Diagnosis of bone tumors is difficult because of their variability, insidious onset, and similarity to other disease processes. The age of the patient, duration of symptoms, and the roentgenograms are important in making a diagnosis.

Palpation is carried out to see whether the swelling springs from one aspect of the bone or the whole circumference. Benign

extostoses are localized and other tumors grow from the whole circumference of bone. Palpation will help to tell if the tumor arises from the external surface or the internal structure.

1. **Incidence** - Age is often helpful in diagnosis. Certain groups of tumors are characteristic of specific age groups although exceptions to the rule do occur. In children under 10 years of age, the most frequent solitary tumors are bone cysts and Ewing's sarcoma. In the age group 10-25, osteogenic sarcoma is most common. Multiple myeloma is common in people 40-70 years of age. Multiple tumor lesions of bone are usually benign in children and malignant in adults. Generally the benign tumors are common in the age group under 25 and the malignant tumors in the age group over 25. Secondary tumors usually are seen in adults. If osteogenic sarcoma occurs in an adult then it is usually complicating Paget's disease of bone.

### 2. Localization -

a) If the swelling encircles the whole circumference and is situated at one end, it is likely to be a giant cell tumor.

b) If the swelling is situated at the periphery on one side of the bone only, and located near the epiphyseal line, it is probably an epiphyseal exostosis.

c) When the swelling expands the bone midway between the two ends, consider Ewing's sarcoma, and a simple bone cyst.

### 3. Pathological Chemistry -

With some bone tumors, changes in certain constituents of the blood serum and urine are noted and are helpful in making a diagnosis.

Osteoblasts produce alkaline phosphatase and its concentration in the serum is higher than normal with tumors of osteoblastic origin, e.g., osteosarcoma. Tumors that produce rarefaction of bone cause an increase in alkaline phosphatase although they are non-osteoblastic. Multiple myeloma is an exception because normal levels of alkaline phosphatase are found in the



presence of bone destruction. It is noteworthy that elevation of alkaline phosphatase occurs during treatment which suggests that the tumor is responding, not progressing. This is especially true in treatment of carcinoma of the prostate and its metastases.

Elevation of serum protein (especially gamma globulin) and the presence of Bence-Jones protein in the urine are of value in the diagnosis of multiple myeloma. The level of calcium in the serum and urine is also an aid to the diagnosis. Hypercalcemia in malignant lesions is frequently associated with widespread metastatic disease in the skeleton. Frequently widespread skeletal involvement from breast cancer produces hypercalcemia particularly in response to the administration of estrogens. Hypercalcemia may also mean a destructive bone tumor and occurs characteristically in association with primary hypertension.

#### 4. Radiographic Assessment -

The radiological features of bone tumors are frequently of great value in making a diagnosis.

X-ray investigation reveals the location of the lesion. It gives some idea what the tumor has done to the original osseous tissue at the site of the growth. Indication of any response which the lesion may be producing in the bone adjacent to it shows up on x-ray examination. The gross characteristics of the lesion can be arrived at. Furthermore, radiology reveals an insidious symptomless tumor which might otherwise go unnoticed until it is too late.

Some examples are:

1. Osteochondroma—The x-ray reveals an outgrowth from the bone directed shaftward, away from the epiphysis. It is sharply demarcated and sits on an osseous base of normal bone density which is directly continuous with the cortex. The exostosis is capped with cartilage.

2. Giant Cell Tumor—It is usually an area of radiolucency with multilocular

areas in the tumor at the epiphyseal ends of long bones. The surrounding cortex is thinned out and swollen. The rarefaction extends to the cartilage and occasionally may invade an articulation.

3. Bone Cyst—The area is swollen and the cortex is thin. The periosteum is smooth. The defect is a single or multilocular area of rarefaction occurring in the diaphysis particularly in the proximal part of the humerus.

4. Osteogenic Sarcoma—The lesion contains areas of new bone formation (which show as opaque areas) and of bone destruction. The shadow sometimes shows spicules of new bone at right angle to the shaft, giving it a sunray effect. In advanced cases the lesion has invaded the surrounding tissues producing a shadow beyond the cortex.

5. Multiple Myeloma—Generally there are small or large punched-out rarefactions. These punched-out areas of osteolysis show no osteoblastic reaction around them or within them. These lesions are found in the calvarium, ribs, vertebrae, pelvis, and in some long bones.

#### PATHOLOGY

Generally it is necessary to remove a piece of the tumor to obtain a diagnosis. Then it is possible to carry out definitive treatment. Open biopsy is the best method for interpreting the pathology. If it cannot be carried out without harm to the patient, the surgeon should do a needle biopsy although there is difficulty in interpreting the results. The double tourniquet method of open surgical biopsy is practiced. Two tourniquets are tightly wrapped around the leg at a suitable level for amputation. An incision exposes the tumor and a piece is excised for examination. If the tumor is malignant, then amputation is performed between the tourniquets which are applied to prevent metastases after the biopsy.



Usually definitive treatment is not carried out on an x-ray diagnosis alone but a combination of radiology and pathology which should qualify one another.

### Metastatic Tumors

The skeleton is a common site for spread of a primary carcinoma. They arise mainly from prostate, kidney, breast, lungs, thyroid. Metastases from prostate are consistently osteoblastic and those of breast and kidney are osteolytic though a few are osteoblastic. Carcinomatous metastases from thyroid are osteolytic and from lungs are osteoblastic. The histology is usually that of the primary tumor.

## TREATMENT AND PROGNOSIS

Rest of the part, to prevent pathological fracture and relieve pain is the usual initial treatment.

### 1. Benign Tumors

Excision is usually performed. After excision it may be necessary to pack the cavity with small bone grafts. Some tumors are curetted but recurrence is high after treatment. The prognosis is good in most benign tumors.

### 2. Malignant Tumors

a) Surgery—Generally cure can only be obtained by removing the growth by operation. An amputation may be performed in certain cases using the double tourniquet technique discussed before. The operation may be palliative where cure is not possible and is done to relieve pain. For example, intramedullary fixation is performed either to prevent a fracture or as a method of treatment for a pathological fracture. Another technique is to take out the head of the femur and insert a prosthesis.

b) Radiation—Ewing's sarcoma is very radiosensitive; and multiple myeloma although not curable is treated with irradiation as a palliative measure. Secondaries from the breast respond well to radium treatment. Other secondaries also are treated in this way generally to relieve the pain and prolong life.

c) Hormonal Therapy—It has been proven that bone tumors grow in a constant specific hormonal environment in the body. Any change that suddenly upsets this balance either by reduction in the amount of hormones or by a change of hormones in the body system might change the course of the disease process producing a good prognosis or relieving pain. For example, cortisone is used sometimes to relieve the pain in Ewing's sarcoma. Hormones are used to control metastases from the breast, prostate and thyroid. In breast carcinoma with metastases, the most useful procedure is oophorectomy, especially in the premenopausal patient. This operation produces a decrease in serum calcium which is usually elevated and may be used as a guide to the value of further hormone treatment. Corticosteroids are used as adrenocortical suppressants to stop the growth and recurrence of metastatic carcinoma of the breast. It is 50% successful. Metastases from the prostate are controlled by estrogen with or without orchidectomy.

d) Chemotherapy—This form of treatment is still in the developmental stage but is of value for the palliative treatment of some forms of cancer.

Isotopes, such as  $I^{131}$ , are being administered to patients with functioning carcinoma of the thyroid and its metastases to bone.  $P^{32}$  is used in cases of multiple myeloma. Alkylating agents, such as nitrogen mustard (Mustargen) and thio-Tepa suppress bone tumors (especially multiple myeloma) by impairing protein synthesis in the nucleus and cytoplasm.

Antimetabolites such as amethopterin (Methotrexate) block essential metabolic pathways in cellular metabolism. Their greatest effect is produced on rapidly dividing cells in malignant tissue.

Most malignant tumors of bone have a poor prognosis. The worst cure rates occur in osteosarcoma. If treatment is carried out early enough, cure rates are found in metastases from breast and prostate controlled by hormonal therapy.



## SUMMARY

Tumors of bone is a complex subject with many fascinating aspects to it. Early diagnosis has been emphasized as the key to successful treatment. Radiology helps but usually the diagnosis is made on the microscopic appearance of the tumors. The more common tumors such as osteochondroma, multiple myeloma, and osteosarcoma have been used to illustrate proper methods of study and treatment. Although treatment of benign tumors is satisfactory the results of treatment of malignant tumors are bad. This is due to the variability and insidious nature of many of the neoplasms. They tend to metastasize early and sometimes are multifocal in origin (Ewing's sarcoma and multiple myeloma). The etiology is generally obscure, and surgery, radiation, chemotherapy and hormonal treatment are mainly of a palliative nature.

The author wishes to express his appreciation to Dr. J. A. McCredie for his help in the preparation of this paper.

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# Inflammatory Diseases of Bone

ERNEST SPRATT, '64

Since the introduction of antibacterial drugs, there has been a marked improvement in the incidence, course and prognosis of bone inflammations. However, these diseases still present a problem in treatment because of the increasing number of antibiotic-resistant bacteria. At present, the infections of greatest concern are tuberculous, syphilitic and pyogenic staphylococcal osteomyelitis.

## DEFINITIONS

Periostitis refers to inflammation of the periosteum, osteitis refers to the cortex, myelitis refers to the bone marrow, osteo-

myelitis is used when the inflammation involves both cortex and bone marrow and osteochondritis when the metaphyseal and epiphyseal junction are involved.

## GENERAL CLASSIFICATION

### I. Acute Pyogenic Osteomyelitis

1. Hematogenous
2. Non-Hematogenous
  - i) infection from without
  - ii) direct extension

### II. Chronic Osteomyelitis

1. Chronic pyogenic (non-specific)
2. Typhoid osteomyelitis



3. Tuberculous osteomyelitis
4. Syphilitic osteomyelitis
5. Brucellosis

## I. ACUTE PYOGENIC OSTEOMYELITIS

This infection in bone is characterized by suppuration of the soft parts of bone including the contents of the marrow cavity, the Haversian canals and the periosteum.

### Etiology

The hematogenous form is commonest in the young age group (2 to 10 years) where active bone growth is taking place. Direct trauma to bone causing effusion of blood (a nidus for bacterial growth) makes the incidence of osteomyelitis three times greater in the male child than the female child. *Staphylococcus aureus* accounts for eighty percent of infections; the other twenty per cent are due to *Staphylococcus albus*, *Streptococcus hemolyticus*, *Diplococcus pneumococcus*, *Hemophilus influenzae*, *Neisseria gonorrhoeae*, *Escherichia coli* and sometimes other gram negative enteric bacteria.

The non-hematogenous form has a much lower incidence and usually occurs because of contamination after trauma or spread of soft tissue infection.

### Pathology

Heavy strain seems to account for some areas of bone becoming infected more than others. The commoner sites are the lower end of the femur, the upper end of the tibia, the upper end of the humerus and less commonly, the neural arches of the spine.

In the case of hematogenous infection, the organisms are blood-borne from a distant lesion. This may be a carbuncle or furuncle in the skin, or a transient bacteremia may result from unrecognized foci of infection in the bowel or insignificant infection of the teeth or upper respiratory tract. Since there is rich vascularization, the bacteria form a suppurative abscess in the metaphyseal marrow. The infection spreads down the marrow cavity but also

outwards to the cortex, penetrating the endosteum. A subperiosteal abscess forms resulting in elevation of the periosteum until it may rupture, allowing suppuration into the surrounding soft tissue. Frequently, the vascular supply is obstructed resulting in ischemia of bone causing necrosis and sequestration. If septic thrombi form they may dislodge and form pyemic abscesses elsewhere in the body. The osteoblasts of the periosteum react by forming new bone known as the *involucrum* over the sequestrum. Excessive neo-osteogenesis produces a characteristic sclerotic pattern known as Garré's sclerosing osteomyelitis. The microscopic picture shows suppurative and ischemic destructive necrosis with fibrous and bony repair.

Bacterial invasion of bone occurs by two methods in the non-hematogenous infection. Direct spread from neighboring soft tissue occurs in maxillary osteomyelitis following an infected tooth or mastoid involvement in otitis media.

Secondly, direct exogenous contamination often occurs in open fractures, gunshot wounds, open bone surgery or around traction pins.

### Clinical Manifestations

Osteomyelitis often presents with generalized findings of acute infection such as gastro-intestinal tract upset, fever, rapid pulse and leukocytosis. The local signs are very important but unfortunately may be absent in some cases. The diagnosis is often suggested by severe throbbing pain located at the end of a long bone. Muscle spasm and restriction of movement of the limb may be evident in advanced stages. The overlying subcutaneous tissue may be swollen and edematous and the adjacent skin erythematous and warm.

### Diagnosis

A history of previous minor trauma or cutaneous infection gives a valuable clue to the diagnosis. After the second week, x-ray evidence of infection is present. Osseous changes of destruction and repair may be noted. Multiple small lytic



defects appear in the metaphysis followed by demineralization of surrounding bone in a coarse trabecular pattern. The involucrum appears as dense wavy strips on either side of the metaphysis and shaft. Dense outlines surrounded by rings of granulation tissue indicates sequestra formation.<sup>3</sup> Blood culture is valuable diagnostically but is positive in only fifty per cent of cases.

The differential diagnosis should include simple fractures, rheumatic fever, sepsis, cellulitis, Perthes' disease, osseous tumor, early stage of poliomyelitis and scurvy.

### Treatment

Most treatments for this disease can be placed in one of three broad approaches:

#### 1. Early Surgical Intervention

According to Harris,<sup>4</sup> surgery should be undertaken during the first three days following the onset of the illness. He recommends that the cortical bone be drilled to allow proper drainage of the marrow cavity besides merely draining the subperiosteal abscess. He feels that this operation will prevent interruption of the blood supply which causes necrosis and sequestration. The exudate obtained from the surgical procedure may be used for sensitivity determinations. Without surgery, the physician must rely on a sensitivity from a blood culture which is much less reliable and requires twenty-four hours longer. Harris feels that it is a simple procedure and relief from local pain may be dramatic following operation.

#### 2. Early Antibacterial Drug Therapy

It has been noted by Blockley and Mann<sup>1</sup> that there are a great number of penicillin-resistant bacteria which commonly cause osteomyelitis. However, they found that very few organisms were resistant to drugs such as erythromycin and methicillin. Contrary to Harris, they feel that, even without a sensitivity report, there is an excellent chance that the organism will be sensitive if the proper antibiotic or combination of antibiotics is used. Often the diagnosis is obscure and surgery may be

very difficult and unrewarding without the evidence of radiological changes. Therefore, this group advocate only antibiotic treatment until such time as sequestration or other osseous changes are present.

#### 3. Antibacterial Agents and Surgery

The third approach is probably the most logical, although it is really a compromise. Koenig and Rogers<sup>7</sup> state that there should be no surgical intervention unless the following indications are present:

- i) a soft tissue abscess
- ii) extreme local bone tenderness (produced by pus under pressure)
- iii) systemic manifestations not relieved by conservative management.
- iv) radiological evidence of devitalized bone.

Where antibiotic therapy is indicated, a blood specimen for culture and sensitivity is withdrawn. Koenig and Rogers suggest immediate use of aqueous penicillin intramuscularly in divided doses up to ten million units per day. Since many strains of bacteria are resistant, methicillin may be used in dosages of one gram every four hours intramuscularly or twenty-five mgms. per kilogram body weight in infants. This may be supplemented by 500 mgms. of chloramphenicol, erythromycin or tetracycline. Rapid resistance developing early, drugs such as erythromycin and novobiocin should not be used extensively.

Antibacterial treatment should be maintained from three to six weeks. The duration is determined by the disappearance of clinical findings.

### Prognosis

With better management the incidence of acute osteomyelitis is decreasing with fewer cases persisting in a chronic form. In some cases, pathological fractures may occur in weakened areas of bone or there may be extension into joints causing a suppurative arthritis. The most serious complication is further hematogenous dissemination of the infection with development of pyemic abscesses in the liver, kidneys, and even the heart valves.



## II. CHRONIC OSTEOMYELITIS

### 1) Chronic pyogenic (non-specific)

Chronic pyogenic osteomyelitis is the sequela of inadequate treatment of the disease process in the acute phase. The acute signs and symptoms have subsided but infection is manifested by a draining sinus, a recurrent cellulitis or localized abscess formation.

#### Pathology

The typical lesion is a Brodie's abscess. A chronic nidus of infection is walled off by inflammatory fibrous tissue produced by attempted healing. Destruction of cancellous marrow spicules with erosion of cortical bone is commonly seen. The condition may regress to the acute stage following trauma or decreased host resistance to infection.

#### Clinical Manifestations

The findings are localized with progressive or recurrent infection characterized by necrosis of bone, suppuration, draining sinuses, sclerosis, fibrosis and strangulation of small vessels creating local tissue ischemia. X-ray findings may be confused with tuberculous or syphilitic osteomyelitis, skeletal lesions of sarcoidosis, eosinophilic granuloma, and benign or malignant bone tumors.

#### Treatment

According to Murray<sup>10</sup>, chronic osteomyelitis persists because of the presence of sequestra, empty cavities or dead spaces which encourage bacterial growth and excess scar tissue. The avascular center of the scar becomes necrotic allowing exposure and contamination. With this in mind, the aims of treatment should include:

- i) Surgical removal of all abnormal tissue including infected granulation tissue, sequestra and avascular scar tissue.
- ii) Closure of the resulting cavity with normal skin, fat, muscle or bone.
- iii) Control of responsible bacteria with proper antibiotic agents.

Since there are many approaches to the cure of this disease, each case must be

assessed individually to determine the proper treatment.

One of the more popular procedures is the Orr treatment.<sup>10</sup> After the excision of sequestra and other infected granulation tissue, the entire wound is kept open by vaseline gauze packing until the dead space has healed. When this has taken place, a skin graft may be applied.

In other cases, following débridement the dead space may be filled with fat, muscle, bone graft, or a skin graft may be applied initially.

Excision of involved bone or amputation may be indicated in very severe cases to prevent dissemination of infection. Antibiotics are seldom curative when used exclusively and supportive measures such as rest and immobilization are helpful following surgery.

#### Prognosis

The disease may be complicated by exfoliative dermatitis or even squamous cell carcinoma in a draining sinus. Chronic osteomyelitis is still a common cause of invalidism and recurrent illness.

### 2. Typhoid Osteomyelitis

Typhoid osteomyelitis, usually involving ribs, tibia or spine is a rare complication appearing about two months after an attack of typhoid fever. Radiologically, there are large osteolytic lesions but very little fibrosis. In the spine, two or more discs may be involved with new bone formation in the surrounding spinal ligaments. After intensive treatment on a broad spectrum drug such as chloramphenicol surgical exploration of the disc space followed by curettage of any abscess cavity is helpful.<sup>9</sup>

### 3. Tuberculosis

From a pathological standpoint, this disease differs from other forms of osteomyelitis because there is no periosteal osteogenic new bone formation. The lesion is mainly destructive with marked softening, slight caseation, cold tuberculous



abscess formation and granulation tissue development.

Clinically, there may be fusiform swellings of the fingers (tuberculous dactylitis) or caseous necrosis of the bodies of the vertebrae (Pott's disease), destroying the discs but sparing processes, spines and articular processes. On x-ray examination, metastatic carcinoma may appear similar but it does not involve the discs. Tuberculous osteomyelitis has a slow progressive course with excessive muscle spasm, night fever and weight loss. Treatment should consist of complete rest under sanatorium care, early anti-tuberculous drug therapy and fusion of the involved vertebral bodies after the disease process is quiet. A common complication is a psoas abscess which develops when suppuration tracks along the posterior common ligament perforating the sheath of the psoas muscle.

#### 4. Syphilis

The lesions are located in the diaphysis rather than the articular ends. On examination, there may be a firm, painful, localized periosteal node or a diffuse osteitis of the shaft. In contrast to tuberculous osteomyelitis, syphilitic lesions are osteosclerotic with excessive neo-osteogenesis. Gummatous destruction of the bones of the nose and hard palate give the typical saddle nose. Treatment is based on arresting the disease process.

#### 5. Brucellosis

Skeletal brucellosis may be manifested by local pain, heat, tenderness, swelling, and erythema. The roentgenographic picture is that of medullary destruction, often with periosteal thickening. Spondylitis, in which the brucellar organisms invade an intervertebral disc, should be kept in mind when one encounters a possible so-called disc syndrome in a patient associated with animal husbandry. There is usually narrowing of the intervertebral space and eventual bony fusion. According to Martin et al,<sup>8</sup> a combination of streptomycin and tetracycline is the treatment of choice.

Along with other supportive measures, surgical intervention is seldom necessary in the case of spondylitis. However, energetic surgical treatment is recommended by Martin et al for brucellosis of the bones and joints.

The author wishes to express his gratitude to Dr. M. S. Smout for his assistance in the preparation of this paper.

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# Metabolic Bone Diseases

ELIZABETH ROSS, '64

Perhaps one of the truest maxims in diagnostic medicine is "Before one can name the entity one must know the possibilities." In accordance with this view, it is proposed in this paper to outline a simple classification of metabolic bone diseases which include generalized or systemic bone diseases that influence all bones of the body to a greater or lesser degree. Not included are non-metabolic or localized bone diseases in which areas of uninvolved normal bone are found in association with an involved area.

Bone, a dynamic not a static structure, normally evolves through three stages:

1. Protein matrix or osteoid produced by osteoblasts.
2. Ossification or the laying down of inorganic calcium complex (calcium-phosphate-carbonate) in the matrix.
3. Resorption by the osteoclasts:

Errors in any of these three stages, or the metabolism of any component necessary to them, will result in either an increased or a decreased bone production.

The three most common conditions all result in a decreased bone mass and hence radiological changes of increased lucency when 30-50% of normal bone density is lost. Each corresponds to a defect in a different stage of bone production. Included are:

1. Osteoporosis — or deficient osteoid production
2. Osteomalacia and rickets — or deficient mineralization
3. Osteitis fibrosa cystica — or increased osteolysis associated with compensatory new bone formation.

Disease associated with increased radiodensity are rare but include:

1. Osteosclerosis — decreased resorption
2. Hyperosteo genesis — increased osteoid production.

Each disease and its subdivisions will be considered separately.

## A. DECREASED RADIO DENSITY

### I. Osteoporosis

Osteoporosis includes any metabolic abnormality that results in a diminished osteoid production. Too little bone is produced, but what there is, is normally ossified and resorbed. Defects may occur in any of the elements necessary to osteoid production.

Protein synthesis is defective in various endocrine conditions:

1. Deficiency of the anabolic gonadal hormones either estrogen and androgen as seen in post-menopausal osteoporosis, or that related to ovarian agenesis and Frölich's syndrome.
2. Excessive production or administration of the antimetabolic glucocorticoids (e.g. Cushing's disease) which decrease protein synthesis by promoting the use of amino acids for gluconeogenesis rather than for matrix formation.
3. Excess utilization of protein in prolonged hyperthyroidism and diabetes mellitus.
4. Pituitary dysfunction resulting in either Cushing's disease or acromegaly acts to produce defective osteoid production by affecting the adrenal cortex and gonads respectively.

Osteoblastic activity may be depressed by lack of the stimulus of stress and strain resulting in the osteoporosis seen in immobilized persons.

Qualitatively abnormal osteoid is produced in cases of avitaminosis C (scurvy) due to defective production of collagen, its precursor.

Senile osteoporosis is generally regarded as resulting from a combination of decrease in hormone production by the gonads,



decreased activity, and inadequate diet in terms of protein and vitamin C.

Osteogenesis imperfecta (*fragilitas ossium*) is an inherited disorder of connective tissue, probably interfering with the maturation of collagen and hence resulting in defective osteoid production.

## II. Osteomalacia and Rickets

Osteomalacia and rickets are essentially the same disease in that both result from a deficiency of ossification of normal osteoid tissue. However, the former term is used only if disease occurs in the mature skeleton after the epiphyses have closed. The latter term is used if the epiphyses are still open. Any abnormality in calcium phosphate or vitamin D metabolism may result in this condition.

(a) Inadequate intake of any of these three may result from dietary deficiencies but in the Western Hemisphere this is extremely rare. However, it is still seen in depressed populations, particularly if there is a superimposed lack of exposure to the ultra-violet rays of the sun which act on the provitamins ergosterol and 7-dehydrocholesterol to produce D<sub>2</sub> (calciferol) and D<sub>3</sub> (cholecalciferol) respectively.

Any of the malabsorption syndromes such as chronic steatorrhea, sprue, fibrosing pancreatic disease, disturbances of the biliary system or long-standing ulcerative colitis result in inadequate absorption of the fat soluble vitamin D. As vitamin D stimulates the absorption of calcium, but not phosphate, the former substance is secondarily not absorbed. Further decrease in calcium and phosphate absorption results from their precipitation with the excess fatty acids to form unabsorbable soaps. Rapid transit due to associated diarrhea adds to the lack of absorption.

Relative deficiency of calcium and phosphate may occur in the face of excessive osteoid production as is seen in the healing stage of osteitis fibrosa cystica. Losses via the placenta and in lactation also tend to relative deficiencies of essential minerals.

Renal insufficiency either glomerular or tubular in nature results in excessive loss of one or more of the essentials of ossification and hence either renal osteomalacia if it occurs in adults, or renal osteodystrophy if it occurs in children before the epiphyses have closed. Diseases in this group all have a primary renal lesion which, probably as a result of a low serum calcium level, leads to parathyroid hyperplasia. Excess parathormone stimulation decreases ossification of the osteoid and apertic considerations it must be remembered that primary hyperparathyroidism may lead to nephrocalcinosis and secondary renal damage.

Primary glomerular dysfunction may be acquired, as in disease such as pyelonephritis, chronic glomerulonephritis, arteriosclerotic kidney disease, and far advanced myeloma and amyloidosis, or may be due to a congenital abnormality such as polycystic kidneys, horse-shoe kidney or stenotic lesions that predispose to pyelonephritis. The electrolyte imbalance results from phosphate retention by the glomerulus and as phosphatemia increases a compensatory loss of calcium occurs. As uremia develops tubular dysfunction is superimposed on the picture.

Renal osteomalacia is usually of the acquired type while renal osteodystrophy is usually congenital. In either case bone lesions do not appear until two years after the onset of the primary kidney disease.

Defects in the proximal convoluted tubule, where normally phosphate, glucose and amino acids are reabsorbed, may lead to a diminished reabsorption of one or all of these substances. The term hypophosphatemic vitamin D-refractory rickets includes all of the six possible types which are:

1. Vitamin D-resistant rickets.
2. Vitamin D-resistant rickets with amino-aciduria.
3. Vitamin D-resistant rickets with amino-aciduria and acidosis (de Toni-Debre-Fanconi syndrome).



4. Cysteine storage.
5. Hyperglycinuria.
6. Lowe's Disease (oculocerebrorenal syndrome) characterized by hypophosphatemia, amino-aciduria, acidosis, glaucoma and mental retardation.

The tubular defect may be due to:

1. A congenital enzyme deficit.
2. A congenital malformation of the most proximal portion of the tubule (swan neck deformity).
3. A toxic agent, e.g. copper in Wilson's disease, abnormal protein in multiple myeloma, cadmium, lead or cysteine poisoning acting to produce structural changes such as hypertrophy, vacuolization and degeneration of lining of the tubules, peritubular focal fibrosis or lack of alkaline phosphatase.
4. Excess of glycogen storage.

Distal tubular disease results in hyperchloremic renal tubular acidosis or Batten - Albright's syndrome. Inhibition of carbonic anhydrase activity leads to decreased bicarbonate reabsorption and hence the necessity of calcium being used as a base to excrete acid radicals. A similar state results from long standing hyperchloremic acidosis due to non-renal causes.

(b) Hypophosphatasia which results in osteomalacia or rickets in the presence of normal serum calcium and phosphorus levels, is a rare disease that appears to be due to a lack of the enzyme alkaline phosphatase, in both cells and serum, which is necessary for the ossification of osteoid. Inherited as an autosomal recessive, the disease may manifest itself at any time from the prenatal period to adulthood. The later it presents, the better the prognosis.

### III. Osteitis Fibrosa Cystica

Osteitis fibrosa cystica or von-Recklinghausen's disease (not related in any way to von Recklinghausen's neurofibromatosis) is characterized by increased osteolysis, increased excretion of phosphate in the urine, and replacement of focal areas of bone destruction by excess fibrous tissue,

to form what is known as brown tumors (osteoclastoma). This disease is the result of the activity of excess parathyroid hormone secreted by a parathyroid adenoma. Exactly similar clinical and radiological results are obtained in parathyroid hyperplasia either primary or secondary.

### B. INCREASED RADIODENSITY

Disease of increased bone density are rare. Osteosclerosis is commonly seen in a localized but rarely a generalized form. However, a generalized form may occur in connection with long standing hypothyroidism, in which although longitudinal growth is inhibited cortical growth is increased. Also resulting in increased bone density is osteopetrosis, otherwise known as marble bones or Albers - Schönberg disease. A familial and congenital disease, it is due to a defect in osteoclasts and chondroblasts. There is excessive calcification of osteoid tissue and an absence of true ossification as shown by lack of bone lamellae and osteoblasts.

Hyperosteogenesis refers to conditions of increased radiodensity resulting from an excessive stimulation of the osteoblasts. This stimulus may be either a physiological stimulus resulting from excessive stress as seen in physical activity, or compensatory bone formation of healing osteomalacia or osteitis fibrosa cystica, or due to external agents such as radiation, excessive intake of fluorine (fluorosis), elemental phosphate, beryllium or vitamin A.

The differential diagnoses of the conditions discussed depend upon:

1. Radiological findings with regard to alteration in bone density.
2. Serum calcium, phosphate and alkaline phosphatase levels.
3. Urinary calcium and phosphate levels and if renal osteodystrophy is suspected, pH, and amino acid levels to determine the type.

In the accompanying table the expected findings in each of the major diseases discussed are listed. Knowledge of the primary defect, plus the fact that the body at



## Metabolic Bone Diseases

all times attempts to keep the ratio of calcium and phosphate constant and that alkaline phosphatase activity is a reflection of osteoblastic activity enables one to work out for oneself the expected change, if any, in these three areas.

### SUMMARY OF METABOLIC BONE DISEASES

#### A. DECREASED RADIODENSITY

##### I. Osteoporosis - defective osteoid production

###### (a) Endocrine dysfunction

###### (i) Gonadal deficiency

Senility  
Menopause  
Ovarian agenesis  
Frölich's syndrome  
Acromegaly

###### (ii) Glucocorticoid excess

Cushing's syndrome  
Cushing's disease  
Iatrogenic

###### (iii) Miscellaneous

Hyperthyroidism  
Diabetes mellitus

###### (b) Vitamin defect

###### (i) Avitaminosis C

###### (c) Immobilization

###### (d) Congenital

###### (i) Osteogenesis imperfecta (Fragilitas Ossium)

##### II. Osteomalacia and Rickets - defective mineralization

###### (a) Deficiency of calcium, phosphate or vitamin D due to:

- (i) Inadequate diet
- (ii) Inadequate exposure to ultra-violet rays of sun.
- (iii) Inadequate absorption

G.I.T. diseases resulting in steatorrhea and diarrhea.

###### (iv) Excess excretion

*Glomerular* - phosphate retained.  
*Proximal Tubular* - phosphate and amino acids not reabsorbed.  
*Distal Tubular* - acidosis and calcium loss.

###### (v) Excess utilization

Placenta and lactation  
Healing osteitis fibrosa cystica  
(b) Hypophosphatasia - normal mineral supply but lack of alkaline phosphatase.

##### III. Osteitis Fibrosa Cystica - increased resorption and fibrous hyperplasia

###### (a) Parathyroid adenoma

#### B. INCREASED RADIODENSITY

##### I. Osteosclerosis - defective resorption

###### (a) Osteopetrosis

###### (b) Hypothyroidism

##### II. Hyperosteoegenesis - increased matrix formation

###### (a) Excessive physical stress

###### (b) External agents

- (i) Radiation
- (ii) Fluorosis
- (iii) Excessive beryllium intake
- (iv) Excessive elemental phosphate intake
- (v) Hypervitaminosis A

DISEASE	SERUM			URINE		
	Radiodensity	Calcium	Phosphate	Alkaline Phosphatase	Calcium	Phosphate
I. Osteoporosis	Down	Low or slightly high	Low	High (except senile when normal)	Low normal or high	Low
II. Osteomalacia and Rickets						
1) Diet or absorption defect	Down	Normal or low	Normal or low	High	Low	Normal
2) Kidney defect	Down	Low	High (glomerular) or low (tubular)	High or normal	High or normal	Low (glomerular) or normal or increased (tubular)
III. Osteitis Fibrosa Cystica	Down	High	Low	High	High	High
IV. Osteosclerosis (hypothyroidism)	Up	Low	High	Normal	Low	—

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# Clinical Considerations in Hypercalcemia

TELAHUN BEKELE, '64

## Significance of Hypercalcemia

Hypercalcemia used to be considered as a rare disturbance in calcium homeostasis, but more recently attention has been directed toward hypercalcemia as a feature of other disease states unrelated to primary parathyroid hyperfunction.

Hypercalcemia has been reported to occur in 25 percent of all patients with breast carcinoma, 30 percent of those with carcinoma of the lung, 40 percent of those with multiple myeloma, 30 percent of those with sarcoidosis and in from 5 to 25 percent of all patients with recurrent renal stones. In addition, diseases such as vitamin D intoxication, milk-alkali syndrome, thyrotoxicosis, adrenal steroid insufficiency and secondary hyperparathyroidism are associated with significant hypercalcemia. Other diseases in which hypercalcemia is recognized are idiopathic hypercalcemia of infancy and immobilization of patients having bone fractures or Paget's disease.

## Pathophysiology of Hypercalcemia

Changes in the normal metabolism of calcium result in hypercalcemia. The intestine, bone and kidney are the principal sites at which disturbances can occur to result in hypercalcemia.

Hypercalcemia secondary to increased intestinal absorption may occur after an increased calcium intake, an increased action or concentration of vitamin D, elevated levels of parathyroid hormone or a decrease in the local inhibitors such as phosphate, phytate and hydrogen ion.

If the excess plasma calcium is not incorporated into bone or if there is excessive destruction of bone due to metastasis or acidosis, hypercalcemia may be produced unless the excess calcium is removed by a

compensatory increase in bone formation or renal excretion.

Finally, if the serum ionized calcium level is such that it exceeds the capacity of the kidneys to remove it, hypercalcemia will result. Failure of normal excretion is secondary to decreased glomerular filtration rate either due to prerenal or renal causes. An additional mechanism of hypercalcemia is a rise in the serum calcium binding capacity without affecting the ionized levels.

## Etiology

Neoplasms are the most common cause of hypercalcemia. The predilection of certain types of cancer, particularly breast, lung, and kidney for invasions of the bones has long been recognized. Eight to nine percent of patients with other cancers which have spread to bone show hypercalcemia. Moreover, hypercalcemia may occur in association with neoplastic disease despite the absence of demonstrable metastasis in bone. It has been reported to occur in association with cancer of the stomach, cervix, uterus, urinary bladder, ovary and testicles. Hypercalcemia in breast cancer as well as other malignancies is twice as common in patients under treatment with estrogens or androgens.

Metastatic osteolysis or infiltration of bone by primary lymphomatous and leukemic disorders often produces excessive skeletal destruction. This leads to increased hypercalciuria, and hypercalcemia begins when the urine reaches a critical load of 500 mg. per day. If nausea, vomiting and decreased food and water intake cause a dehydration, the resultant fall in the glomerular filtration rate depresses the kidneys' ability to excrete calcium. Hypercalcemia will then occur at a lower rate of osteolysis.

In the absence of demonstrable metastasis, it has been postulated that the tumor



## —Hypercalcemia—

produces a parathyroid-like substance, a vitamin D-like substance or a parathyroid hormone-stimulating-substance to account for the associated hypercalcemia.

In hyperparathyroidism, an excess of the hormone acts on the intestine, kidney and bone to produce an elevated serum calcium level. In sarcoidosis an increased sensitivity to vitamin D or the presence of a vitamin D-like substance has been postulated. An excess of vitamin D causes bone destruction. Multiple myeloma causes hypercalcemia presumably by the rapid release into the blood stream of large quantities of calcium salts. Bone destruction is the cause for the hypercalcemia in patients with hyperthyroidism or those acutely immobilized by Paget's disease, poliomyelitis or body casts. The etiology of hypercalcemia in the milk-alkali syndrome is obscure but it appears to be a combination of increased calcium intake and mild renal failure. In idiopathic hypercalcemia of infancy, it is established that such infants absorb too much calcium and have high serum levels of vitamin D-like activity.

### Clinical Manifestations

As was first observed by Collip in his pioneer experiments the clinical manifestations of hypercalcemia may be limited to the gastrointestinal tract, the genitourinary tract, the skeletal system or the neurologic system.

A mild loss of appetite and anorexia may appear early, as gastrointestinal disturbances. Further increase in the serum calcium may be followed by nausea, vomiting, and constipation. Dry mouth leading to excessive thirst and then to polyuria is often an early distressful symptom.

Muscle weakness and fatigue are often presenting symptoms of hypercalcemia and may later be associated with generalized hypotonia and decreased or absent superficial and deep reflexes.

Involvement of the neurologic system may manifest as drowsiness, lethargy, stupor, disorientation, confusion, memory defects,

personality changes, speech defects and psychosis. These defects may progress to coma and death.

Calcific depositions in the eye, kidney or peripheral arteries may often alert the physician to unrecognized hypercalcemia. In the absence of previous local eye disease, band keratopathy and conjunctival calcification are physical signs which are specific for hypercalcemia. The calcification usually begins on the nasal or lateral aspect of the cornea and is characteristically separated from the corneal margin by a clear zone.

### Differential Diagnosis

Accurate differentiation is mandatory if unnecessary parathyroidectomies are to be avoided and rational treatment is to be instituted both for the etiologic disease and for the hypercalcemic state.

When a neoplasm or blood dyscrasia exists, the history, physical examination and the usual clinical studies may provide sufficient evidence for precise diagnosis. Vitamin D intoxication must always be considered particularly in hypercalcemic children in whom relatively small doses may be toxic. Moreover, in adults use of large amounts of vitamin D as therapy for arthritis or for other reasons may induce extreme hypercalcemia.

In patients with hypercalcemia of no obvious cause, the diagnosis of hyperparathyroidism must be seriously considered. When the following findings occur concomitantly in a patient they are almost diagnostic of hyperparathyroidism: (a) a history of recurrent renal stones, (b) the careful repeated demonstration of hypercalcemia, (c) the presence of hypophosphatemia of less than 3 mg. percent and (d) an associate occurrence of peptic ulcer or pancreatitis. If there is no other obvious cause, these findings should lead to a neck exploration for removal of a parathyroid adenoma.

It should be noted that although certain special adjunctive tests, such as the intravenous calcium tolerance test, tubular re-



absorption of phosphate and the response to steroid are well recognized, their aid in the differential diagnosis of hypercalcemia is very much limited.

Few additional blood analyses are helpful in the differential diagnosis of hypercalcemic states. Hyperglobulinemia is unusual in patients with hyperparathyroidism and its presence most often indicates a malady such as sarcoidosis or multiple myeloma. The alkaline phosphatase activity in the serum may be increased in a variety of disorders but high values are seldom present in patients with hyperparathyroidism unless they have radiologically demonstrable osteitis fibrosa. Determination of the carbon dioxide combining power may also be useful, for this is frequently normal or low in patients with hyperparathyroidism whereas in those with hypercalcemia of other etiology it is often high. An increased urinary calcium is rarely encountered in the milk-alkali syndrome, but may occur in vitamin D intoxication before any evidence of clinical hypercalcemia. Needless to say, the serum calcium level is of little value in differentiating hypercalcemic states.

Roentgenographic changes which are helpful in the diagnosis of hypercalcemia are nephrocalcinosis, arterial calcifications, metastatic lesions in bone, absent lamina dura and subperiosteal erosions. Except for the latter two, which are often diagnostic of hyperparathyroidism, the rest are of little help in differentiating hypercalcemic conditions.

Occasionally examination of the bone marrow has been most helpful in revealing the underlying disease in patients with multiple myeloma or leukemia. In patients having hypercalcemia in association with lymphomas biopsy of apparently "innocent" lymph nodes has also been rewarding.

#### Management of Hypercalcemia

As a supplement to the general discussion of hypercalcemia a brief comment on the management of hypercalcemia will be invaluable. The first step is to treat the

specific cause. The second is to decrease the calcium intake by either lowering the calcium intake or administering adrenal steroids or sodium phytate. The third is to promote increased urinary loss of calcium by hydration and solute diuresis. The last step is to reduce the plasma ionized calcium level by using EDTA or sodium citrate.

Finally, if the patient does not have renal stones, an elevated alkaline phosphatase level or demonstrable X-ray lesions, his mild hypercalcemia can be best handled by continued observation until the diagnosis is proved by further events.

#### Summary

Attention has been directed to the significance of hypercalcemia as a clinical entity. The pathophysiology and the clinical manifestations of hypercalcemia have been presented. The discussion has also included a survey of the various causes of hypercalcemia with a few comments on the differential diagnosis.

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## News and Views

On Tuesday, October 28, 1963, the third year medical class at U.W.O. had the privilege of hearing Dr. W. J. McGanity, Professor of Obstetrics and Gynecology at the University of Texas, deliver a lecture, summarizing his studies into the nutritional needs of pregnant women. Professor McGanity was visiting the Department of Obstetrics at the Annual "Refresher Course" given by the Department.

In his remarks, Professor McGanity made a number of comments which were of a most practical and worthwhile nature. Initially he made the point that in Canada and the United States the safety margin in the recommended food allowance is so great that for the average pregnant woman there must be a reduction in food intake to 60% of the allowance before there are any biochemical signs of dietary need and there must be a reduction in intake to 40% of the allowance before there are any clinical signs of dietary inadequacy. As we are all aware, the satisfactory food intake in North America does not hold true in many other regions of the world. Nor does the high calorie intake in North America mean that there is not a relative deficiency in certain vital nutrients.

Contrary to popular belief, Professor McGanity pointed out that the maternal food intake during pregnancy has no bearing on the ultimate weight of the child. The only weight relationship between mother and child that his group have ascertained in their studies is a linear relationship between the birth weight of the infant and the postpartum weight of

the mother as a percentage of "standard weight". Thus one would expect to find (for example), an increased incidence of prematurity in underweight mothers.

All women are vulnerable to an iron deficiency anemia as a result of blood loss during menstruation and at delivery. Professor McGanity felt that most obstetricians tend to under-estimate the total blood lost during delivery. He felt that during a normal delivery the loss is at least 500 cc. (250 cc. of blood lost externally and 250 cc. further loss as a result of blood trapped in the placenta). With cesarian section a minimum figure would be 1000 cc. The significance of this in regards maternal care is that Hb. determination is every bit as important at the six week check-up after delivery as in the pre-natal period, and that the best indication for iron supplement is in repeated pregnancy or in excessive blood loss during menstruation and at delivery.

Gary Ferguson, '65

The first Wallace Graham Memorial Lecture was presented on November 13, at the University of Western Ontario Medical School by Dr. Evan Calkins. This distinguished teacher and scientist, Professor of Medicine at the University of New York (Buffalo), chose as his subject, "Amyloidosis—A Continuing Puzzle".

Amyloid is a homogeneous, waxy and translucent glycoprotein which in routine tissue stains appears as an intercellular eosinophilic substance much like hyaline



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collagenous connective tissue. Laboratory findings have shown that there is also an abnormality of the gamma globulin in the disease entity.

Dr. Calkins stated that amyloidosis is often found in association with rheumatoid arthritis, multiple myeloma and tuberculosis. It is frequently seen as an important cause of death in paraplegia and in leprosy. The relationship of these findings he explained, is not fully understood at present.

Opposed to the rigidity of classifying the disease entity into several components, Dr. Calkins prefers to use two general categories. "Typical" amyloidosis is found principally in the ground substance, that is, in the blood vessel walls of such parenchymatous organs as the liver, spleen, kidney, adrenals, pancreas and lymph nodes. Such cases are secondary to other disease processes. "Atypical" amyloidosis includes the rarer primary cases not dependent on any predisposing disease. The lesion may present as a tumor-like or diffuse involvement of such mesenchymatous structures as heart and blood vessels, skeletal muscle, kidneys, intestines, skin, tongue and larynx.

A familial type of 'atypical' amyloidosis is found among Mediterranean people of Portuguese descent and among some peoples descended from the Jewish Phoenician slaves.

Amyloidosis is diagnosed by using intravenous injections of recrystallized congo red in distilled water. If amyloid is present, the congo red will leave the serum in about ten minutes. One usually gets a positive in 60% of typical cases, but only 5% of 'atypical' cases. Dr. Calkin's group has however increased the accuracy of diagnosis of the former to 80% by adding a gingival biopsy. Rectal and kidney biopsies yield positive diagnoses in 70% and 89% respectively.

Dr. Calkins and his group had shown that repeated immunological phenomena can cause a precipitate of the antigen-

antibody complex as evidenced by the discovery of gamma globulin in amyloid deposits. Further, they have successfully produced the above phenomena by the injection of casein. A new outcome of their work has been the discovery of refractile fibers in the amyloid deposits which are not seen elsewhere. No specific treatment exists. Corticosteroids have been of only limited value in its treatment.

Dr. Calkins concluded his discussion with a summary that included some of the following possible etiologic factors in amyloidosis: heredity, age (incidence increases in the elderly), inflammatory diseases, diet, drugs (steroids) and radiation. This was a thorough and lucid discussion which demonstrated that amyloidosis is indeed a continuing puzzle.

Fred Nash, '65

#### THE 18TH ANNUAL JOHN A. MACGREGOR MEMORIAL LECTURE

This year the 18th Annual John A. Macgregor Memorial Lecture was presented in the Medical School Auditorium on November 20, 1963 by Dr. Stanley L. Robbins, Professor of Pathology at Boston University School of Medicine and Assistant Director of the Mallory Institute of Pathology in Boston. The subject of Dr. Robbins paper was "A Hard Look at Coronary Artery Disease". Dr. Robbins was educated at the Massachusetts Institute of Technology where he received his Bachelor of Science degree and Tuft University where he received his M.D. Dr. Robbins has carried out extensive original research in Pathology; his special interests being diabetes, cardiovascular disease, and the nucleoproteins of malignancy. His "Textbook of Pathology" has been widely acclaimed and greatly cherished by many students of medicine.



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In his address Dr. Robbins described the results of research which he and his colleagues have been conducting on an extensive series of post-mortem hearts. His group has been particularly interested in a specialized but remarkably simple angiographic study of the coronary vessels and the relationship of their findings to coronary occlusive disease. A permanent two-dimensional picture of the state of the arteries may be obtained on an x-ray film. The findings of injection can then be compared with the findings of post-mortem examination of these hearts. It was found that about 50% of occlusions visible on x-ray study were not discernible on gross examination at post-mortem, a most curious finding indeed.

Dr. Robbins has been most interested in discerning whether or not with an infarct the smaller radicles of the coronary vessels become occluded. Such knowledge is of great interest to cardio-vascular surgeons who are now exploring the feasibility of coronary endarterectomy as a possible surgical treatment for occlusive heart disease. His studies have shown that occlusion is limited to the main stem coronary vessels, that the radicles are not involved and that contrary to popular opinion the coronary arteries are not end arteries but are richly anastomosed. He showed a number of excellent slides

of his x-ray films which demonstrated most clearly an anastomotic network between the main coronary arteries. The curious and puzzling problem is however, that though these anastomoses exist they appear to have little role in protecting the victim of coronary thrombosis against an infarct.

The series of hearts used in these studies to date number over 500, the average age being 68 years. For the total series 23% demonstrated occlusions, 20% severe coronary vascular disease, 39% lesser degrees of coronary vascular disease, and 18% no disease at all. The group with no disease at all represented a proportionate age distribution to those with occlusion and Dr. Robbins felt that this group represents a group which have been little studied and might yield much useful and valuable information.

Dr. Robbins expressed a most significant conviction when he stated that he did not believe arteriosclerotic coronary disease was a natural process of aging which accumulated like dust, but rather it is a definite disease process which some get when they are young and others when they are old. The reason for this is one of the great mysteries of medicine.

Gary Ferguson, '65



# Physiology of the Thymus

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The thymus has been an organ of mystery for centuries and until recently no better definition of its function was available than that of Galen who stated that it acted as a cushion between the sternum and the great vessels. The recent intense interest in organ transplantation and in the problem of homograft rejection has stimulated renewed interest in thymic physiology.<sup>1,2,3</sup> A simplified review of some of the newer concepts of the role of the thymus gland in the immunological defense mechanisms of the body is therefore in order.

The embryological origin of the thymus is the epithelium of the third branchial pouch, from which site paired anlage descend through the neck to the anterior mediastinum. This route explains the presence of ectopic thymic tissue and thymic cysts in the cervical region. The cysts are identified as thymic in origin by the presence of Hassall's corpuscles in their walls. The relative size of the thymus is greatest at birth, while the absolute size is maximum just before puberty. The gland then atrophies with advancing age.

Microscopic examination of the thymus reveals a cortex consisting of lymphoid follicles, which under normal conditions do not have germinal centers. The medulla of the gland consists of loose reticular tissue through which are scattered Hassall's corpuscles. The function of these corpuscles has been a source of speculation for many years and investigators have searched in vain for evidence of an endocrine secretion. Anatomists have pointed out that Hassall's corpuscles are found around degenerating vessels and nerves and it is believed that the cells are derived from the reticular cells of the medulla, representing possibly de-

generating cells that failed to give rise to a line of lymphocytes. Atrophy of the thymus with age involves mainly the cortex so that the lymphoid follicles gradually disappear, but Hassall's corpuscles can be identified at all ages.

Until the last few years, medical interest in the thymus during this century has centered upon the conditions of status thymicolymphaticus and myasthenia gravis. An enlarged thymus gland has been found in infants who die suddenly without an explainable cause, the so-called status thymicolymphaticus. This apparent hypertrophy may, however, merely represent a normal thymus gland, for in chronic illness the thymus shrinks greatly, so that a child who dies after a prolonged illness has a gland that is much smaller than that in one who dies suddenly. The relationship between the thymus and myasthenia gravis is somewhat unpredictable in that gland may be of normal size or a thymoma may be present. Similarly, surgical removal of the thymus in cases of myasthenia is at times accompanied by a spectacular cure of the condition, and at other times effects no change in the course of the disease.

Ordinarily the function of an organ is studied by its removal, observation of the deficiency state produced, and replacement therapy. The experimental investigation of thymic function was hampered by the fact that thymectomy in adult animals apparently caused no deficiency state and extracts of the gland failed to produce demonstrable changes in the experimental subject. However, certain relations between the thymus and other endocrine organs have been established. Hyperthyroidism is associated with enlargement of the thymus, which is believed to be related to inactivation of the thyroid stimulating hormone of the pituitary by the thymus. In states of adrenal cortical hyperplasia and with corticosteroid therapy the thymus atrophies be-



cause of the lympholytic effect of the adrenal hormones, a response that is utilized when cardiomegaly cannot be differentiated from an enlarged thymic shadow in the chest x-ray of an infant: administration of a corticosteroid for a few days causes atrophy of the thymus and reveals the true size of the heart. The thymus gland is enlarged in the presence of adrenal cortical insufficiency, a relationship that has been considered significant in the problem of status thymicolymphaticus. Testosterone and estrogens are mildly thymolytic. Prefrontal lobectomy in animals leads to enlargement of the thymus and the lymphoid tissues and there is one report of a human who shot himself in the head necessitating a surgical prefrontal lobectomy: when this individual died of other causes several months later the thymus was greatly enlarged.

Recent interest in the homograft rejection phenomenon and the role of lymphoid tissues in immune defense mechanisms once again directed attention to thymic function. In the experimental animal thymectomy in the neonatal period, that is between birth and the third day, resulted in an absence of the animal's immune response. Depression of the response to viral and bacterial stimuli and to allogeneic and heterogeneic skin grafts occurred. Homografts were accepted, lymphopenia developed, and the number of lymphocytes in the spleen and lymph nodes was greatly decreased. The animal died of a wasting illness like "runt disease". In the neonatal chicken, removal of the bursa of Fabricius, an organ similar in structure to the thymus but located posterior to the rectum, impaired the animal's antibody production.

Thus, removal of the thymus gland in the neonatal period resulted in failure of development of the immune defense mechanisms. Subsequently, attempts were made to restore the animal to normal. Neither saline extracts from the thymus nor cells from the neonatal gland were effective, but a thymus graft implanted in the first week restored the immune mechanisms. If

the donor and the host were of the same strain, skin grafts from all other strains were rejected; but if the donor and host were of different strains, skin grafts from both of these strains were accepted while those from other strains were still rejected. Injection of lymphocytes from normal adults also restored immunity to an animal that had undergone neonatal thymectomy if administered within the first week. After about one week neither a thymic graft nor injection of adult lymphocytes restored immunity.

Thymectomy in the adult experimental animal does not greatly affect its immune response. If at least three weeks elapse from birth to thymectomy, only a temporary lymphopenia and a decrease in the weight of the spleen and lymph nodes result. Homografts are rejected and antibody levels are normal or slightly decreased. Even at this stage, however, the thymus has some function in immunity. If a sublethal dose of total body radiation is administered to an adult experimental animal, the immune response is temporarily depressed and then recovers completely. If the animal has undergone a prior thymectomy, recovery from sublethal radiation is slower and the degree of immunity finally achieved is frequently less than normal.

Another relationship between the thymus and immunity in the adult is found in investigations of the AKR strain of mice. This strain is very prone to develop leukemia that begins in the thymus gland, 50 percent of the animals dying within one year and 85 to 95 per cent of all animals succumbing to the disease. Not only does thymectomy before six weeks of age result in a greatly reduced incidence of leukemia, but a subsequent thymic graft restores the incidence of leukemia to its previous high level. Thymectomy after the development of leukemia, however, has no effect on the disease. Similarly, thymectomy reduces the incidence of radiation-induced lymphomas



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in mice, while thymic grafting restores the potentiality for the development of lymphoma.

From this experimental evidence it is clear that the presence of the thymus in the neonatal period is essential for development of the immune mechanisms of the animal and for population of the lymphoid tissues with cells. However, the method by which this is accomplished is unknown. Does the thymus have a humoral influence on the development of lymphoid tissue? Does the thymus produce the progenitors of adult lymphocytes? Or, does the thymus merely provide an environment that is suitable for the development of the immune capabilities of lymphoid cells? Evidence that sheds some light on these questions will now be considered.

After neonatal thymectomy and thymic implantation within the first week, development of lymphoid tissues proceeds at a normal pace. Are the lymphoid tissues recolonized from cells of thymic origin, or do the lymphocytes arise from the host with the assistance or stimulation of the grafted thymus? This question has been partially answered by experiments involving the T6 strain of mice. A group of T6 mice, which have an easily identifiable marker chromosome at the metaphase of cell division, underwent neonatal thymectomy followed by thymic grafts within one week from another strain of mice that did not have this marker chromosome. It was found that 80 to 100 per cent of the cells in the thymus and lymphoid tissues originated in the host and thus that the host cells were responsible for the subsequent immunological reactivity of the animal.

It appears, therefore, that cells of immunological potential remain in the animal that has undergone neonatal thymectomy, but this potential cannot be expressed in the absence of the thymus. That these cells probably reside in the marrow is demonstrated by the following experiment. Total

body radiation was given in a lethal dose to destroy completely the blood cell production in the marrow of experimental animals. An intravenous injection of bone marrow resulted in repopulation of the marrow with red blood cells, neutrophils, and platelets, as well as reappearance of lymphocytes in the blood stream and nodes. However, if a prior thymectomy had been performed, the red blood cells, neutrophils, and platelets reappeared after marrow injection but the lymphocytes did not return.

The conclusion drawn from these experiments is that, after neonatal thymectomy and subsequent thymic graft, host cells (stem cells) invade the thymus and find an environment that is suitable for lymphoid differentiation and multiplication so that full immunological competence is eventually regained. Another hypothesis that cannot be completely excluded is that the thymus produces a Lymphopoiesis Producing Factor that stimulates lymphocytic growth, as has been suggested by Metcalf. However, neither homogenates of the thymus nor extracts of the gland have yet produced any change in the lymphocyte count in normal or thymectomized animals.

At this point it is necessary to review some of the theories of antibody production. The Instructive theory postulates that the antigen acts as an instructor or template on which the antibody is formed and that all antibody production is acquired after birth on the basis of exposure to the antibody. The tissues of the individual himself have certain characteristics or self-makers that distinguish them from foreign tissues, and antibody production against "self" is forbidden. The other hypothesis is the Selective theory popularized by Burnet, in which the antibody capabilities are considered to be a genetic endowment. The stem cells give rise to clones or families of cells capable of forming antibodies. At birth, clones are present that are capable of forming specific antibodies against all conceivable antigens and contact with



the antigen in the postnatal period triggers the production of antibodies. It is postulated, however, that contact of an antigen with an immunologically competent cell in the prenatal period causes inhibition of the development of this clone so that all cells capable of forming auto-antibodies are eliminated by contact with "self" antigens in embryological life. These families of cells capable of producing antibodies against "self" are called forbidden clones.

The production of new clones of cells cannot be continued in postnatal life because forbidden clones might be created accidentally. Theoretically, the whole process should take place in some sequestered location where the information is stored and from which it is disseminated throughout the body, after which the central registry is eliminated. At once the parallel between this process and the history of the thymus is evident. The thymus is largest at the period of immunological deficiency early in life, but appears to be isolated from the body in the postnatal period. The lymphoid follicles in the thymus have no germinal centers and thus are not immunologically active in the postnatal period, and both the follicles and the thymus itself atrophy with age. Although the thymus is rich in lymphoid cells and fails to produce antibody after systemic antigenic stimulation, direct injection of antigens into the thymus produces histological changes in the lymphoid follicles that are usually associated with the process of antibody formation, that is, the development of germinal centers. Thus, in the postnatal period it appears that the thymus is isolated from the rest of the body and that a blood-thymic barrier exists. In this manner, perhaps, the development and propagation of forbidden clones is prevented unless some breakdown of the barrier occurs.

Disturbances in the thymus gland have been associated with several diseases. A few cases of thymoma with acquired agammaglobulinemia have been reported and an atrophic thymus has been found in cases of

congenital agammaglobulinemia. Congenital lymphocytosis in infants is characterized by emaciation, repeated infections, underdevelopment of the spleen and lymph nodes, absence of gamma globulin, and an atrophic thymus gland. The relationship between the thymus and leukemia in mice has been discussed and Metcalf has tried to incriminate his Lymphopoiesis Producing Factor in human cases of leukemia. Certainly, it appears that an increased incidence of leukemia in later life may follow radiation of the thymus gland in infancy. Occasionally thrombocytopenia or granulocytopenia has been observed in an individual with an atrophic thymus. Auto-immune hemolytic anemia of an acquired type, several cases of which have been reported in humans, occurs spontaneously in a certain strain of mice. At three to 12 months of age, mice of this strain develop hemolytic anemia with a positive Coombs' test, and the disturbance can be transmitted by the injection of spleen cells. The thymus shows germinal centers and plasma cells, that is, there is evidence of antibody production in the thymus, and thymectomy prevents the development of the hemolytic state.

With all this evidence that the thymus is intimately involved in the immune response of the body, the relation between the thymus and another mysterious disease, myasthenia gravis, becomes even more fascinating. It is now believed that myasthenia is caused either by a deficiency of acetylcholine production or by a diminished sensitivity of the motor end-plate to acetylcholine. With the evidence at hand both an increased rate of destruction of acetylcholine and a circulating curare-like substance are unlikely. The end-plates in myasthenic muscle have less than normal sensitivity to acetylcholine and to the depolarizing block of decamethonium. It is believed by some that the choline released by breakdown of acetylcholine causes a continuing end-plate block of a competitive type, and, in this same theme, intra-arterial injection of choline, which has no effect in



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normal individuals, produces a neuromuscular block in patients with myasthenia. Of course, such a mechanism would also explain the cholinergic crisis in patients with myasthenia caused by therapeutic overdosage with prostigmin and related compounds.

It is known that the thymus is not the source of the myasthenic substance because thymectomy in a mother prior to pregnancy may still be associated with neonatal myasthenia in the baby. Pregnancy itself has an unpredictable effect on myasthenia, each pregnancy in any one individual having its own effect. The delivery and the labor itself are usually well-tolerated, and precautionary measures are usually directed towards the transient neonatal myasthenia in the infant.

Some unusual forms of therapy in myasthenia have been based upon the effect of adrenal steroids on the thymus. Not only have cortisone and ACTH been reported by European investigators to produce an improvement in myasthenia, but carotid sinus denervation, which they claim results in adrenal cortical hyperplasia, has been carried out by the French in myasthenia and is reported to have a favorable effect in 60 per cent of the cases.

The pathological changes in myasthenia are found in the muscles and the thymus. The muscular abnormalities consist of focal areas of decreased density of the end-plate sarcolemma within the secondary synaptic clefts, abnormal branching of the motor nerve terminals, and occasionally acute coagulation necrosis of the muscle. Of particular interest are accumulations of lymphocytes, or lymphorrhages, particularly in the perivascular areas of the muscles. A thymoma is found in about 15 per cent of the cases, but even more striking is the high incidence of germinal centers within the lymphoid follicles of apparently normal thymus glands.

The evidence for an immunological abnormality in myasthenia gravis is strong.

First, signs of an inflammatory process frequently occur, such as an increased sedimentation rate and low grade fever. Also, it has been found that the 7S gamma globulin is bound to the skeletal muscle in myasthenia gravis and furthermore, this binding is associated with fixation of complement, an indication of an immunological antigen-antibody reaction. Finally, if gamma globulin from a myasthenic patient is injected into a normal individual it becomes bound to normal skeletal muscle.

There is evidence, therefore, that the thymic lesions in myasthenia may represent an immune response to an antigen, and that the disturbance in myasthenia is an immunological rather than a chemical or humoral one. Thus, myasthenia may be an auto-immune disorder in which the thymus reacts to a protein derived from the end-plate of the skeletal muscle. On the other hand, it is also possible that under the protection of the normal blood-thymus barrier a forbidden clone has arisen spontaneously within the thymus and on escaping from the gland has produced auto-antibodies to skeletal muscle.

## SUMMARY

Although the thymus has guarded its secrets for centuries, it happens that some information regarding its function is available at last. At least in the experimental animal, a functioning thymus gland in the neonatal period is necessary for the development of the immune defense mechanisms of the body. Even in the adult the thymus plays a permissive role in the discovery of the defense mechanisms after injury. Atrophy of the thymus has been found in agammaglobulinemia, in lymphocytosis, and in acquired hemolytic anemia. Some abnormality of the thymus gland is usually present in cases of myasthenia gravis, and there is evidence that the disease is primarily an immunological disturbance. Perhaps just as the pituitary and hypothalamus are the master centers



for the control of endocrine function, the thymus may be the master gland concerned with the control of the immune response.

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## Endocrine Diseases And The Eye

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The human eye is of the greatest importance to both patient and physician alike. For the patient the eye has no equal as a peripheral organ of sensation; for the physician it represents a sensitive index of many systemic disease processes. In this article a classification of the more important systemic diseases is given and the ocular manifestations of the endocrine diseases are discussed in detail.

### CLASSIFICATION

#### I. Vascular Diseases

1. Arteriosclerosis
2. Hypertension
  - a—Renal retinopathy
  - b—Toxic retinopathy of pregnancy
3. Subacute bacterial endocarditis

#### II. Blood Dyscrasias

1. Pernicious anemia
2. Thrombocytopenic purpura
3. Leukemia

#### III. Endocrine Diseases

1. Pancreas
  - a—Diabetes mellitus
2. Thyroid gland
  - a—Hyperthyroidism
  - b—Hypothyroidism
3. Parathyroid gland

- a—Hyperparathyroidism
  - b—Hypoparathyroidism
4. Pituitary gland
    - a—Basophil tumor
    - b—Acidophil tumor
    - c—Chromophobe tumor
  5. Adrenal gland
    - a—Adrenal cortex
      - Addison's disease
      - Tumors
    - b—Adrenal medulla
      - Pheochromocytoma
      - Neuroblastoma
  6. Thymus gland
    - Myasthenia gravis

#### IV. Dietary Deficiency

Avitaminosis A, B<sub>1</sub>, or C.

#### V. Chronic Granulomatous Diseases

1. Tuberculosis
2. Sarcoidosis
3. Brucellosis
4. Syphilis
5. Toxoplasmosis

#### VI. Systemic Viral Diseases

1. Herpes simplex
2. Herpes zoster
3. Poliomyelitis
4. Rubella
5. Rubella



## VII. Collagen Diseases

1. Disseminated lupus erythematosus
2. Periarteritis nodosa
3. Rheumatoid arthritis

## VIII. Phakomatoses

1. Neurofibromatosis
2. Tuberosus sclerosis
2. Angiomatosis retinae
4. von Hippel-Lindau disease
5. Sturge-Weber-Dimitri disease

## PANCREAS:

### Ocular manifestations of Diabetes Mellitus

#### 1. Retinal changes:

These represent the largest group of the ocular manifestations of diabetes mellitus. The commonest of these is *diabetic retinopathy*, which is present in approximately 45 per cent of diabetics. Although the incidence is higher among older people, only the length of time the disease has been present determines the presence and severity of diabetic retinopathy.

The retinal changes in diabetic retinopathy consist of:

- a - *Hemorrhages*. These are located in the posterior part of the fundus, usually between the upper and lower temporal branches of the retinal vessels. Frequently they are close to the macula and may involve it.

The *earliest hemorrhages* are few, scattered, discrete small punctate spots, globular in shape and a dark red in color.

Outside the macular region the hemorrhages are tiny pinhead-sized and have been shown to rise from *aneurysmal dilatations* of the venous end of the capillaries situated in the deeper retinal layers.

In *later stages* the hemorrhages are larger in size but of a similar dark red color and are now frequently accompanied by *arteriolar hyalinization and obliteration* leading to total atrophy of the neighbouring capillary bed.

*Large subhyaloid and pre-retinal hemorrhages, neovascularization, vitreous hemorrhages and retinitis proliferans* occur at the later stages of a steadily increasing retinopathy. When either subhyaloid or vitreous hemorrhages occur early and alone they often clear up completely. However, when present together, it is a sign of poor prognosis, especially if accompanied by neovascularization protruding from the surface of the retina. Organization of the blood clot results in the formation of thick fibrous tissue causing destructive changes such as localized *separation (detachment) of the retina and diabetic glaucoma*. This process is known as *retinitis proliferans* and frequently results in blindness. The newly formed blood vessels, together with the dilated pre-existing venules, often protrude forward into the vitreous. Because they lie anteriorly to the retina their appearance is somewhat like that of retinal separation and this may lead to an incorrect diagnosis. Minor *vitreous opacities* are often present as well.

- b - *Exudates*. These are also characteristically seen in the central posterior part of the fundus. At first they are small white specks clustered in small groups but later they increase in size and coalesce to form larger white patches with a very irregular outline. They are sometimes found in the macular region in a pattern much like *retinitis circinata*.

With increasing size their color changes to a yellowish white and still later they become waxy in appearance.

- c - *Changes in retinal veins*. The earliest changes consist of *overdistension and fusiform enlargement* resulting in a sausage-like appearance for a length of about a disc diameter. At these places the veins appear darker than normal. The swelling are localized and are limited to the central part of the fundus. Later the distended portion may become *tortuous and varicose* and weird *looping for-*



mations result in and on the retina from the joining up of new blood vessels and distended pre-existing venules. Neovascularization arises from the venous distensions. Vitreous hemorrhages may result from the dilatations. In young adults the changes in the veins may be the first signs of diabetic retinopathy with none of the more usual type of diabetic retinopathy changes being present.

These venous changes differ from thrombosis of a main vein in that they are localized, do not extend out to the periphery, and do not involve the veins close to the disc.

- d - *Cholesterol crystals* are occasionally seen as glistening white spots at the sites of old hemorrhages.
- e - *Pigmentary changes* are rarely seen in diabetic retinopathy and are of minor importance.

The features of diabetic retinopathy as just described often persist for a long time without much change in appearance but occasionally sudden gross hemorrhages occur, rapidly followed by the development of retinitis proliferans with its disastrous effect on vision.

Diabetic retinopathy appears to be due to the *fatty infiltration of the endothelium of capillaries, pre-capillaries and venules* resulting in a weakening of their walls. Also fatty deposits are found immediately outside these vessels.

## 2. Lenticular changes:

Lenticular changes are the second most common ocular manifestations of diabetes mellitus.

- a - *Diabetic cataract*. These are the lens changes that occur in *juvenile diabetics*. It is not common, is usually bilateral and progressive, and often comes on unexpectedly. The younger the patient the faster it develops. It starts with flocculent, snowflake, milk-white, cortical opacities, immediately under the lens capsules, usually posteriorly. As

the process continues more cortex is involved and diffuse grey mistiness occurs, the white opacities coalesce and a grey-white appearing lens results. These changes are irreversible.

- b - *Other Lenticular changes*. These occur in *middle aged and elderly diabetics*, and consist of posterior subcapsular opacities. They are centrally located and are saucer-like in appearance. Because of their location they have serious effects on vision even when they are slight. They differ from senile and secondary cataracts in that they have a rounded defined edge and are denser in the center. *Milk-white floccules* in the cortex are sometimes seen also. They consist of subcapsular vacuoles with iridescent points and rod-like opacities when seen against the fundus reflex. Rarely a *rosette type opacity* has been observed. It clears up completely when adequate treatment of the diabetes is started.

## 3. Iris changes:

- a - *Non-inflammatory reactions* are common in diabetes and consist of:

- (i) *Rubeosis iridis* is seen especially in *juvenile diabetics*. The condition consists of numerous small interwoven blood vessels on the iris near the pupillary margin, tufts of blood vessels on the iris near the periphery, and a peculiar profuse formation of new blood vessels at the extreme periphery. Using gonioscopy they can be seen to spread from the root of the iris over the angle to form peripheral vascular synechiae. The newly formed blood vessels are very fragile and their rupture leads to hyphema. Diabetic glaucoma is a frequent sequela.

- (ii) *Edema of the iris*. This may be followed by *glycogenous degeneration and depigmentation*. Clinically the appearance is that of a ring of increased pigmentation around the pupillary margin. Rarely unpigmented degenerated areas can be seen elsewhere in the iris.

- (iii) *A sluggish or absent pupillary response* is sometimes found and is due to



*glycogenous infiltration* of the sphincter and dilator muscles of the iris.

- b - *Inflammatory reactions* of the iris due to diabetes are not common. When present they are characterized by a very marked circumcorneal injection, chemosis, and in the early stages an albuminous exudate fills the pupil. The latter disappears quickly when the diabetes is treated. Also very numerous blood vessels are present on the iris, especially near its pupillary margin, and heavily pigmented posterior synechiae may result. The symptoms associated with diabetic iritis are slight.

#### 4. Pressure changes:

- a - *Due to the dehydration*, which occurs with diabetic coma, the volume of the vitreous gel decreases. Clinically this results in an eyeball which is extremely soft. The soft eyeball is an important diagnostic sign in diabetic coma.

- b - *Secondary glaucoma* nearly always follows rubeosis iridis.

#### 5. Eyelids.

There is an increased incidence of *xanthelasma* in diabetes mellitus. These are non-neoplastic flat or slightly raised yellow streaks and patches occurring beneath the skin. Most commonly they are found at the inner end of the upper eyelid. They appear to be related to a high blood cholesterol level and they are found in conditions other than diabetes mellitus.

#### 6. Transitory visual disturbances:

- a - *Changes in refraction.*

During onset or relapse of the disease *myopia* of 2 or 3D or more may occur. It usually disappears when the disease is treated. During treatment of diabetes *hypermetropia* commonly occurs. It usually lasts from 10 days to 3 weeks and then passes off gradually.

- b - *Changes in accommodation:*

*Weakness of accommodation* may be

present also, but it too passes off readily with treatment of the disease.

- c - *Other transitory changes:*

*Subjective changes* due to hypoglycaemia as caused by excessive insulin are general mistiness, diplopia, inability to focus when reading, photopsiae, micropsia or macropsia, strange luminosities, and central scotoma. These subjective changes appear to be due to hypoglycaemia of the brain and they are relieved in 10 to 15 minutes when sugar is taken.

#### 7. Rare ocular manifestations:

- a - *Lipemia retinalis.*

In diabetes mellitus the serum-lipids may increase greatly. When their concentration is 5 mg. per cent retinal lipemia may result, especially in young people. The entire fundus is of a pale pink color and the retinal vessels are distended and are still paler than the fundus background. The disc is normal in color and vision is not affected. These cases are usually accompanied by diabetic acidosis and are in danger of coma. The condition clears up in a matter of days when carbohydrates and insulin are given.

- b - *Optic neuritis.*

Diabetic optic neuritis may occur in all ages and is usually bilateral. It is characterized by a rapid painless onset of a central or pericentral scotoma with well defined edges. The scotoma is usually absolute but may be for blue only. It clears up rapidly when the diabetes is treated. Diabetics also are more susceptible to alcohol and tobacco amblyopia.

- c - *Ocular motor effects.*

A rare complication of diabetes mellitus is paralysis of the oculomotor nerve trunks. The older age group is more commonly affected. The onset is rapid and unilateral but frequently becomes bilateral if the diabetes is not



treated. Rarely the resulting diplopia is the earliest symptom caused by the presence of diabetes mellitus. The majority recover with treatment of the diabetes.

## THYROID GLAND:

### Hyperactivity (Thyrotoxicosis; Graves' Disease)

#### 1. Lid retraction—Dalrymple's Sign.

Normally the upper lid is 1 to 3 mm. below the limbus. When the upper lid is at or above the limbus 'lid retraction' is said to be present. Occasionally lid retraction is accompanied by a horizontal fold in the skin of the upper lids when the eyes are lightly closed. When present this fold is located 6 to 10 mm. above the free margin of the lid. It is most obvious in cases of unilateral lid retraction. A rim of sclera below the cornea is not due to lower lid retraction but is caused by exophthalmos. Lid retraction may give a normal eye the appearance of exophthalmos; however, in true exophthalmos a rim of sclera can be seen above and below the cornea.

Lid retraction may be confined to one side but frequently is bilateral. Rarely unilateral lid retraction is accompanied by dilatation of the ipsilateral pupil.

Lid retraction in many cases is the first sign of thyrotoxicosis. Upon treatment it usually improves and may disappear completely, but it may persist and in some cases makes its first appearance indicating an extrathyroid factor in its development.

Besides thyrotoxicosis, lid retraction may also occur in post-encephalitic Parkinsonism, lesions of the upper brain stem, orbital pseudo-tumors, and myasthenia gravis.

Lid retraction is caused by spasm of the levator palpebrae superioris muscle. The spasm may be due to more than

one factor, one from the thyroid gland, and one from the pituitary gland.

#### 2. Exophthalmos.

A forward displacement of the eyeballs in the orbit occurs in 27 per cent of cases of primary thyrotoxicosis. The average forward displacement varies from 2 to 5 mm. It is usually bilateral and axial but it may be unilateral and at times is asymmetrical. Lagophthalmos, or the inability to close the eyes, may be present in severe cases. Bulging and puffiness above the upper lids is a common concomitant feature and may be the presenting sign in thyrotoxicosis or 'exophthalmic ophthalmoplegia', in which case it is known as 'concealed' exophthalmos. The lower eyelid may also bulge and must be differentiated from edematous bulging which pits on pressure.

There are two kinds of exophthalmos, one associated with thyrotoxicosis and the other is thyrotrophic in origin. Thyrotoxic exophthalmos is due to spasm of the smooth muscle of the lids in association with weak and hypotonic extra-ocular muscles. The eyeball can be pushed backwards into the orbit by means of pressure.

Thyrotrophic exophthalmos is a frequent sequel to partial thyroidectomy, but may also be found in hypothyroidism and in tumors of the pituitary gland. Thyrotrophic exophthalmos is thought to be due to an excessive secretion of the thyrotrophic hormone of the anterior pituitary gland, which causes a lymphocytic reaction and fibrosis in the orbital fat, and in the extrinsic ocular muscles. Especially in its advanced stages it is associated with chemosis, and swelling of the eyelids. The eyeball cannot be pushed backwards into the orbit by means of pressure.

#### Differential diagnosis of exophthalmos is:

1. Spontaneous cavernous fistulous aneurysm. This usually unilateral condi-



tion is frequently post-traumatic often pulsates synchronously with the pulse, and has a cephalic bruit over the eye which can be abolished by pressure on the ipsilateral common carotid artery.

2. Orbital tumors and pseudotumors. These are almost always unilateral.
3. Pseudoexophthalmos. In this condition there is no sclera visible between the cornea and the margin of the lower eyelid.

### 3. Ophthalmoplegia.

A mild to moderate degree of weakness of the external eye muscles is found in 40 per cent of cases of thyrotoxicosis. Slight symmetrical weakness of elevation of the eyes is common and may be due to weakness of the superior rectus muscle or due to contracture of the inferior rectus muscle. Impaired abduction is sometimes seen also but downward movement of the eyes is rarely affected. In cases where the ophthalmoplegia causes loss of elevation of the eyes, compensatory neck extension is sometimes seen. In these cases lid retraction is usually marked.

Occasionally ophthalmoplegia is seen with little or no exophthalmos and may be irreversible. In general, there appears to be an inverse relationship between the degree of ophthalmoplegia and the general signs of thyrotoxicosis. The easily over-looked ophthalmoplegias associated with well marked general thyrotoxic signs are at one extreme, while at the other extreme are the patients with exophthalmic ophthalmoplegia, with little or no evidence of hyperthyroidism.

### 4. Progressive Exophthalmos. (exophthalmic ophthalmoplegia)

Progressive exophthalmos is a combination of ocular signs representing an extreme degree of thyrotrophic exophthalmos. It consists of progressive bilateral, or occasionally unilateral,

exophthalmos, with chemosis, swelling of the eyelids, and external ophthalmoplegia. The majority of cases have lid retraction, but this may be replaced by ptosis, if the ophthalmoplegia is severe. Other signs often present are lagophthalmos, fullness above and below the eyelids due to orbital overfilling, and ectropion of the lower lid. Backward pressure on the eyeball meets with firm resistance and is sometimes painful.

Changes in the fundus oculi are sometimes seen in severe cases and consist of papilledema and retinal hemorrhages followed by optic atrophy. The condition is often accompanied by well marked subjective phenomena, consisting of pain in and around the eyes, photophobia, excessive lacrimation, diplopia, and visual failure.

Progressive exophthalmos is insidious in onset and appears to be due to the same cause as is thyrotrophic exophthalmos, and evidence of hyperthyroidism is usually mild.

### Hypoactivity (Hypothyroidism, Myxedema, and Cretinism)

#### 1. Eyelids.

In myxedema the palpebral fissure is slit-like and is surrounded by the puffy swelling of the eyelids and the adjacent skin. Below the lower eyelid a large baggy swelling appears which does not pit on pressure. Because of the presence of periorbital swelling, the face as a whole has a characteristic appearance. Loss of the hair of the outer one-third of the eyebrow is common, but not pathognomonic.

#### 2. Cornea

Discrete superficial grey spots may be present in the cornea.

#### 3. Lens

Small flaky opacities in the superficial cortex of the lens have been described but they do not interfere with vision.



4. **Optic Nerves**

Bilateral retrobulbar neuritis may also be present. If the hypothyroidism is not treated, optic atrophy may result.

5. **Field Defects**

Bitemporal hemianopsia and visual failure sometimes occurs and is due to hypertrophy of the pituitary gland in response to the hypothyroidism, with consequent pressure effects on the optic chiasma. In other instances the hypothyroidism is secondary to a primary pituitary tumor.

The ocular changes of hypothyroidism are reversed by thyroid hormone administration.

**PARATHYROID GLANDS:**

**Hyperparathyroidism (Von Recklinghausen's Disease of Bone)**

This is a rare condition due to excess parathyroid hormone, caused usually by an adenoma. The serum calcium concentration is raised and consequent ocular changes consist of deposits of calcium containing crystals in the bulbar conjunctiva.

**Hypoparathyroidism**

A decrease or loss of parathyroid function is followed by a subnormal serum concentration of ionized calcium with all its consequences including hyperirritability of the nervous system and tetany. Ocular signs consist of blepharospasm, twitching of the eyelids, and lacrimation. If the hypocalcemia is of long duration small discrete punctate opacities may occur in the lens. They are usually bilateral and rarely interfere with vision. Occasionally, however, such cataracts develop very quickly and may require operative removal.

A common cause of hypoparathyroidism is accidental surgical removal of the parathyroid glands.

**PITUITARY GLAND:**

The ocular aspects of pituitary dysfunction manifest itself mainly through the direct mechanical effect of tumor formation on the optic chiasma; characteristic bitemporal field defects occur, and the oculomotor nerves may become involved through lateral expansion of the tumor, resulting in abnormalities of eye movements. The pituitary tumors may also affect other endocrine glands and these, in turn, may give rise to ocular manifestations.

**Basophil Tumor**

These are usually too small to cause local pressure effects on the optic chiasma, but, because of their effect on the adrenal glands, they give rise to a secondary hypertension which may cause a diabetic retinopathy similar to that produced by essential hypertension. It may also give rise to thyrotrophic exophthalmos and exophthalmic ophthalmoplegia, as well as thyrotoxicosis.

**Acidophil Tumor**

Apart from its mechanical pressure effects on the optic chiasma this tumor frequently gives rise to gigantism or acromegaly. A direct ocular effect of this condition is the increased prominence of the supraorbital ridges.

**Chromophobe Tumor**

These are by far the most common tumors of the anterior pituitary gland. Their main symptoms and signs are due to their direct pressure effect on the optic chiasma. An important complication is the progressive involvement of the optic nerve which may lead to blindness. Some of these tumors cause pituitary insufficiency. The resulting hypothyroidism may cause its characteristic ocular manifestations to be present.



## ADRENAL GLAND:

### Adrenal Cortex

1. *Adrenal cortical insufficiency (Addison's disease)*

In this condition the eyelids, together with the rest of the face and other parts of the body, become pigmented with a bronze colour.

2. *Tumors*

Carcinomas of the adrenal cortex may be associated with orbital or intra-ocular metastases.

### Adrenal Medulla

1. *Pheochromocytoma (Chromaffin-cell tumor)*

This is a rare, usually benign tumor of the adrenal gland and is sometimes bilateral. The tumors tend to occur in the 2nd, 3rd, and 4th decade of life and they actively produce adrenaline which gives rise to secondary hypertension. If present for some time, a typical picture of hypertensive retinopathy, indistinguishable from that of primary essential hypertension, results.

2. *Neuroblastoma (Sympathico-blastoma)*

This malignant tumor occurs in children in the first few years of life and orbital metastases are common. The metastases cause exophthalmos, either unilaterally or bilaterally, in 80% of cases. Intraorbital and intracranial metastases frequently cause papilledema and extraocular muscle paralyses.

## THYMUS GLAND:

### *Myasthenia gravis.*

This condition appears to be related to persistence, hyperplasia or neoplasia of

the thymus gland. Ptosis of one or both upper eyelids is often the first symptom of the disease. The ptosis may be unilateral or bilateral and is soon associated with diplopia due to paralysis of one or more of the external ocular muscles. Complete external ophthalmoplegia of one or both eyes may result.

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# Strabismus

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## STRABISMUS

Strabismus or squint is an eye disorder in which the two optic axes of vision cannot be directed to a given object simultaneously due mainly to an imbalance of the extraocular muscles. Often no definite cause can be assigned to the condition.

## ABNORMAL RETINAL CORRESPONDENCE IN SQUINT

The structure of the retina is such that the macula is the only spot upon which an image can be accurately appreciated. As the image moves off the macula, its distinctness or the brain's appreciation of the image will deteriorate. The images presented by a single given object must fall on the two maculae for the eyes to function harmoniously in presenting an accurate image. If this fails, the deviating eye will present impressions from its macula that do not enforce, but disturb, impressions from the fixed macula which holds the attention.

Control of convergence is usually not consolidated by an infant until the age of six months although conjugate eye movements are present at the beginning of the fourth month. If the two maculae correspond and ocular movements are perfect, the infant will develop normal visual correspondence and fusion as a conditioned function. However, if the visual axes are not parallel and retinal correspondence is not obtained, the brain will adopt a correlation between only one macula and an eccentric point in the other eye. As a result, binocular vision fails.

Strabismus may be presented in the the following ways:

- (a) unilateral—in this form, the same eye always deviates
- (b) alternating—here, either eye may deviate, but when one eye deviates, the other remains constant

- (c) constant—the squint remains permanent
- (d) periodic—with periodic squint the eyes may occasionally be free from squint.

Strabismus may be classified into two major types:

1. non-paralytic or comitant
2. paralytic or non-comitant.

Comitant or non-paralytic strabismus accounts for the majority of cases and is due to the fact that although all the extraocular function, they do not work together properly. The second type of disorder is characterized by paralysis of an extraocular muscle.

## NON-PARALYTIC OR COMITANT STRABISMUS

The great majority of these cases present before three years of age. In this type of squint, the visual axes are not parallel in distant gaze although the eyes retain their co-ordination. The angle of squint is always the same regardless of the direction of gaze; i.e., the squinting eye will always deviate to the same degree when the eyes are carried in different directions. The final lower pathway in the afferent tracts that control the ocular movements is unchanged in this condition. However, either the visual impressions afferent to the cortex from one eye are defective or the fusional reflexes are not fully developed and have broken down causing an ocular deviation. Thus, defective supranuclear innervation is the prime causative factor.

The child with comitant strabismus usually suppresses the resultant double image. As a result of this suppression, the child will not complain of diplopia in the majority of cases. If, however, an older child is made conscious of the double vision or double images, the double images are



found to be equidistant in all fields of gaze due to the squint angle being equal in all parts of the motor field. Other results of diplopa, such as head tilting and a sensation of dizziness or vertigo, are rarely noted. Another clinical feature is that there is no notable limitation of motion present in either eye. Furthermore, the deviating eye itself often has defective vision and in these cases the defective vision may be the cause of strabismus.

Comitant strabismus may be due to a weakness in an intraocular muscle leading to a refractive error. Nervous instability and cerebral birth injuries may also be predisposing factors. Occasionally this defect may be the result of an acute disease, e.g., measles.

Comitant strabismus is divided into three subdivisions:

- (a) convergent squint or esotropia;
- (b) divergent squint or exotropia;
- (c) vertical.

(a) Convergent strabismus is the most common form and nearly always begins in childhood, usually between two to four years of age. It is usually acquired as opposed to congenital. The deviation is convergent and horizontal, with many cases having a slight upward deviation as well. To see near objects clearly, the child must accommodate, and in cases of hyperopia over accommodation results. Because convergence is proportional to accommodation, overconvergence results giving rise to esotropia. Although the squint is usually of a small degree, it is greater for near vision than for distant vision.

This form of comitant strabismus appears to be associated with heredity as in 50% of the cases the parents have been known to be affected. Other suggested causes are debilitating diseases, nervous instability with abnormal tonic innervation, and even frightening experiences have been reported as instigating this type of squint.

Proper diagnosis depends mainly on a good history of the patient with emphasis on a possible history of squint in the family. Measurement of the degree of squint is also important. Any suspected case should be quickly referred to an ophthalmologist for further tests.

Poor or dim vision (amblyopia) may result from the aforementioned diplopa because the child will continually suppress the image from one eye. As a result, disuse atrophy or amblyopia ex-anopsia will result, leaving the child with permanent subnormal vision in that eye. Therefore, a common corrective measure is occlusion of one eye for periods of a week at a time. An attempt is made to encourage the child to use first one eye and then the other to prevent amblyopia. Bifocal glasses may be prescribed at a later age to prevent crossing of the visual axes and in time this overcorrection may be progressively decreased as the condition improves. Anticholinesterase miotics have also been used in order to constrict the pupil and induce ciliary spasm to reduce accommodative strabismus. Orthoptic exercises may be of some value as well. In purely accommodative cases, surgery is not indicated.

(b) Divergent Strabismus: This form of squint may be referred to as exotropia and is characterized by an abnormal turning of one or both eyes outward. An excessive divergence tonus is believed to be the causative factor. Divergent strabismus may present as periodic or constant. The periodic or intermittent form appears more frequently and is termed intermittent exotropia. It usually has little refractive error and begins just after birth as a rule. It is often noticed in a child when the child tires and one eye deviates laterally. Deviation may also occur when a child looks at distant objects and suppression develops with a notable deviation. It eventually leads to near vision and a constant exotropia develops. Because excessive divergent tonus is involved, surgical correction is often required preferably before the condition of constant exotropia develops.



Prior to surgical correction, orthoptic exercises are of little benefit; however, post-operatively they may aid to combat suppression and build fusional amplitudes.

Exotropia is common at a later age in many people and predominates among myopes or near-sighted people. This condition may occur later in life when one eye loses most of its vision and the better eye is used out of necessity. The faulty eye then assumes a position of rest which is usually a position of divergence. Divergent strabismus increases with age and rarely undergoes remission.

There are cases of divergent squint which are neither paralytic nor strictly comitant. Some are associated with the myopic divergent squint, and may arise from it.

(c) Vertical Strabismus: This form of strabismus is due to hyperaction or hypoaction of the vertical recti and oblique muscles. It may be referred to as hypertropia or hypotropia meaning vertical strabismus with upward and downward eye movements respectively. The affected eye often turns upward. Tilting of the head by an infant is characteristic of vertical strabismus in order to retain binocular vision. Often unconscious suppression of the image occurs as a result of the diplopia. If there is no unconscious suppression of the image, then diplopia will occur. The expression of the child's face may be bizarre because of the attempt to overcome the imperfect refractive powers (ametropia) of the eye.

In adulthood, this form of strabismus is usually a result of central nervous system disease.

#### PARALYTIC OR NON-COMITANT STRABISMUS

The deviation with the paralytic form varies in degree according to the direction of gaze and whether the patient uses the good or affected eye. There may be partial or total paralysis involving a single or

group of extraocular muscles. Nerve trunk lesions are a common cause of paralytic strabismus. Paralysis of the abducens nerve is a common cause due to trauma or infection from meningitis and effects the lateral rectus muscle. Lesions of nerve centres, such as the oculomotor nuclei, may also be causative. In some cases, orbital disease or injury may damage the muscle while the nerves remain intact. The eye fails to move in the direction of the paralyzed muscle and the angle of deviation increases on attempting to gaze in the direction of the paralysis. Paralysis of a muscle is noted by underaction as the eye rotates into its field of action and the good eye will often exhibit overaction. This overaction of the good eye is referred to as secondary deviation as compared to primary deviation or underaction of the affected eye. Secondary deviation is always greater than primary deviation in paralytic squint.

Paralytic strabismus may be seen in intranuclear lesions such as the medial longitudinal fasciculus syndrome where squint is noted in one direction of gaze and not another. An example of this would be noted with the medial rectus muscle. This muscle may function properly in convergence yet fail to adduct the eye in lateral horizontal gaze. If the right lateral rectus muscle was paralyzed, the right eye would exhibit limited movement upon gazing to the right but the left would show normal movements.

Lesions near the corpora quadrigemina of the tectum of the mesencephalon give rise to Parinaud's syndrome. The paralysis with this syndrome includes the upward and downward gaze movements and convergence and pupillary disturbances are often evident. Children with cerebral palsy may have ocular palsy resulting in double vision in some direction of gaze.

#### Varieties of Ocular Paralysis:

If a single extraocular muscle is affected, it is usually the external rectus or superior oblique since each has an independent



cranial nerve innervation. If, however, a group of muscles is affected, the oculomotor nerve is the source of the problem.

Paralysis of all the extrinsic and intrinsic muscles of an eye can occur and is termed total ophthalmoplegia. Paralysis of the extrinsic muscles only is called external ophthalmoplegia and paralysis of the intrinsic muscles (the sphincter pupillae and ciliary muscle) is termed internal ophthalmoplegia.

The characteristic observations of some of the varieties of ocular paralysis are:

- (a) Paralysis of external rectus—The patient will turn his or her face towards the paralyzed side and a limitation of eye movements outwards will be noted. Diplopia occurs upon looking towards the paralyzed side.
- (b) Paralysis of superior oblique — The face will be turned downwards and towards the sound side. Eye movement is limited in a downward direction and toward the sound side. Diplopia occurs upon looking downwards.
- (c) Paralysis of the third cranial nerve—In complete paralysis of this nerve ptosis of the eyelid occurs and diplopia is not necessarily present. If the lid is raised, the eye will be seen to be deflected outwards and upwards due to the two unparalyzed muscles (external rectus and superior oblique) not innervated by the oculomotor nerve.

The treatment of paralytic squint is often by surgery to compensate for or strengthen a weak or paralyzed muscle. In cases of paresis where the deviation has become stabilized, surgery is also indicated. Occasionally, some benefit is derived from orthoptic exercises.

## CONCLUSION

Squint has two main harmful effects on a child:

1. If a child cannot establish normal binocular reflexes, faulty vision habits will develop which will have harmful effects. The child will learn to suppress the resultant confusing images and continued suppression can result in an eventual loss of vision in the deviating eye.

2. A squint will have a bad psychological effect on a child; in particular, as the child reaches school age. At this age, the child will experience reading difficulties and face frustration. The reaction of other children to a squinting child can have a detrimental effect on the latter and lead to a personality defect.

It is important to make an early diagnosis of strabismus because early treatment enhances the prognosis. Treatment should be begun at six to nine months of age to obtain good results.

The goal in treatment of strabismus is three-fold:

- (a) Normal vision must be established in each eye.
- (b) Stereoscopic vision must be developed.
- (c) Cosmetically straight eyes must be provided.

I would like to thank Professor J. C. Rathbun for his aid in the preparation of this article.

## GLOSSARY OF TERMS

amblyopia—reduced vision or dimness of vision which does not depend on visible changes in the eye.

ametropia—imperfect refractive powers of the eye in which the principal focus does not lie on the retina.

diplopia—double vision.

esotropia—marked turning inward of the eye.

exotropia—divergent strabismus; an abnormal turning of one or both eyes outwards.

fusion faculty (optic)—blending of the images of binocular vision into a single perception having the quality of depth.

macula (macula lutea)—small, oval spot on the posterior part of the retina where the visual sense is most acute. It contains a central depression, the fovea centralis.

meiotic—an agent that causes the pupil to contract.



myopia (nearsightedness)—defect in vision that accommodates distinct vision of objects very close to the eye.

orthoptic—concerning the correction of a deviating eye.

vertigo (ocular)—visual sensation caused by disease of the eye which makes stationary objects appear to be moving.

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## The Acute Red Eye: A Differential Diagnosis

T. AUSTIN, Meds '65

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Three per cent of persons presenting to the general practitioner has an ocular complaint. A common sign is that of a red eye. Correct diagnosis must precede proper therapy. There follows a differential of the four major causes of the acute red eye.

- a) Acute conjunctivitis
- b) Acute keratitis
- c) Acute iritis
- d) Acute glaucoma

a) **Acute Conjunctivitis:**

Inflammation of the conjunctiva is the

commonest eye disease in the western hemisphere. Bacterial conjunctivitis is self-limited, lasting 10-14 days, if untreated. The viral form will persist 2-3 weeks, while allergic conjunctivitis is chronic.<sup>1</sup> Before making a diagnosis, pressure should be applied to the lacrimal sac to exclude chronic dacryocystitis.<sup>2</sup>

The cause of acute or sub-acute catarrhal conjunctivitis is most commonly *Staphylococcus aureus*.<sup>3</sup> Other common pathogens are *Diplococcus pneumoniae*, *Hemophilus conjunctivitis* (Koch-Week's



bacillus) and *Hemophilus influenzae*.<sup>4</sup> Purulent conjunctivitis is due to the gonococcus.

A red, painless eye of short duration, a thick exudate (inquire if lids stuck together upon awakening) and the feeling of a foreign body in the eye are major symptoms. Upon examination, the redness is due to posterior conjunctival injection (vessels superficial and discrete, redness more pronounced in fornix).

#### b) Acute Keratitis:

Inflammation of the corneal tissue may be superficial or deep, with or without ulceration. The cornea is a hard, homogeneous, avascular tissue, its central portion being incapable of regeneration. Because of this, keratitis commonly results in scarring and decreased vision or less frequently complications arise which result in loss of vision.<sup>5</sup>

Superficial keratitis results from exogenous infection. Gonococcus and *Corynebacterium diphtheriae* invade normal epithelium, while *Pseudomonas aeruginosa*, staphylococcus and streptococcus are unable to do so.<sup>6</sup> A hypopyon ulcer can follow severe inflammation.

Deep keratitis can be interstitial, seen in congenital syphilis and tuberculosis or disciformis, resulting from vaccinia or herpes simplex.<sup>7</sup>

The patient has a painful red eye. There is photophobia, often intense enough to result in blepharospasm, lacrimation and a decrease in visual acuity. These symptoms may be marked in children or mild in the elderly person.

The cornea is hazy and there is anterior ciliary injection (vessels deep and indefinite, appearing as pink lines which radiate out from the limbus). Ulcers will be stained green by fluorescein.

#### c) Acute Uveitis:

This consists of an inflammation of the iris and ciliary body. The blood supply of

the uveal tract is almost entirely from the posterior ciliary arteries. The choroid is supplied segmentally while the anterior portion receives from the greater arterial circle.<sup>8</sup> Anterior uveitis is an acute, non-granulomatous infection while posterior uveitis is chronic and granulomatous.

The patient has a red, painful eye with lacrimation and decreased vision. Examination shows a flare in the anterior chamber and fine white keratic precipitates on the posterior surface of the cornea. The pupil is small, dilates sluggishly and irregularly, if posterior synechiae exist. The iris is swollen and lusterless and the injection is anterior ciliary. With repeated attacks, annular synechiae result.

#### d) Acute Glaucoma:

Glaucoma is a symptomatic condition, characterized by increased intra-ocular pressure.<sup>10</sup> Acute glaucoma may be primary, due to closure of the anterior angle, or secondary to some intra-ocular pathology. Angle closure glaucoma must be differentiated from anterior uveitis, as use of atropine in the latter is indicated, while in the former it may cause blindness.

Angle closure glaucoma is predisposed to in the hypermetropic eye, with a shallow anterior chamber and anteriorly placed lens. It manifests itself in the fourth and fifth decade. Emotional stress and conditions associated with dilation of the pupil will precipitate an attack.<sup>11</sup>

Secondary glaucoma follows anterior and posterior synechiae, ocular hemorrhage and occlusion pupillae. Other preceding conditions are lens dislocation, traumatic cataract, intra-ocular tumours and central retinal vein occlusion.<sup>3</sup> Treatment is that of the primary cause.

The symptoms are an acute red eye with pain, often sufficient to cause nausea and vomiting, lacrimation, and a rapid diminution of vision. The pupil is semi-dilated, oval and unresponsive to light. The cornea is steamy, iris markings are lost and the conjunctiva and lids are reddened and



## — Acute Red Eye —

macerated. The congestion is posterior conjunctival and anterior ciliary.

Schiötz tonometry shows raised intraocular pressure, up to 70 mm Hg.<sup>12</sup> (normal 10-22) while gonioscopy reveals closure of the anterior angle.

### SUMMARY:

The acute red eye is an ophthalmological emergency requiring immediate diagnosis. Conjunctivitis is indicated by a red painless eye with a thick exudate. If anterior ciliary injection is seen and pain exists, a diagnosis of acute glaucoma must be entertained. Tonometry differentiates between this condition and uveitis or keratitis. An anterior chamber flare indicates uveitis.

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# Clinical Diagnosis of Glaucoma

MARA DREIMANIS, '66

It is estimated that primary open-angle glaucoma affects 2% of the population over forty. All glaucomas account for 12 to 20% of blindness in the United States.<sup>3</sup> Glaucoma constitutes a major ocular disease.

Glaucomas are diseases of the eye characterized by sustained increased intraocular pressure resulting in damage to the optic nerve. They may be primary or secondary. The primary glaucomas are bilateral and may be determined genetically. The sec-

ondary glaucomas follow an antecedent ocular disease and are often unilateral. The increased intraocular pressure may be due to increased rate of aqueous production by the ciliary body, but is most commonly due to resistance to aqueous outflow at the angle of the anterior chamber.

Diagnosis is aided by etiological classification. At present, primary open-angle glaucoma is the only one for which the pathogenetic mechanism is unknown. Unfortunately, it is the commonest glaucoma



and develops so slowly and insidiously that diagnosis is often made only after the optic nerve has been damaged. Some hospitals have initiated the wise practice of routinely testing all patients for glaucoma.

### CLASSIFICATION OF GLAUCOMA

- I. Primary glaucoma
  - 1. Closed - angle
  - 2. Open - angle
- II. Secondary glaucoma
  - 1. Closed - angle
  - 2. Open - Angle
- III. Congenital

### CLINICAL PICTURE OF GLAUCOMA

#### I. Primary glaucoma

Primary glaucomas show no evidence of antecedent ocular disease.

##### 1. Closed - angle

This type of glaucoma occurs typically in hyperopic, narrow-angled eyes with shallow anterior chambers. It is seen more often in women.

The attack is usually sudden and is thought to be brought about by some degree of pupillary block; the peripheral iris becomes apposed to the trabecular meshwork, thus obstructing the filtration angle.

Early in the attack, the patient may complain of hazy vision, "halos" around lights, and frontal headache.

The halos appear after prolonged periods spent in darkness.

The acute attack is associated with pain in one eye, so severe it may cause vomiting and violent headaches.

The clinical picture presents corneal edema, injection of the conjunctiva, loss of iris markings, decreased visual acuity, and a pupil which is oval, semi-dilated, and insensitive to light. The most important diagnostic feature is a shallow anterior chamber and gonioscopy reveals a closed angle.

##### 2. Open - angle

This type constitutes 85% of all glaucomas.<sup>7</sup> It is chronic, slowly progressive, and bilateral. Pain is not a feature. Inheritance plays a role in determining who will get it: 15-20% of patients show familial histories.<sup>3</sup>

In this glaucoma, the angle is open and the rise in intraocular pressure is due to obstruction to aqueous outflow within the trabecular meshwork-Schlemm's canal system.

The disease usually goes unnoticed until extensive ocular damage has occurred. In advanced cases ophthalmoscopic study of the fundus shows:

##### (i) optic "cupping"

There is marked excavation of the disc, the blood vessels bending sharply under the edge to reappear in the floor.

##### (ii) a peripapillary halo

This results from peripapillary chorioidal atrophy.

This glaucoma may proceed to absolute glaucoma (blindness) without pain or other symptoms.

#### II. Secondary glaucoma

Secondary glaucoma poses few diagnostic problems, since the underlying ocular disease usually manifests itself clinically.

##### 1. Closed - angle

Examples are:

- (i) a swollen lens
- (ii) posterior synechiae (iris bombé)
- (iii) occlusion of the central vein of the retina

##### 2. Open - angle

Examples are:

- (i) trauma or inflammation (iritis, etc.)
- (ii) tumors of the eye

#### III. Congenital glaucoma

This glaucoma occurs in infancy or early childhood as a result of an anomaly of the anterior segment of the eye. In-



ed intraocular pressure and elasticity of the infantile sclera produce an increased corneal diameter in both eyes. Photophobia, tearing after 6 weeks, and continuous irritability strongly suggest glaucoma.

## SPECIFIC TESTS FOR GLAUCOMA

### I. Ocular Tensions

Intraocular pressure can be determined by the following methods:

#### 1. Schiötz tonometry

The Schiötz tonometer is a carefully standardized instrument which measures the depth of indentation produced in an anesthetized cornea by a plunger with a known weight on it. Its only disadvantage is that it doesn't take into account variations in scleral rigidity. However, it is widely used and is the most useful instrument for detection of all glaucomas.

With this instrument, normal intraocular pressures range from 10.5 to 21.7 mm. Hg.<sup>3</sup> A pressure higher than these is suggestive of glaucoma.

#### 2. Applanation tonometry

The applanation tonometer is more accurate than the Schiötz. It is based on the Imbert-Fick Law: the Goldmann tonometer measures pressure directly as the force required to flatten a standard area of cornea. This method is independent of scleral rigidity. However, the instrument is less convenient than the Schiötz, and is used in cases of suspected glaucoma rather than in routine tests.

The normal intraocular pressure as measured by this method ranges from 10.4 to 20.4 mm. Hg.<sup>3</sup>

#### 3. Finger palpation

This is of historical interest only. Glaucoma can be detected only when the eye is stone hard.

### II. Gonioscopy

Gonioscopy allows biomicroscopic examination of the angle of the anterior cham-

ber. A contact lens containing a mirror is placed on the cornea, and the angle viewed in the mirror by means of a slit-lamp. This method distinguishes between open- and closed-angle glaucoma.

### III. Examination of the Disc

Optic cupping and a peripapillary halo, both of which are seen in primary open-angle glaucoma, can be detected by an ophthalmoscope.

### IV. Visual Fields

Field defects are prominent in a patient with advanced primary open-angle glaucoma. They may be seen best on a tangent screen as arcuate scotomas (Bjerrum scotoma, nasal step of Roenne) or as progressively decreasing quadrants of vision ending ultimately in blindness.

### V. Tonography

Tonography provides a good estimate of the outflow facility of the aqueous.

The instrument used is an electronic tonometer with a known weight, applied to the cornea for 4 minutes.

The basic principle involved is Poiseuille's Law. A given weight applied to the eye produces a decrease in intraocular pressure depending on the ease with which the aqueous can escape. The slope of the curve is steep in the normal eye, but flat in the glaucomatous eye because of increased resistance to outflow of aqueous. From the tracing one can calculate a value C, for which the range in normals is 0.18 to 0.38<sup>7</sup>.

### VI. Provocative Tests

These tests, by producing stress in the patient, provoke an increase in intraocular pressure, which is exaggerated in glaucoma. These are useful in diagnosis of primary glaucomas.

#### 1. Water-drinking test

One liter of water is given orally before breakfast. This decreases the osmotic concentration of the blood and increases intraocular pressure. A rise in pressure above 6 mm. Hg. (Schiötz)



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is suggestive of primary open-angle glaucoma.<sup>5</sup>

## 2. Dark-room test

The patient is kept awake in a dark room for half an hour. The resulting pupillary dilatation obstructs aqueous flow by pressing the iris into the filtration angle.

A rise in intraocular pressure above 8 mm. Hg. (Schiötz) is suggestive of closed-angle glaucoma.<sup>5</sup>

## 3. Dilatation provocative test (Mydriatic test)

Two drops of euphthalmine (5%) are instilled into the conjunctival sac to produce moderate pupillary dilatation. An 8 mm. Hg. (Schiötz) rise of pressure in one hour is considered diagnostic of closed-angle glaucoma, if gonioscopy shows an actual angle-closure.<sup>3</sup> One eye only should be used to prevent acute bilateral attacks of angle-closure. Pilocarpine should be administered afterwards until the pupil becomes miotic.

## SUMMARY

Etiological classification of glaucoma aids in diagnosis. Once increased intraocular pressure is detected by tonometry, an abundance of tests (including gonioscopy, ophthalmoscopy, visual field tests,

and tonography) establish the type of glaucoma, and appropriate treatment may be given.

Specialists strongly advise routine tests for the early detection of primary open-angle glaucoma. These could be done either by hospitals or, better still, by all physicians.

I wish to thank Dr. J. S. Madronich and Dr. D. W. Mills for their criticism and assistance in preparing this article.

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## Book Reviews

**Medicine and the State:** by M. J. Lynch and S. S. Raphael, 449 pages. Charles C. Thomas, Publishers, Springfield, Ill., 1963, \$11.60 (Ryerson Press).

In this book, the authors, both of whom are with the departments of pathology of Sudbury General Hospital and Sudbury Memorial Hospital, have traced the devel-



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opment of socialized medicine from its beginning in Germany with the passing of the Sickness Insurance Law in 1883—effective 1884—to the present.

Among the systems studied are those of Germany and Austria (the prototype of all socialized medical schemes), Russia, Great Britain, New Zealand, Australia and Sweden.

The book is divided into two parts. Part I is largely historical, describing in detail all aspects of the growth of medical plans in the above countries. Part II is devoted to appraisal of socialized medicine in these countries as it stands today. This appraisal is subdivided into four broad areas: (1) the patients (2) Vital and Disease Statistics (3) The Profession (4) Economic and other aspects.

In the final chapter the writers have stated their conclusions. They feel that the major advantages claimed for the socialized systems cannot be justified by the experience and achievements of any fully socialized scheme. One sentence stands out: "There appears to be no statistical evidence that any socialized medical scheme has resulted in an improvement in health beyond that enjoyed by those peoples still served by the private systems of medical care."

Although the book is well documented with 67 tables, and should be read by all who wish to become informed on the subject of socialized medicine, one cannot help wondering what the conclusions would have been had the authors been other than medical men.

Don Elliott, '64

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## News and Views

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### THE PHYSICIAN, SOCIETY AND MEDICAL EDUCATION

Occasionally our teachers warn us that we must not cure the disease at the expense of the patient. This thought truly conveys the idea that the patient is in fact a whole human being and we should be concerned about him as a whole and not just as a diseased lung, broken arm or painful abdomen. Almost never is the point made in our medical education, that indeed we are dealing with a human individual who breathes and feels and thinks, who has a family that is concerned about him, who has emotions and ideas, who, in short, is an equal member with us in soci-

ety. Medical education tends to lack compassion and humanity (although it abounds with humaneness). The essence and wisdom of a philosophy teaching us that there really is a world about us, composed of human people, is lacking. We as doctors have perhaps a larger role to play in this world, a world which too many doctors seem to have shunned for the more comfortable complacency of lungs and toes and eyes and hearts and golf.

Student doctors must be taught about the whole human patient. It is, after all, the whole patient and not just the diseased part that we want to cure. It is the whole man who must resume his place in



the world from which he came and to which he contributes. Wherever we can, we must eliminate the cause of the patient's disease which may well be found at his job or in his home.

As it is necessary to understand the diseased organ or area as part of a whole patient, so it is important for the doctor to understand the patient within the whole of society. Medical education, once again, fails us in this regard, and as a result physicians have largely failed to include themselves in the important issues that confront us within our society. The physician must assume his rightful and obligatory role in society, or be totally consumed by it.

Except for the isolated individual, doctors by and large have failed to take their place in our society, a place which they alone, because of their particular knowledge and skill, can fulfil completely. Doctors, by and large, have kept their lips tightly closed on the great social, moral, and it may even be argued, medical questions that surround us each day. Doctors have not stood up to be counted, have not taken a stand on issues which not only jeopardize the health of people the world over, but perhaps their very lives. Can we put the blame for this inadequacy on medical education or is it simply that doctors, like most people in our society, don't want to get themselves involved?

Daily the student is told that the best cure is prevention. Where, then, is the mighty voice of the doctor damning the hydrogen bomb and demanding its eradication? Well, at least we have managed to decrease the number of x-ray machines in shoe stores.

Where is the mighty voice of the doctor in such moral and social problems as unemployment. Unemployment might lead to poverty, breeding overcrowding and lack of sanitation and aren't these, in fact, very important etiological factors in many common diseases? Well, at least we have antibiotics to eradicate some of the diseases produced from overcrowding produced

from poverty produced from unemployment which, at its worst, affects only five hundred thousand or six hundred thousand Canadians at any one time.

Where is the mighty voice of the doctor in the all-important questions of human equality and brotherhood amongst all men? Where is the sane, intelligent, knowledgeable voice of the doctor who really knows that the anatomy and physiology of a white man and Negro are quite similar? Where is the doctor who will speak out against and reveal the distorted delusions of the racist?

Silence is comfortable and sometimes safe. If we restrict ourselves to our specific medical problems we can never really be accused of neglect. After all, the doctor does have a busy schedule.

Jerald Bain, B.Sc.Ph.M. '65

## MEDICAL EDUCATION AND MEDICARE IN THE NETHERLANDS

Complete medical training lasts seven years. Premedicine, medicine proper and the equivalent of our internship are completed during that time.

The teaching program is much like that in Canada except that the basic medical sciences such as anatomy and histology are started right from the first. The students get far less clinical experience in their last few years and many find this a real disadvantage.

After seven years the student is graduated and receives the title of 'ARTS' (Physician). He is now allowed to practice medicine on his own. The degree is equivalent to 'Bachelor of Medicine'. If he wants to receive his Doctor of Medicine degree he has to write a thesis. The latter is more a question of prestige than education.

Universal medical care is available in the Netherlands by a state-supported plan that is operated by the 'Ziekenfonds' (fund for the sick).



The money necessary to operate the plan is collected in the following manner:

Below a certain income level the patient pays nothing and the State everything. Above this level the patient's premium, and his family's, is directly proportional to his income tax. He has to pay this premium and the plan is thus compulsory for him. The State pays the rest of his premium.

At a certain income tax level the monthly premium becomes so high that the patient is better off to pay his own medical bills and he is allowed to do so without paying any premium. However, he gets no benefits whatsoever from the state.

Thus only the patient who can show that he is able to pay his medical expenses is free from paying a monthly premium.

The plan includes office calls, house calls, operations, specialists, all diagnostic and therapeutic services, drugs (prescribed), artificial limbs, special institutions, i.e. mental hospitals, etc., hospital care, dental care, and eyeglasses.

The plan has been operated for many years and is highly satisfactory to both patients and doctors.

Little misuse is made of the availability of this intensive and good care. This, most doctors feel, is not a merit of the plan but rather is due to the disposition of the public.

The result of the plan has been that the Netherlands has an infant mortality rate which is, with Sweden's the lowest in the world and a life expectancy which is the highest in the world.

Gerald J. M. Tevaarwerk, '65

## MEDICAL STUDENTS AND PSYCHIATRY

Life is made up of a raft of problems, and one of the biggest is the problem of finding time for everything that should be

done. In our years at medical school, we seem to be plagued by an interminable number of examinations. In the rush to consolidate anything and everything, we lean toward synopses and summaries, and shy away from lengthy discussions. In this atmosphere, syphilitic signs and symptoms may come into focus quite nicely, but certain other parts of the course fail to thrive. Psychiatry is one of the latter. In fact, psychiatry just withers and dies when it's set out in point form.

If you are at all interested, however, you can do much to correct this situation. In Ontario, for example, someone has dreamed up a congenial little arrangement whereby you stay at an Ontario Hospital during the school year, doing physicals and taking occasional night calls in return for your room and board. During the summer the work load is a bit heavier, and you receive a moderate wage for your work. Other medical students share your duties, and you are rarely pushed for time.

Last June I joined such a plan at the Ontario Hospital London. Since that time, the thousands of faces here have fallen into a semblance of order, and in a way have become one large, living, insistent textbook.

As you know, there are many varieties of disordered minds; but from the human-interest point of view, you might say that there are only two groups: those who have no insight, and those who are aware that they're ill. Many of those who have no insight seem to be blissfully happy in their own private worlds, and it seems almost a shame to treat them and bring them back to ours. But when we come to the second group, it's a different story. They seem to have lost the ability to function well in their home environments, and, under the social stigma attached to such a situation, have come to a mental hospital to be treated for an illness which they don't understand.

On any city street you can see people who are unhappy, or frightened, or wor-



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ried, but our admissions have that "something extra". They are desperate people. In their desperation, they cling to any hope which is offered them, and if after a time they find their conditions improving, they are frequently very grateful people. Some don't improve, and you watch them and wonder why.

So if you're curious, or interested in psychiatry or would like to be interested,

find out what opportunities are available in your district. A year in a place like this won't make you an Adler or a Freud, but it will certainly help you to appreciate the human side of mental illness. Perhaps in the future you'll bristle a bit when you hear a psychiatrist referred to as a "head-shrinker".

David Gingrich, '65

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## Visit From Dr. E. Harry Botterell

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On November 29, 1963, the Alpha Omega Alpha Society was fortunate to have Dr. E. Harry Botterell as guest speaker at their annual banquet. The members were inspired by his topic, "Medical Education and Medical Students". Dr. Botterell is a widely acclaimed neurosurgeon who has channelled his services to the Faculty of Medicine at Queen's University where he was appointed Dean of Medicine in 1962. Prior to this, he was a part of the teaching staff at the University of Toronto.

During the afternoon before the banquet, third and fourth year medical students were privileged to attend a neurosurgical theater clinic conducted by Dr. Botterell. Being extremely interested in students, he devoted the entire clinic to teaching, insuring an attentive audience by random questions to various individuals. During his discussion of each case, everyone admired his organized manner and ability to determine the correct diagnosis.

Dr. Botterell brought out many noteworthy facts following the presentation of each case. For example, in the differential diagnosis of a spinal tumor he noted that bladder function is disturbed initially in meningioma but this occurs only in the later stages of subacute combined degeneration. In the examination of a neurological patient, Dr. Botterell commented that vibration sense in soft tissue is as important as pain perception in the determination of the level of a lesion except that vibration sense is unreliable below the knee in elderly people. He also emphasized the importance of early diagnosis in extradural lymphoma. The patient should be treated by radiation in the early stages when back pain is present. By the time radiological evidence is obvious, the patient will have developed paraplegia.

Dr. Botterell especially praised Dr. Drake for his operative advancements on aneurysms of the basilar artery.

Ernest Spratt, '64



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# Physical Medicine

ALASTAIR McD. MURRAY, '64

Physical medicine is the application of physical forces in the rehabilitation of the body, or part of the body which has decreased function through injury or disease. The main physical forces employed are exercise and heat. Massage, electrotherapy and splints are also important. These techniques alone, or in association with medicine and surgery, limit or correct the disease process and restore function to the affected part. Their usage is steadily increasing for the alleviation of symptoms and elimination of morbidity.

## Exercise

The human uses motion in most daily activities. Immobilization can cause abnormal metabolic functions such as osteoporosis of bones with possible renal calculi, decreased  $O_2$  tension, and general apathy in the patient. Thus in sickness as in health, exercise plays a major part.

Since exercise involves the co-ordinate functions of muscle, nerves, bones and joints, the neuromusculoskeletal system may be regarded as a unit. Muscle re-education should be designed to initiate and increase motor awareness and voluntary response. Effective and acceptable exercises are necessary to develop strength and endurance patterns of movement. Activities of daily living must be learned. In the hospital, movements from the bed to the wheelchair, to and from the bathroom, as well as washing, dressing, eating and writing should be mastered.

Therapeutic exercise leads to hypertrophy, strength, endurance, and improved impulse transmission by the central nervous system. This in turn increases the range of voluntary movement. The number of motor neurons excited by the brain determines the number of motor units stimulated and the strength of a contraction. Repeated stimulation causes a

lessened synaptic resistance and easier transmission of the impulse through the central nervous system.

Muscle assessment is important in diagnosis, treatment and prognosis of an injury. Reassessment establishes the improvement, morale and the final degree of recovery.

The most important factors in the movement of an extremity are the strength or power and range of motion. Power indicates muscle function and range of motion involves the state of the joint surfaces. Co-ordination of muscle movement should also be judged.

Most exercises need no special equipment. However, apparatus may be used to relieve monotony and to achieve strength and skill unattainable by ordinary methods. The size of the hospital usually determines the size and facilities of its gymnasium. Both movable and fixed types of equipment are required.

Hydrogymnastic treatment is useful in cases of extreme limitation of movement and for non-weight-bearing limbs. Water produces a floating force on the body and stabilization of these limbs may be necessary. The forces of gravity and buoyancy balance when the limb is moved in the horizontal plane and minimum muscular effect is needed. However, vertical movement is opposed by the forces of gravity or buoyancy. Assistance or resistance can be applied to any motion. On the totally immersed body, buoyancy overcomes gravity. Thus patients can exercise and walk in water whereas it would be impossible in air. Hydrogymnastic therapy is often effective for muscle weakness found in peripheral nerve lesions like polio, for stretching contractures, for mobilizing paraplegics and overcoming trauma.



Exercises may be passive, active assisted, active or resisted. A passive exercise is one in which the part is put through its motions under the complete control of a helping person. Active assisted exercise is similar, but here the patient exerts his own effort which is supplemented by the therapist's assistance. Active exercise is exercise done wholly by the patient. Resistance and progressive resistance exercises have the movements resisted manually or by the addition of weights. The maximum weight which can be lifted is fastened to the part and then lifted ten times in one session each day. Load-assisting exercises act with gravity but load-resisting exercises act against gravity. Brief maximal exercise (B.M.E.) may result in strengthening the contralateral muscles, and muscle strength can be increased with no increase in size. A high-repetition, low-resistance exercise results in greater endurance and stamina but no hypertrophy. Increase in bulk is achieved by completing a series of lifts or repetitions before the weight is released and the patient relaxes. "Cramping", in which increased weight is added to the shortened, tired muscle until only a final limited motion is possible, also results in greater muscle bulk. The important fact to remember is that all these exercises may be done at home as well as in the hospital under the physiotherapist's supervision.

There is a relationship between postural deformity and locomotor disease. Correction of bad posture is difficult because of the individual's lack of awareness. Poor posture is often psychosomatic and reveals the person's unwillingness to maintain a healthy mind and body.

It is necessary to maintain physical fitness in order to cope with life's emergencies. Age, sex and daily work must be considered before deciding upon the proper exercise. Degree of strength, endurance, co-ordination and speed are related to static, functional and specialized fitness. Exercise and training cause an increase in size and power of muscles due to

capillary growth and an increase in the cross-section of the muscle fiber. Disuse results in a loss of this hypertrophy.

Training results in physical fitness. Practice results in skill. The importance of relaxation and sleep must not be overlooked. Certain basic exercises can begin in infancy. During childhood, speed and rhythm exercises are practised. Co-ordination and skill develop during puberty. Speed, strength and co-ordination are at their peak at 20-30 years. Speed decreases but skill, strength and endurance are maintained in the 30-49 group. After 40, only exercises of speed and great strength need to be avoided. A well known proponent of physical fitness, Dr. Charles M. Godfrey, has stated the principles and suggested exercises for an effective home program of physical training.

Every initial general physical examination should include a screening manual muscle test. It must consist of measurements of leg length and girth, range of joint movement, including the spine, and inspection and palpation of muscle-joint structures. The usual sequence is as follows: muscles of the head and neck, upper extremities, lower extremities and trunk. This subjective assessment of muscle function, according to the Medical Research Council (M.R.C.), grades the muscle from 0 (no contraction) to 5 (normal). However, this method is of little value for measuring normal muscle strength under varying conditions, or in testing muscles not affected by gravity. The latter include the abdominals, and muscles which usually do not act alone, for example, the brachialis.

Assessment of degree of joint movement may be visual, aided by an instrument called an arthrometer.

Muscle function is measured by tests for strength, endurance and co-ordination. Strength is the total force exerted by a single contraction of a muscle. Endurance is the muscle's capability of maintaining a sustained contraction or repeated move-



ments of a certain range over a period of time. Co-ordination is the ability of a muscle to function with speed and accuracy.

Muscle testing is important in the early diagnosis of the various neuromuscular diseases. It locates precisely the level of a peripheral nerve lesion and aids in the determination of the disease process and in evaluation of therapeutic exercises, especially of post-fracture and contracture problems.

The development of muscle power results from decreasing the number of repetitions and increasing the amount of resistance. Effort to increase imposed limits results in strength gain. Weight lifters exercise every day, whereas body builders exercise only on alternate days to allow muscle anabolism.

Isometric or static exercise increases muscle strength and possibly bulk, but isotonic exercise produces endurance, strength and greater muscle hypertrophy. Nevertheless, static exercise has its application under certain conditions.

Proprioceptive neuromuscular facilitation is a technique which uses facilitatory cerebral "circuits" to increase strength, in theory.

Doing exercises formally is tiring and boring to the patient. Physical resistance through directed effort can be provided by occupational or work therapy. Exercise resulting in productivity is more satisfying and less fatiguing. Routine daily movements are used to promote endurance, increased range of motion, strength and co-ordination.

Activity should be directed to the specific part to be strengthened. Participation in such sports as volleyball and table tennis gives mental relaxation and physical improvement, as well as stimulating alertness and developing character.

#### Heat

Heat may be applied to a soft tissue or bony juncture lesion in its acute or con-

valescent stage. The site of the injury determines the type of heat generator to be used.

Infra-red lamps are used most often for surface heat. A simple method of raising superficial tissue temperature and blood flow is to immerse the part into a hot whirlpool bath. Paraffin wax baths also produce surface heat.

Concentration of penetrating heat waves in a local area is obtained by electrically or electronically directed machines such as short-wave diathermy, micro-therm and ultra-sonic waves. Short-wave diathermy uses the body as a filament where heat is created in the electric field. The conditions treated are bursitis (frozen shoulder), pelvic inflammatory disease, myositis, fibrositis, low back pain, spasm and pain of cervical muscles. Micro-therm can produce penetrating temperature elevations up to 8°C in its electromagnetic field. It must be applied with caution to bony and edematous areas, and is contra-indicated in ischemic areas. Ultra-sound generated heat can increase blood flow in soft tissues, periosteum and bone by dispersing energy from sound waves. Pregnancy, malignancy and nerve tissue disallow its use.

Heat improves circulation, relieves painful spasm and aids relaxation, which in turn improves free joint movement. Heat is given only if sensation is normal and if it provides relief. Care must be taken to avoid burns and shocks.

#### Cold

The same principles hold in the application of cold to an area. One indication for the use of cold is immediately following injury. Ice or ice water can be applied by a towel or whirlpool bath to the injury. Frostbite and phlebitis must be avoided. Cold may be used in rheumatoid arthritis, fibrositis and in some spastic conditions.

#### Ultra-Violet Light

Ultra-violet light is used as a general tonic for debilitated patients. It may steri-



lize a wound by killing bacteria. Dermatological uses include treatment of psoriasis and pityriasis rosea, and diagnosis of such skin lesions as ringworm. Its vitamin D-producing properties are indicated by its use in the treatment of rickets.

### Splints and Prostheses

Splints are used to prevent deformity, to stabilize a joint, and to give a feeling of security.

There are two types of splints, orthotic and therapeutic. Orthotic splints allow and aid some function, i.e. they are working splints, permitting rest and work at the same time. Therapeutic or resting splints are used in treatment by immobilization. A splint should allow for adjustments to maintain proper positioning, as muscles tend to relax.

Orthotic splints include long leg splints for flail limbs, and ischial weight-bearing splints. The drop foot splint may have one standard bar on each side of the leg or two standards if no position sense is present. It stretches the Achilles tendon and maintains the foot at a right angle to the leg to compensate for the lack of dorsiflexion. A hand splint is used to support the paretic hand. The paretic arm is supported by a sling which assists balance and may prevent the shoulder-hand syndrome.

Therapeutic splints are usually made of plaster of Paris and are used in the immobilization of painful rheumatoid arthritic joints. For peripheral nerve injuries "lively" splints, i.e. spring loaded, of metal are prescribed.

Crutches and canes, properly fitted, give support and balance, and allow a patient with decreased lower limb function to exercise and carry out tasks of daily living. Crutch tops should rest against the chest wall, not the axilla. The patient is taught to support body weight through the hands. Canes and hand grips of crutches should come to wristwatch

level. Walkers are useful in the patient's re-learning to walk with or without prostheses.

The proper wheel chair prescription and hydraulic lift aids also help the patient's adjustment to daily living.

Another important field of physical medicine is that of prosthetics. Artificial limbs for amputees, cosmetic devices such as glass eyes and plastic ears, and built-up shoes for rheumatoid arthritics may need to be provided.

Before hospital discharge it may be necessary to instruct the patient's family in continuation of exercises and use of prostheses at home.

### Massage

Massage is a time-honoured therapy. The physiological effects ascribed to it are not proven. These simulate muscle action and include an increased circulation and supply of blood and lymph and exchange of body fluids; and so theoretically influence the heart, lungs and brain.

Massage provides local heat by friction and analgesia by an unknown mechanism in soft tissue injuries. It is employed as a mobilization technique, that is, in conjunction with splints to release points and fibrous tissues.

Peripheral Compression Units are now employed for massage. Positive squeezing pressure by the circulator cuff can be applied to the limbs for the relief of edema and restoration of circulation, as, for example, in post-mastectomy cases. Percussion devices are used for regeneration and arborization of nerve fibers. Here pain thresholds may be raised by repeated minor trauma. This phenomenon is utilized when scars are concussed to decrease hyperaesthesia or when an amputation stump is tapped to prevent phantom limb pain. Mechanical vibrators also cause a traumatic analgesia and are used following cases of herpes zoster. Pressure sores are prevented by the use of special mat-



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tresses in which the air pressure is alternated, so creating an air circulation. The whirlpool bath also effects massage through water pressure.

Although massage to normal tissue may be valueless, properly applied massage in the proper spot results in marked improvement.

### Manipulation

Throughout the ages, joint manipulation has been a most controversial subject. John Hunter taught that joint trauma caused adhesion formation and that after a sufficient period of rest, mobility must be promoted by gradually increasing movement. He insisted, however, that nothing was more likely to cause joint contracture than premature movement. For years, distrust of manipulation was evident. One hundred years ago Sir James Paget re-assessed the possibilities of manipulation. Today, active movement following injury is universally accepted, although forced manipulation under anesthetic is still a subject of contention.

Manipulation is a stretching process designed to obtain the full range of movement of a part. It is not a reduction of a subluxation, nor is it the replacing of a slipped disc. It may achieve pain relief by the reduction of spasm in muscles and soft tissue.

One of the best known techniques is the "pump handle" manipulation. The patient is placed on his side, upper hip flexed with the knee resting on the table, and lower hip extended. The operator stands facing the patient, and after rotating the upper shoulder away from himself with one hand, applies pressure to the rim of the pelvis and rotates it toward himself with his other hand. The zygapophysial joints on the side that is uppermost are thus manipulated. The maneuver is repeated with the patient lying on the opposite side. There are also alternate methods which can be used.

Manipulation may be used with or without anesthesia. The surgeon usually uses anesthesia in manipulations of the shoulders, back and knees. Physiatry concerns itself with manipulation in soft tissue injuries without the use of anesthesia. Manipulation is contraindicated in any neurological pathology.

Stretching is a therapeutic manipulation used in the lengthening of contracted structures such as muscle, ligaments, connective tissue and skin. These may have been pathologically shortened by fibrosis due to trauma, infection, ischemia, edema, muscular dystrophy and by restricted mobility due to any cause. In soft tissues, contractures result from fibrosis of elastic and/or fibrous tissue. Prevention of contractures or inhibition of their progress is accomplished by passive, active assisted and active stretching, preceded by local heat. Serial plaster stretch splints, by which a uniformly exerted pressure is achieved, are also used.

### Traction

In applying traction to a body the following conditions must be considered: the intensity and direction of the applied force; the state of motion or rest of the body; the shape and texture of the body and the surface on which it rests. A force in excess of that needed to overcome the friction of the parts is necessary if traction to the recumbent human body is to be effective. A weight of 6 to 18 lbs. is applied commonly to the neck in flexion, but more may be necessary.

Traction is used to make the patient comfortable and to eliminate pain by immobilization, elimination of muscle spasm, and separation of bony surfaces. It may be continuous, sustained, or intermittent, and may be applied in vertical or horizontal planes.

Cervical spine traction can be achieved manually with or without a halter and pulley system or by mechanical devices. Manual traction is not effective on the



lumbar spine. Here the weight and pulley system or a traction table achieves the best results.

Clinically, cervical traction is used to stretch muscles and ligaments, and the whole or a segment of the spine. All painful conditions of the back and neck do not indicate its use. Traction is indicated when symptoms arise from pressure on nerve roots as in spondylosis, disc degeneration and prolapse, osteoarthritic conditions, torticollis and cervical spine injuries such as "whiplash". Contraindications include spinal infections such as osteomyelitis, tuberculosis, osteoporosis, malignancies, cord pressure, hypertension, diseases of the cardiovascular system, rheumatoid arthritis, pregnancy, and old age.

### Electrodiagnosis

Electrodiagnosis is another field of physical medicine. It tests the reaction of degeneration (R.D.) of damaged muscles and nerves when stimulated by a tetanizing current. A failure to contract in response to short duration current means there is no longer muscle innervation due to a lower motor neuron lesion. R.D. absence signifies an intact peripheral motor nerve. A partial reaction of degeneration (P.R.D.) may exist.

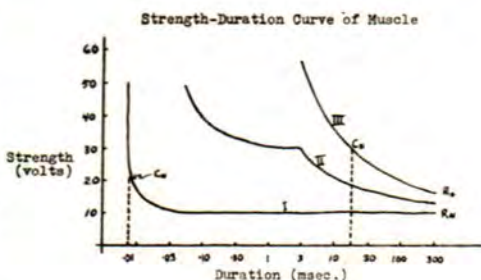
The required current strength depends on the specific nerve or muscle structure and on several associated conditions such as age, skin resistance, subcutaneous fat and edema. Higher voltage is needed for deep muscles than for superficial ones. The application of electricity may be quantitative and qualitative. Qualitative application is fast and simple and employs the continuous (direct, galvanic) current or the alternating (tetanizing, faradic or sinusoidal) current. Faradic current, that is, short duration current, stimulates nerve; and galvanic current, that is, long duration, stimulates muscle tissue. The excitability characteristics of a tissue are revealed by the Strength-Duration Curve (S.-D.C.) A typical nerve response means

a normal innervation but a typical muscle response means denervation is present. The shape of the curve indicates the amount of denervation, and thus the ratio of innervated to denervated fibers. The use of the S.-D.C. is limited to superficial fibers only. However, peripheral nerve regeneration of deep fibers may be assessed by electromyography. The actual lesion site is located by electromyography alone.

A nerve conduction test is carried out firstly, to see if conduction is possible and to determine which muscles are innervated, secondly, to locate the areas of block as in neuropraxia, and thirdly, to discover any innervation anomalies.

The greatest field of use of the S.-D.C. is as an aid in diagnosis and prognosis of peripheral nerve lesions. The S.-D.C. should be a part of the routine physical examination. It should also be a factor in the assessment of prognosis, in such diseases as poliomyelitis, facial palsy, myopathies, and peripheral neuritis. Improvement seen by the S.-D.C. precedes clinical recovery.

The figure below shows the S.-D.C. of normal, partially innervated, and completely denervated muscle. The rheobase is the least amount of current which when applied for an infinite duration will cause minimal contraction. The chronaxie is the time required for minimal contraction when a current of twice the rheobase is applied.





R<sub>N</sub>— Normal Rheobase 10V

C<sub>N</sub>— Normal Chronaxie < .01 mSec

R<sub>D</sub>— Denervated Rheobase 15V

C<sub>D</sub>— Denervated Chronaxie 20 mSec

- I— Normal. A complete innervation of the muscle.
- II— Abnormal. A partial innervation of the muscle. This curve is typical of a regeneration process.
- III— Abnormal. A complete denervation of the muscle. This curve is typical of a complete nerve lesion.

### Electromyography

Electromyography may be defined as the recording and study of the intrinsic electrical properties of skeletal muscles. The machine consists of electrodes, a pre-amplifier, an amplifier, a calibrator and a recording apparatus. It is similar to an electrocardiograph.

The normal skeletal muscle at rest produces an undisturbed isoelectric base line or "electrical silence". During a contraction requiring minimal effort, a single motor unit discharge can be studied. With increased contraction and muscle tension the many motor units involved produce an asynchronous discharge. With maximum tension, there is both temporal and spatial summation of the motor units and an irregular electrical pattern occurs. Isotonic and isometric contractions can be differentiated.

Electromyographic examination is used in C.N.S. diseases like poliomyelitis, amyotrophic lateral sclerosis and syringomyelia. Extent of peripheral nerve degeneration and regeneration may also be determined. A peripheral lesion can be distinguished from a plexus or root lesion. Changes in duration, form and amplitude of the motor unit, as well as pattern changes, will identify a myopathy, that is, a primary muscle disorder, such as myasthenia gravis, myotonia and muscular dystrophy.

In 1958, A. D. McLachlin and J. A. McLachlin<sup>6</sup> produced electrical muscle contraction to stimulate walking during surgical procedures. Recently research projects in rheumatoid arthritis and spastic conditions have employed electromyography.

Kinesiology is the study of movements of the body. Electromyography is used to study muscle actions in patterns of voluntary movement, contra-lateral function, and the role of the muscle as a prime mover, synergist, stabilizer, accessory mover, antagonist and co-contractor.

### Speech pathology

Another aspect of physical medicine concerns the diagnosis and treatment of disorders of communication and auditory incapacities. In recent years there has been an increase in the incidence of brain damage, hearing problems, and multiple handicaps due to an increased defective infant survival rate. Differential diagnosis in these areas is difficult and requires continuous evaluation and prolonged observation by a team of specialists. Individualized therapy must follow the team diagnosis. The Children's Psychiatric Research Institute in London, Ontario, provides service in diagnosis, treatment, research, and placement of mentally retarded or emotionally disturbed children with varying types of coincidental speech problems.

### CONCLUSION

The scientific application of the proper physical therapy during convalescence aids immeasurably in the rehabilitation program. The hospital or rehabilitation center, family and patient must all co-operate to achieve as complete a restoration as possible for the patient. The days saved in convalescence may be spent in useful productivity in society.

The author wishes to thank the following for their help in the preparation of this paper: Charles M. Godfrey, M.D., D. of Phys. Med.,



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M.C.P.A., Clinical Teacher, Division of Rehabilitation Medicine, Faculty of Medicine, University of Toronto, Mrs. V. D. Evans, M.C.P.A., Supervisor, Department of Physical Medicine, and her staff, Toronto East General Hospital, Toronto, Ontario, and Miss M. I. Miller, M.C.P.A., Charge Physiotherapist, Department of Physiotherapy, and her staff, Victoria Hospital, London, Ontario.

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# Hemiplegia with Abdominal Pain and Vomiting

## Discussion of a Case

T. BEKELE

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A sixty-eight year old Polish housewife was admitted to hospital with a left-sided hemiplegia on the evening of April 8th, 1963.

She was apparently in good health until the afternoon of the day of admission when she had a sudden onset of paralysis of the left arm and left leg with some transient dizziness and difficulty with vision. She claimed that she fell on the floor and was unable to get up. Her speech was

slurred and difficult to understand. She did not lose consciousness or experience headache. She denied any trauma or any previous similar episode. Past history of hypertension or rheumatic fever was also denied. Family history was not remarkable.

Several years before she had a cholecystotomy followed by cholecystectomy and appendectomy. Five years prior to admission the patient was admitted to another hospital with an acute abdomen which



required a laparotomy. A diagnosis of chronic recurrent pancreatitis was entertained. She was treated symptomatically. Two years later she was readmitted with another episode of abdominal pain associated with vomiting. On that occasion her hospital course was complicated by pulmonary embolism and right-sided heart failure. She developed coarse auricular fibrillation. She was managed conservatively and discharged without any digitalis medication and was advised to report regularly to the Out Patient's Clinic. She remained in good health for the following two years until her present complaint of left-sided hemiplegia.

Physical examination revealed a mildly obese woman who appeared to be bright, alert and well oriented. The pulse was 78 and irregular; the blood pressure was 110 systolic and 80 diastolic. Her temperature was 98°F. The pupils reacted equally to light and accommodation. The fundi showed narrowed arterioles but no hemorrhages, exudates or papilledema. The carotid pulsations were equal bilaterally and there were no bruits over the carotid arteries, eyes or skull. The chest revealed a few basal rales bilaterally. The heart was not enlarged. The rhythm was irregular, consistent with auricular fibrillation. There were no murmurs. Examination of the abdomen showed three right-sided scars but no masses or areas of tenderness. The spleen and liver were not palpable. There was a very slight edema of the left lower leg and the pedal pulses were good bilaterally.

Neurological examination revealed a left lower facial weakness with a left homonymous hemianopsia. There was no nystagmus. The tongue was deviated slightly to the left. There was a left hemihyesthesia including the left side of the face as well as a left sensory deficit. Vibration sense was intact bilaterally. The left arm showed complete flaccid paralysis, while a fair power was retained in all muscle groups in the left leg. Muscle tone in the left leg was slightly increased. Tendon reflexes were

increased in the left arm and left leg. Both plantar responses were flexor.

Urinalysis showed a specific gravity of 1.021, a pH of 7 with a trace of protein. It was negative for sugar and acetone. The sediment contained 40 to 50 pus cells and 20 to 30 red blood cells per high power field. There was gross bacteria but no casts. The hemoglobin was 14.8 grams and the white cell count was 8100 with 87 per cent neutrophils, 12 per cent lymphocytes and 1 per cent monocytes. Platelets were plentiful. The sedimentation rate was 25. The urea nitrogen was 16 mg. per 100 ml., the fasting and post prandial sugars were 88 and 115 mg. per 100 ml. respectively. X-ray of the chest revealed fluid at the left base. The heart appeared to be slightly enlarged. Skull x-ray showed no abnormalities. An ECG revealed auricular fibrillation with a slight right bundle branch defect. The spinal fluid showed no increase in cells. The glucose was 80 mg. per cent and the protein was 75 mg. per cent. Colloidal gold, VDRL and the Kolmer Wasserman were all non-reactive.

Initially she was kept on complete bed rest and maintained on digitalis therapy. Soon after her entry to hospital physiotherapy was instituted and she regained some power in her left leg but remained completely paralyzed in the left arm.

On the fifty-fifth hospital day, her clinical condition was much improved, except for intractable symptoms of digitalis intoxication which had started a few days earlier. The drug was discontinued temporarily. Five days later she complained of upper abdominal pain and vomiting. The pain was described as sharp on one occasion and crampy on another. It was steady and continuous, and did not radiate to any specific area. She did not appear jaundiced. An upper gastrointestinal series at this time revealed a small hiatus hernia but no other abnormalities of the esophagus, stomach or duodenum. An oral cholecystography revealed no function. An intravenous cholangiogram failed to dem-



onstrate the biliary tree. A laparotomy was planned but was cancelled as the patient developed hypotension on the administration of the anesthetic. Following this she showed gradual improvement.

For the subsequent weeks she complained of recurrent epigastric pain and appeared acutely ill. On the eighteenth day, the blood pressure was 120 systolic and 70 diastolic. Examination during this time revealed a minimally distended abdomen with some tenderness in the epigastric and left lower quadrant regions. The hemoglobin was 15.8 grams with a hematocrit of 54 per cent. The white cell count was 14000 with 83 per cent neutrophils, 8 per cent lymphocytes and 9 per cent monocytes with a normal platelet count. The reticulocyte count was 0.9. The bilirubin was 2.9 mg. per 100 ml. with 0.3 direct. The urea nitrogen was 31 mg. per 100 ml. The alkaline phosphatase was 3.0 sigma units per ml. The thymol flocculation and cephalin cholesterol flocculation were described as 1 plus and 2 plus, respectively. The serum amylase and the SGOT were 85 and 22 units per ml. respectively. The sodium was 128, chloride 86, and potassium 3.5 m.Eq. per litre. The  $\text{Co}_2$  combining power was 23 mEq. per litre. Urine culture grew a heavy growth of *E. coli.* and the stool was positive for occult blood. X-ray of the abdomen showed distended gas filled loops of small bowel, cecum, ascending and transverse colons, but the distal colon was free of gas. An electrocardiogram showed auricular fibrillation with a slow ventricular rate and no evidence of recent myocardial infarction.

On the eighty-fourth day, a laparotomy was being considered when the patient became confused and developed hypotension. For the next few weeks despite vigorous conservative management and continuous gastric suction, she became more confused, unco-operative and irrational. On the one hundred and second day, the patient was critically ill and continued to complain of severe epigastric and left lower quadrant pain. The blood pres-

sure was down to 80 systolic and 56 diastolic. The pulse was 96 and irregular. The temperature rose to 100.2°F. She became jaundiced. There were rales bilaterally. The abdomen became more distended and diffusely tender to palpation. Bowel sounds were diminished. For the next few days she required intermittent Aramine and continuous intravenous medications. On the one hundred and sixth day, she became very irrational, sweated profusely, developed laboured respiration, and expired.

## DISCUSSION

**J. Curtis:** In summary, this 68 year old woman had a past history of possible pancreatic disease, pulmonary embolism and atrial fibrillation. On admission she was affected with left-sided hemiplegia, dysphasia, left homonymous hemianopsia and transient vertigo. She had not lost consciousness or experienced headache. Atrial fibrillation was detected. Her hospital course showed some improvement but after two months she developed acute upper abdominal pain and vomiting. Improvement was gradual for three weeks, then the condition worsened — abdominal pain increased, hypotension supervened, she became irrational and died within three weeks of the beginning of the exacerbation.

**B. Williams:** Was there a palpable mass in the abdomen at any time and did her fundi show any definite arteriosclerotic changes?

**T. Bekele:** There was no palpable mass and her fundi showed narrowed arterioles but no other abnormality.

**M. Grace:** Was she ever in heart failure?

**T. Bekele:** She showed no obvious signs of heart failure at her present admission except for the bilateral rales she developed terminally.

**D. Reid:** Did she have any problem with her renal output?

**T. Bekele:** No. Mr. Grace, would you care to comment on the differential diagnosis



as you see it from the clinical side?

**M. Grace:** This patient presents three main features for diagnosis:

1. Hemiplegia
2. Atrial fibrillation
3. Severe recurrent epigastric pain.

Sudden hemiplegia, with preservation of consciousness, is usually due to cerebral embolism. The left atrium is a common source of emboli and this lady was apparently in atrial fibrillation. There is no history of a myocardial infarction and there are no physical findings of bacterial endocarditis.

Cerebral thrombosis is possible, but usually has a gradual onset, and is most common during a period of rest. This lady does not have findings often associated with atherosclerosis such as high blood pressure or peripheral vascular disease. Thus thrombosis does not seem as likely as embolism.

Cerebral hemorrhage can be ruled out because it gives rapid loss of consciousness and is usually associated with hypertension.

The obstructed vessel is probably the right middle cerebral artery since the most marked paralysis affects the left arm, and the left side of the face and tongue. Left sided sensory loss and left homonymous hemianopsia are often associated with obstruction of this artery. The atrial fibrillation is probably due to senile heart disease with atherosclerosis. There is no apical murmur to suggest mitral stenosis and there is no history of rheumatic fever. This fibrillation is not due to hypertension. Thyrotoxicosis can produce atrial fibrillation in the elderly with few other clinical manifestations and is a slight possibility here.

The persistent epigastric pain could be due to many conditions. The patient has a history of gall bladder disease and chronic pancreatitis was diagnosed at the later laparotomy. Thus chronic re-

lapsing pancreatitis is a distinct possibility as the cause of her pain. Her symptoms may have been due to intermittent small bowel obstruction, perhaps due to adhesions. Stones in the common bile duct could give this type of pain, but there is usually intermittent jaundice, and often fever. Further attacks of cholecystitis could occur if Hartmann's pouch was not removed at laparotomy.

Impairment of blood supply through the superior mesenteric artery is also possible. An embolus would probably produce a more acute picture than was seen here, but gradual thrombosis of an atherosclerotic superior mesenteric artery could produce this type of pain and might be associated with epigastric tenderness. Other causes such as peptic ulcer or peritonitis cannot be ruled out entirely.

There is also the possibility that various symptoms of this lady are associated with one of the collagen diseases such as lupus erythematosus or polyarteritis nodosa.

**T. Bekele:** Is there such a condition as mitral stenosis without a murmur?

**M. Grace:** Yes, early mitral stenosis may give no murmur at all, except perhaps after exercise. In late cases the presystolic part of the murmur disappears with atrial fibrillation. The rest of the diastolic murmur may be very faint, even absent because of poor blood flow through the stenotic mitral valve.

**J. Curtis:** Could cerebral thrombosis or a sudden hemorrhage, perhaps from a berry aneurysm, produce these neurological manifestations?

**M. Grace:** Thrombosis of the middle cerebral artery could certainly produce this clinical picture but it would be unusual for thrombosis to occur so rapidly without preceding symptoms of cerebral ischemia.

Cerebral hemorrhage usually occurs suddenly and may produce many neurological symptoms. It usually produces



unconsciousness or severe headache and is associated with hypertension. This patient does not fit this picture. A ruptured aneurysm produces severe headache and a stiff neck, and usually does not give lateralizing neurological signs. However hemiparesis can follow rupture of an aneurysm at the bifurcation of the middle cerebral artery.

**T. Bekele:** Perhaps Mr. J. Henderson would comment on the laboratory findings and add other diagnostic possibilities.

**J. Henderson:** A consideration of laboratory and radiological findings suggests some additional diagnostic possibilities which might not be apparent from clinical examination alone.

There appears to be some evidence of urinary tract disease. Findings to suggest this include an elevated urinary pH, proteinuria, the presence of pus cells and red cells in the urine, and the rise in urea nitrogen levels from 16 mg. per cent on admission to 31 mg. per cent a month prior to death. The manner of the patient's demise is certainly compatible with death in uremia, and it is likely that the urea nitrogen levels continued to rise up to the time of death. The increasing leukocytosis, together with evidence of urinary tract disease, would lead one to consider the possibility of urinary tract infection (perhaps with intestinal obstruction on the basis of reflex paralytic ileus), however a renal tract malignancy is not out of the question.

It seems a little unlikely that the persistent and rather severe upper abdominal and left lower quadrant pain which this patient complained of could be accounted for on the basis of kidney infection or on the basis of a small hiatus hernia demonstrated on x-ray. In this connection one might consider chronic pancreatitis, pancreatic malignancy, or disease of the bowel, either carcinoma or diverticulitis. The question of chronic pancreatitis has been discussed previous-

ly. In support of carcinoma of the pancreas are a history of some duration of upper abdominal pain and distress, a gradually rising serum bilirubin with terminal clinical jaundice, some evidence compatible with thrombotic tendency (cerebral and pulmonary embolism, possible mesenteric infarction), and hepatic function tests compatible with hepatic metastases. Findings to support the diagnosis of bowel malignancy include a history of abdominal pain and distress, clinical and radiological evidence of a distal bowel obstruction (perhaps in the transverse colon), a positive stool test for occult blood, a slightly elevated ESR, and findings compatible with hepatic or even cerebral metastases.

It is reasonable and plausible to believe that the atrial fibrillation, abdominal pain, and hemiplegia are not all three inter-related. Yet it is tempting to try to associate them. Certainly this patient could have suffered a cerebral embolism secondary to atrial fibrillation and a thrombus in the left atrium. One might consider also a pancreatic neoplasm with hepatic (and perhaps cerebral) metastases and a thrombotic tendency. The sudden onset of hemiplegia could be due to hemorrhage into or around a metastatic brain tumor. The abdominal pain, perhaps most readily explained on the basis of chronic pancreatitis, could also be caused by pancreatic or bowel malignancy with extension to contiguous structures or to mesenteric artery disease with terminal occlusion by an embolus or thrombus. It is conceivable that the right bundle branch block demonstrated on ECG (perhaps also the atrial fibrillation) might be brought about by a small septal malignant metastasis.

In summary, then, I would like to add to Mr. Grace's discussion the possibilities of renal infection with death in uremia, and bowel or pancreatic neoplasm with hepatic and perhaps more widespread metastases.

**D. Reid:** How significant is the presence of red blood cells in the urine?



**J. Henderson:** Hematuria is practically never an innocent finding. It is produced by some lesion in the urinary tract, however insignificant that lesion may occasionally be, and we should not dismiss this finding until we have good grounds for believing it does not betray a lesion contributing to this patient's clinical condition.

**T. Bekele:** How much importance do you attach to the presence of pus cells in a partially paralyzed bedridden elderly patient?

**J. Henderson:** To me, pyuria signifies inflammation in the urinary tract. This may vary from an acute fulminating pyelonephritis or large areas of tumor inflammation and necrosis in let's say a hypernephroma to little areas of non-specific irritation in the urinary tract mucosa. As I recall there were 40 to 50 pus cells per high power field. In answer to your question I would simply like to make the observation that "partially paralyzed bedridden elderly patients" are perhaps more prone than most of us to suffer urinary infection of any type, and I certainly do not think the finding of pyuria may be rightly dismissed as of no importance.

**M. Grace:** How frequently do you see cerebral metastases from carcinoma of the colon or pancreas?

**J. Henderson:** Blood born metastases are common in the later stages of both these diseases. I do not know off hand what the incidence of cerebral metastases would be.

**T. Bekele:** Mr. Don Reid, do you care to make a diagnosis?

**D. Reid:** This lady likely threw off an embolus from her left auricle to her right middle cerebral artery. She was predisposed to this on account of her auricular fibrillation. I assume that her fibrillation could be accounted for on the basis of arteriosclerotic heart disease as there is no history of rheumatic heart disease nor was the murmur of mitral

stenosis heard. Her fibrillation would also predispose her to throw off small emboli to the superior mesenteric artery, thus explaining some of her abdominal findings.

Her urinary examination would suggest the possibility of a urinary tract infection, perhaps a cystitis or a pyelonephritis. However if these urines were not catheter specimens the pus cells could be due to contamination.

Her upper abdominal pain could be on the basis of obstruction to her common bile duct. However she had an elevated indirect bilirubin which is not suggestive of obstructive disease. The obstruction, if present, could be either extra-ductal, intramural or intraductal, and either benign or malignant. However, her low sedimentation rate, high hemoglobin and prolonged course suggest a benign process.

Therefore I consider this patient to have had: left hemiplegia from embolism from the left side of the heart (predisposed by atrial fibrillation); repeated emboli to her superior mesenteric artery; mild urinary tract infection; and a stone in her common duct.

**M. Grace:** Is superior mesenteric artery emboli compatible with such a long history of abdominal pain?

**D. Reid:** Superior mesenteric artery emboli could produce such a long history of abdominal pain if the embolic attacks were of such a nature that the emboli only partially occluded the mesenteric vessels or if the emboli repeatedly landed in small divisions of the vessel.

**T. Bekele:** Did the digitalis withdrawal precipitate her abdominal pain or do you think it was incidental?

**D. Reid:** Withdrawal of digitalis therapy probably did not precipitate her to throw off more emboli, so therefore this would probably be unrelated to her abdominal pain. Reinstitution of the digitalis, making the heart more efficient, could conceivably increase her risk of embolization.



**T. Bekele:** I would like to know if Mr. Williams agrees with the rest of the discussants?

**B. Williams:** We all seem agreed that this woman's presenting complaint was due to a cerebro-vascular accident and it fits the four criteria of a stroke very well, i.e. sudden in onset, culminating rapidly, gradual recovery and may be localized anatomically.

Similarly we agree that the CVA was most likely due to embolism of a mural thrombus within the fibrillating left atria. The commonest causes of atrial fibrillation, as discussed by Mr. Grace, are mitral stenosis, thyrotoxicosis and senile heart disease. This patient obviously qualifies for the latter category. Bundle branch block is a decidedly less common arrhythmia and I was hoping for a clue to the diagnosis in this light. Unfortunately, of the fifteen causes of bundle branch block listed in Cecil & Loeb, the commonest causes are arteriosclerotic heart disease and hypertensive heart disease with senile heart disease running a close third. Nevertheless, to pursue this line of thought further, of the remaining twelve causes only two are possibilities in this case. One is bundle branch block as a fatigue manifestation of tachycardia, but I believe that tachycardia was not a prominent feature of this case. The remaining possibility is, "acute myocarditis of obscure origin associated with cardiac enlargement, heart failure and embolic phenomenon". This entity is admittedly rare, but since the more common possibilities have been discussed by the panel, I feel justified in tracking down a "canary".

This woman did show cardiac enlargement on x-ray, was possibly in some heart failure and demonstrated embolic phenomenon to her brain and probably to her superior mesenteric artery. Almost any acute infectious disease process may cause inflammation of the myocardium but clinically significant findings are rare and usually only associated with four conditions—rheumatic fever, diph-

theria, scrub typhus and collagen diseases. The clinical picture does not seem compatible with the first three, but may be with the fourth.

Time and space do not permit a complete discussion of the collagenoses, and at any rate their manifestations commonly overlap. Eighty-five per cent of cases of systemic lupus erythematosus occur in women, mostly between fifteen and forty years but may occur at any age. In its favour in this case is its usual slow course with acute exacerbations and long remissions; it may precipitate attacks of abdominal pain simulating a surgical acute abdomen; it may produce a scattered glomerulitis manifesting as microscopic hematuria and proteinuria; it may produce acute pancreatitis; it may be associated with visceral or peripheral thrombosis and embolism, and it may produce a pleural effusion. Against its existence in this case is the lack of joint manifestations, a low sedimentation rate, and the absence of pericarditis. The typical malar butterfly-rash is not required to make the diagnosis of SLE and it may never appear even in fatal cases. Although SLE may produce a hemiplegia, I do not believe that it was the direct cause in this case. Periarteritis nodosa, which affects the larger arterioles, is also a possibility, but it is more common in men.

In summary, I believe this woman's difficulties were due to multiple embolic phenomenon from a fibrillating left atria, and that the explanation for the cardiac arrhythmias is an underlying relatively quiescent collagen disease. Therefore my diagnosis is atrial fibrillation with right bundle branch block and left atrial mural thrombi with the possibility of an associated acute myocarditis, an embolism of the right middle cerebral artery, an embolism of the superior mesenteric artery, and a collagen disease, possibly systemic lupus erythematosus.

**T. Bekele:** It seems to me that when one suspects the possibility of a "chronic"



collagen disease, some degree of clinical manifestation referable to the lung or to the kidney would be evident. This woman had no cough, hemoptysis or hypertension. Though she had a few red cells in the urine her renal output was good. Don't you think we can safely rule out the presence of any of the collagen diseases?

**B. Williams:** Regarding hypertension in collagen diseases, clinical manifestations of heart disease in rheumatoid arthritis has only been described recently and is rare. Similarly hypertension is not a feature of rheumatic fever or of dermatomyositis. Polyarteritis and scleroderma usually demonstrate hypertension when renal damage is marked. Significant hypertension occurs in less than 20% of cases of SLE and even patients with marked renal impairment are often normotensive. This may be of value in differentiating SLE from other causes of chronic renal failure.

Renal manifestations of the collagen diseases vary tremendously. In rheumatoid arthritis, clinical involvement is uncommon though diffuse proliferative glomerulitis has been described. Urinalysis in rheumatic fever is usually normal though traces of albumin and microscopic hematuria may be present. (At the opposite extreme, involvement in Goodpasture's syndrome and Wegener's granulomatosis is fulminant and fatal). In periarteritis, multiple infarcts are the rule though damage is not usually extensive enough to produce renal failure. Scleroderma has no clinical evidence of glomerulitis except terminally or in a very few cases in which renal failure develops abruptly with resultant death. In SLE, the kidneys are frequently attacked and most patients show at least microscopic hematuria and proteinuria, as was seen in this case. Early, the kidney may be the only organ involved and in severe cases it may manifest as either acute nephritis or the nephrotic syndrome. In SLE the renal component is of major importance because it may be

refractory to steroids and is a principal cause of death.

Lung lesions are not a feature of rheumatoid arthritis. Interstitial pneumonia and hemorrhage may be seen in rheumatic fever and pleurisy is usually present in severe cases. Involvement of the lung in dermatomyositis and periarteritis is unusual although in the granulomatous angiitis variant (Wegener's granulomatosis) of periarteritis it is the predominant feature. Scleroderma commonly manifests with bilateral rales at the lung bases, as was described in this case. At least 75% of cases show nodularity or linear streaking on chest x-ray. Finally, in SLE pleuritis and effusion with a patchy, migrating lobular pneumonia are frequently seen. The simultaneous appearance of pleural and subpleural involvement should lead the radiologist to suspect SLE.

**T. Bekele:** Mr. Curtis, could you comment on the final cause of death?

**J. Curtis:** I think the prime cause of death was shock. Toward the end, she became irrational (which often occurs in elderly people before shock is manifest), hypotensive, and terminally she sweated profusely and was dyspneic. Shock may be interpreted as due to bowel infarction, leading to peritonitis, extensive fluid and blood loss into the bowel lumen, bowel wall and peritoneal cavity. Thus, the shock would be a combination of neurogenic and hypovolemic shock with or without septic shock. In addition, it is probable that terminal bronchopneumonia was a contributing factor.

**T. Bekele:** Thank you, gentlemen.

The clinical and anatomical diagnosis are as follows:

#### Clinical Diagnosis:

1. Arteriosclerotic heart disease with chronic auricular fibrillation
2. Cerebral thrombosis—embolic
3. Mesenteric thrombosis—embolic
4. Generalized peritonitis
5. Terminal bronchopneumonia



**Anatomical Diagnosis:**

1. Chronic rheumatic endocarditis with mitral stenosis (severe) and tricuspid stenosis.
2. Left atrial thrombosis.
3. Cerebral embolism and infarction
4. Superior mesenteric artery embolism with infarction of the small intestine.
5. Generalized peritonitis.
6. Chronic passive congestion of liver and spleen.
7. Old embolic infarcts of kidneys.

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## Book Review

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**Review of Medical Physiology:** by William F. Ganong, Lange Medical Publications, Los Altos, California, 1963. \$6.50.

Lange publications have just recently come out with this new book in their "Review" series. It is an excellent companion in the physiology laboratory, and is a quick reference for any physiological information.

Its value lies in its lucid presentation and conciseness. Although it should not replace a text on the subject of physiology, the student will find it beneficial in areas where any text is apt to cause confusion. After reading through the appropriate section in this book he is better able to return to the text and derive more benefit therefrom. It should be remembered that it is a review of the subject and therefore cannot replace the more detailed authority.

Its organization is straightforward, and its section headings help the student greatly in acquiring an overall integrated picture of the situation. All sections are excellently denoted with diagrams, detailed drawings, and photographs.

The first chapters are concerned with general physiological properties of nerve and muscle, while the later ones deal with the physiological functions of the body in particular. The sections on "Endocrinology and Metabolism" and "The Nervous System" are especially noteworthy.

Unfortunately a bibliography is lacking which is helpful to any interested student. Otherwise, this is a fine book and a functional asset to anyone's medical library.

Richard E. Moloy

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## Student Research

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### PITUITARY TUMORIGENESIS IN MICE

Subcutaneous transplants of pituitary glands cause pseudopregnancy-like cycles and stimulate mammary growth and lactation due to increased secretion of prolactin (LTH). These transplants often develop into tumors (acidophile adeno-

mas) under such conditions. The pituitaries probably become tumors because of one main reason, the removal of hypothalamic control. Experiments have been and are being done at present to investigate hypothalamic control of the pituitary gland and the relation of this control to the occurrence of pituitary tumors. Montemurro



and Gardner have shown that hypothalamic tissue transplanted subcutaneously with a pituitary gland inhibits the growth of the gland and its secretion of LTH. Nervous tissue does not transplant successfully and therefore, Dr. Montemurro decided to transplant pituitaries into the brain at various sites. Whole glands were transplanted into the cortex, thalamus, and hypothalamus of C57B1. mice. Control mice received transplants of liver or submaxillary gland. The estrous cycles of the mice were studied in an attempt to determine any hormonal activity of the transplant. Mice with pituitary glands transplanted in the hypothalamus showed minimal alteration in their estrous cycles. Mice with pituitaries in the cortex or thalamus had a high incidence of pseudopregnancy-like cycles indicative of LTH secretion by the transplant. Mice with liver in the hypothalamus showed cycles with prolonged estrous. This experiment is to continue for another six months at which time the animals will be autopsied and data will be gathered on the incidence of pituitary tumors and the histology of target organs and the transplants and in situ pituitaries. It is expected that pituitary glands in the hypothalamus will show a lower incidence of tumors because of the hypothalamic control.

Donald J. Wigle, Meds. '66  
Cancer Research Laboratory,  
Summer of 1963.

## EFFECTS OF STIMULATION OF THE HYPOTHALMUS ON HEAT LOSS IN THE RAT

Man, in common with other mammals and with birds, is able to maintain a constant body core temperature in spite of wide variations in environmental temperature. Regulation of body temperature within the narrow limits compatible with life is fundamentally a function of the hypothalamus, which maintains a balance between the various factors influencing heat gain and heat loss: "The hypothalamic temperature regulating system probably consists of a

heat loss center, whose activity is directed towards increasing heat loss and decreasing heat production, and a heat conservation center whose activity is directed towards decreasing heat loss and increasing heat production. The activity of these centers is largely governed by central and peripheral thermoreceptors.

Precise localization of the thermoregulatory centers has been attempted by various experimental techniques, e.g. electrical and thermal stimulation, electrical recording, and ablation. Such techniques have permitted localization of the heat loss center, in dogs, cats, goats, sheep and rabbits, to the preoptic region of the hypothalamus. A similar location for the heat loss center in rats has been postulated on the basis of ablation techniques alone. In our experiments, an attempt was made to confirm the location of the heat loss center in the rat, using electrical stimulation techniques. Tail skin temperature was used as an indicator of thermoregulatory center activity, since one of the most important mechanisms for controlling heat loss in the rat is by regulation of blood flow through the tail.

### Methods

Operative procedures were carried out using a Horsley-Clarke stereotaxic instrument. As a guide for positioning the electrode tip, the atlas of stereotaxic coordinates compiled by de Groat was used. Part of the frontal bone in the midline was removed, and a unipolar electrode, consisting of an insulated stainless steel wire, 0.01 inch diameter, bared at the tip for one mm., was lowered through the cerebral hemisphere on one side into the hypothalamus. An electric current was then applied for about two minutes, and the effect of this stimulus on tail skin temperature was recorded. The electrode was then removed, re-inserted into a new position, and the stimulus re-applied. Systematic exploration of the entire hypothalamus was carried out in this manner.

### Results

Stimulation in the preoptic and anterior hypothalamic areas produced no significant



changes in tail skin temperature. However, stimulation in the caudal hypothalamus (lateral mammillary region) resulted in a significant rise in tail skin temperature, which was reproducible in the same rat and in several different rats.

### Discussion

The electrical stimulations carried out in this experiment failed to confirm the presence of a temperature regulation center in the preoptic or anterior regions of the hypothalamus of the rat, despite the fact that derangement of temperature regulation can be produced by ablation in these areas. Heat loss mechanisms however, were activated by stimulation in the region normally considered, at least in other species, to be concerned with heat conservation. These results suggest that a heat loss center in the rat is located in the caudal hypothalamus, but the possibility must also be entertained that vasodilator fibres from a more rostral heat loss center were being stimulated, the center itself not being amenable to stimulation by the techniques used.

This work was supported by a grant from the Medical Research Council.

The author wishes to express his appreciation to Dr. J. A. F. Stevenon for freely making available the resources of the Department of Physiology, for his assistance in formulation of the problem, and for his general guidance throughout the course of the experiments. The encouragement and valued assistance of Dr. J. J. Seguin is gratefully acknowledged.

R. H. Hollands, '65,  
M.R.C. Undergraduate Scholar,  
Department of Physiology,  
Summer of 1963.

### CHANGES IN BODY TEMPERATURE OF CHILDREN DURING ANESTHESIA

During the months June to September I was engaged by Dr. Spoerel, head of the department of Anesthesia, to study the temperature changes during anesthesia of children 6 years and under. Our study was prompted by three cases in which rising temperature during the period of anesthesia endangered the life of the patients.

### Method and Equipment:

For the study, a multilead telethermometer was used and the following readings were recorded.

1. Rectal, 2. Skin, 3. Under the drapes, 4. Room, and 5. Esophageal temperatures when technically feasible. Readings were taken every ten minutes and recorded along with pertinent data of history, pre-operative temperatures, premedicants, anesthetic agents and techniques, the number of drapes and the degree of coverage by the drapes.

### Summary of Results:

107 cases were studied under the age of six years:

1. Influence of age: In very small infants the rectal temperature usually fell while over the age of one year a rise was generally observed. The average age of 56 cases who showed a rise in rectal temperature was 3.7 years. Eleven cases, average age of 3.4 years, showed no change in temperature. The average age of 38 cases who showed a fall in rectal temperature was 22.7 months.

2. The rate of change of rectal temperature in degrees C/hour was plotted against weight in kg./m<sup>2</sup> and a good correlation was obtained indicating that the heat production or retention is a function of the surface area and body mass. A child whose body mass is less than 17 kg./m<sup>2</sup> will likely experience a fall in body temperature while those above 25 kg./m<sup>2</sup> usually show a rise.

3. Room temperature and rectal temperature showed a good correlation. The group who experienced steady rectal temperatures was exposed to a room temperature of 24 to 25 degrees C. The majority of children who had surgery in a room of 23 degrees C. or less experienced a fall in rectal temperature; and the majority of those operated on in 26 degrees C. or above showed a rise in rectal temperature.

4. Duration of operation aggravates the rise or fall in rectal temperature and once the trend is established it will continue.



5. The average number of drapes employed was three to four and the air temperature under the drapes invariably rose 6-10 degrees C. This variation of course is influenced by such factors as room temperature, skin temperature, the number of layers of insulating drapes and the length of the operation.

6. At the end of every procedure the air temperature under the drapes and the skin temperature were approximately the same and this was very close to the rectal temperature.

7. A series of tonsillectomies were studied; of these 11 were not premedicated preoperatively and these were compared against a premedicated group.

	Atropine pre-op.	no atropine
Rectal rise	0.67 C./hr.	0.60 C./hr.
Skin rise	4.9 C./hr.	2.5 C./hr.

## SUMMARY:

The temperature changes associated with anesthesia and surgery have been studied in 107 children under the age of 6 years. The factors dominating these changes are the room temperature and the patients body mass in relation to the surface area. Other factors are the extent and thickness of surgical drapes, premedication and the duration of the procedure. In the cases studied no serious changes in body temperature were observed but in several cases, rate of change was sufficient that a prolongation of surgery and anesthesia may have led to catastrophe.

Ivan A. Hunter, Meds '65,  
Department of Anesthesia,  
Summer of 1963.

## News and Views

### THE JOSEPH P. KENNEDY, JR. FOUNDATION FOR MENTAL RETARDATION

The Joseph P. Kennedy, Jr. Foundation was established in 1946 by the wealthy Boston industrialist, Joseph P. Kennedy and his wife in honour of their eldest son, killed in action during World War II. The aim of the Foundation is "to discover the cause of mental retardation and seek ways of preventing this tragic and costly burden." To facilitate this purpose the Foundation supports fourteen institutions for the care and treatment of the retarded as well as providing financial support to major researchers in this field and awards for significant achievement. This does more than simply recognize significant research contributions, it serves to draw public attention to this great problem, attract young professional people to this once forgotten field and encourages civic and governmental organizations to

provide better care and training for the retarded.

The Foundation has donated generously to its award winners and research scholars in order that they may continue and expand their researches. The birth of a retarded child into their family undoubtedly stirred the original efforts of the Kennedys but later achievements have reinforced their original 'investment' into this poor 'market.'

The 1963 Joseph P. Kennedy, Jr. Foundation Symposium and Annual Awards Dinner was to be held in New York in early December of last year but the assassination of President John F. Kennedy forced their postponement until the fifth of February, 1964.

The University of Western Ontario's Dr. Murray L. Barr, Professor and Head of the Department of Microscopic Anatomy, was the recipient of a 1962 Kennedy Foundation Award for his dis-



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covery of sex chromatin and his later development of this important finding. It is interesting to note that, in many locations the sex chromatin particle is referred to as the 'Barr body' and yet the school of his origin has not yet paid him this honor.

At the most recent Symposium held February 5, 1964, twelve papers were presented on various phases in developments in the research and therapy of mental retardation.

Psychological aspects of mental retardation were discussed by Leonard E. Ross, Ph.D. and Samuel A. Kirk, Ph.D., the latter a 1962 Kennedy Award Winner. Ross, from the University of Wisconsin, compared the learning processes in normal and retarded children and dealt with conditioning situations in the retarded. He stressed that basic research into the problems of learning in the retarded has been overlooked largely and is one area that must be developed if we are to treat the retarded successfully in the future. Kirk, from the University of Illinois, and the author of a widely-employed book for parents of retarded children entitled, "You and Your Retarded Child", continued this theme of the psychological aspects of retardation. He stressed that the skills of a retarded child should be evaluated from many aspects and that therapy be designed to counteract the weakest points. He described successful results to this method of therapy. The future holds much in this area of research into cause and treatment of retardation.

Treatment and re-education of retarded children in France was outlined by a world leader in this field, Robert P. L. Lafon, M.D., of the University of Montpellier. Lafon has been instrumental in organizing facilities for the diagnosis, treatment and re-education of the retarded children in the region of Montpellier on a system that would be rivalled in excellence by very few. During his talk, he emphasized the need for precise diagnosis, the importance of home life and parental interest in the

welfare of the retarded child, the need for making the child feel he is essential and useful, the necessity for trained personnel working together with an informed and interested government agency. The unique person in the French system is the "educateur", or specialized educator, with some training in Psychology, Education, Medicine, and Sociology. This person is thus well-prepared to aid the retarded child.

Lionel S. Penrose, M.D., F.R.S., Director of the Galton Laboratory, University College, London and winner of a 1963 Award as Lafon, discussed the peculiar condition of mosaic mongolism in which only some of the clinical features of mongolism are apparent and in which only a proportion of the body's cells exhibit the chromosomal modification that typifies the Langdon Down anomaly. It is interesting to observe that Dr. Penrose served as a Psychiatrist at the Ontario Hospital, London as well as being a member of the Department of Psychiatry in the early 1940's here at Western. His extensive research and many writings have made him an authority in this field.

Two further papers were given concerning the role of chromosomal abnormalities in the etiology of mental retardation. Dr. Murray Barr discussed very capably the work of his group here at Western dealing with chromosomal anomalies in spontaneously-aborted fetuses and chromosomal translocations in Mongolism. Western should indeed be proud of the significant contribution being made by Dr. Barr, Dr. Carr and their associates.

Jerome Lejeune, M.D., of the University of Paris and a 1962 Award Winner, discussed a new syndrome characterized by depletion of a segment of the short arm of the fifth chromosome. This condition is characterized clinically by mental retardation, small chin, late development of infant milestones and an unusual cry which Lejeune described in one of his patients as "Il crie comme un chat."



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Other papers dealt with biochemical aspects of mental retardation. Examples of maple syrup urine disease, caused by defective metabolism of the branched chain amino acids, and homocystinuria were presented by Moore, Efron and Young of Harvard and Waisman and Gerritsen of Wisconsin respectively. The latter is a rather recently described condition associated with failure to thrive, poor developmental milestones, ectopia lentis and impairment of the metabolic processes involving homocystine, methionine and taurine. The former emphasized that the abnormal collection of valine, leucine and isoleucine must be detected early in order that retardation be avoided. Both mentioned the importance of careful electrophoresis to make an early diagnosis in order that proper dietary management could be undertaken.

J. Menkes, M.D. of Johns Hopkins and G. M. McKhann of Stanford continued the discussion on a biochemical theme. Menkes discussed the alteration in the fatty acid pattern of a child with familial absence of corpus callosum. McKhann considered an unusual cause of mental retardation, metachromatic leukodystrophy, in which one sees an alteration in the metabolism of sulphur-containing cerebrosides.

D. N. Medearis, M.D. of Johns Hopkins concluded the discussion by commenting on the role of cytomegalovirus as an etiological agent in mental retardation. It has been shown that cytomegalic inclusion disease can cause mental retardation. Interesting forms of the human and murine diseases were discussed.

From cursory analysis of these papers, it can be seen that the researches in this field are concerned seriously with attempts to elucidate the etiologies of mental retardation. The aim is to enable its prevention and to obtain better treatment for the unfortunate victim. Specific etiological aspects discussed here were biochemical, viral and chromosomal while management of the retarded child was considered briefly

with diagnosis but mainly with remedial measures. The hope is that the retarded child will become sufficiently adjusted to society in order to serve a worth-while role therein.

This year the Kennedy Foundation paid tribute to six men for their contribution to mental retardation research and leadership. Three American political figures, Sen. Lister Hill of Alabama, the Hon. Bert T. Combs, former Governor of Kentucky, and Rep. John E. Fogarty of Rhode Island were honored for drawing this problem to the attention of the public and thus enabling extensive financial assistance for the care of the retarded and research in this field.

Three scientific figures were honored, including Dr. Grover Powers, Professor Emeritus of Pediatrics at Yale for his early and prolonged interest in the treatment and welfare of the retarded child; Dr. Robert P. L. Lafon, Professor of Neuropsychiatry at the University of Montpellier, France for the establishment of community centers in many French centers for the care of mentally retarded; and Dr. Lionel S. Penrose, Galton Professor of Eugenics at the University of London, for his prolonged research into the etiology of mental retardation and his extensive and provocative writings on this subject.

The tribute paid to these men is certainly well-deserved but, in addition, it serves a more valuable function in that the attention of many people is focussed on this very important problem. The impact of this approach to the problem of mental retardation can be seen with the many research developments over the past few years. Many factors unsuspected a few years ago are now clearly proven and it would seem this trend will continue. This great upsurge in scientific interest and financial support has led to the change in public attitude so essential for the successful management of the retarded population. Where the public formerly treated the mentally retarded as unwanted out-



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casts, it has now begun to realize a true understanding of this unfortunate condition.

Research by dedicated men and financial support from various commercial organizations were inevitable events but the change in the public attitude was far from certain. Therefore the most important function of Kennedy Foundation is to change this attitude even further in order that the retarded be properly treated and some-day enjoy many of the aspects of life shared by the more fortunate members of the community.

### THE HIPPOCRATIC BANQUET

The annual Hippocratic Banquet was held on January 10th, with Guest Speaker, Dr. John Hamilton, Dean of Medicine at the University of Toronto. As well as the honor awards winners, it was interesting to note the array of Deans, and Ex-Deans that graced our head table: Dr. Hamilton, Dr. Hall, Dr. Collip, Dr. Warwick, Dean Hoskin and Dr. Bocking. The last mentioned started the evening off in true medical fashion in his reply to a toast to the school with a story which amused and surprised the most modest of us. Special thanks should be extended also to Dr. David Johnston who replied to the Toast to the Alumni, giving us some enlightening information about Dr. Crane who founded the Alumni Association of the University of Western Ontario.

Dr. Hamilton, who is bilingual, began his talk in perfect French but gave his address proper "en anglais". (We are interested to note that his paper is to be published in French.) Having referred to our chairman as "Midwife Kinch" and justified the fact that the University of Toronto could only afford to send him to London by Greyhound bus—Dr. Hamilton proceeded to delve into the problems of the future of medical education. Several points which he talked about have stuck in my mind and I would like to share them with you. He pointed out the diffi-

culty of Deans and boards in selecting medical students showing the maximum promise of success, both academically and in achieving the education and understanding to serve the society of the future; to look ahead, to provide leadership, and to take responsibility. The students need to have a practical knowledge of each service. The speaker felt that there are definite types of personalities distinguishable early in their medical training and certainly by the interne stage, for example; the internist as against the surgeon or the future Dean.

Our attention was drawn again to the trend to specialization and Dr. Hamilton explained this partly on the theory that almost all the teachers in medical schools are specialists. Too few general practitioners are on the staff; however, the fact that their schooling has been limited to only some five years makes questionable the adequacy of their training, for teaching as well as practice in an unlimited field. One cannot be an authority on any one subject now—for even the specialties, for example Surgery, are subspecialized; as into Cardiovascular, Neurosurgery, Urology, Abdominal and so on. Recent advances in Medicine generally, are emphasizing afresh the importance in every field, of biochemical and other basic science discoveries.

Dr. Hamilton ended his discussion with the following points:- that medical teachers are or should be chosen for their ability to teach, and their wealth of knowledge. However, appointments to professorship cause such learned men to lose their autonomy, and no single man can remain a supreme authority. The demands of administering a large university or hospital department are so great that the original excellence of the great teacher and investigator may suffer. Some way should be found for such men to achieve the acclaim they so rightly deserve without being made the heads of departments.

It is realized that these are but a few of the gems that Dr. Hamilton left with



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us. I know it was a special treat for all of us who attended the Banquet whether undergraduate, clinician, or staff member, to meet and hear him.

It is hoped that this year's success will set a precedent for more enthusiasm in subsequent years, for student support of the banquet has been getting steadily worse.

Noelle Grace

### A VIEW OF PREMEDICINE

The Premedical Course has traditionally been the minimum prerequisite for entering the Faculty of Medicine. The reasons for its existence have been variously stated, but basically Premed is supposed to serve as a means of selection of suitable candidates for the profession of Medicine, and as years of maturation and scholastic preparation for the actual study of Medicine. I would like to present a purely personal evaluation of how well Premed serves these three ends, and to present some suggestions for change.

Those of us recently through Premed still have vivid memories of the fantastic competition, the constant self-remainder being "only the top half is going to make it". In the past two years this fraction has dwindled to one-third or one-quarter. Competition in the top 10% of a class is inevitable, but competition from the top to the bottom is absolutely stifling; there just isn't time to do anything but work at amassing marks. The argument has been of course that this competition separates the good candidates from the bad. I do not believe that this is correct. To succeed in any scholastic endeavour, the prime need is an interest in the field of study. However, very few individuals are interested in the wide range of required subjects in Premed which in themselves have little resemblance to the fields of study in the Medical School. It is therefore frequently the case that a student is keenly interested in Medicine and hence would a student do well as a medical student and as a doctor,

but, through lack of sufficient interest in six different courses is unable to drive himself into that upper 50%. A good doctor has been lost.

Let's for a moment put ourselves in the position of the grade thirteen student trying to decide what course to enter at university. Very few really have made a firm decision and those that have probably used the wrong reasons. Those who think that they might want to be a doctor will feel obliged to start out in Premed, particularly if they have heard how hard it is to get into Medicine. As I've already pointed out, Premed has little resemblance to Medicine and therefore cannot be used as a sound basis for either strengthening or weakening the decision to enter Medicine. One of two things will happen. Some will be so disillusioned by Premed that they will drop out of the course. The rest, once caught up in the race and still not certain what lies on the other side of the finish line, won't consider dropping out until they get into Medicine and can decide whether or not it's for them. Obviously some who get into Medicine will by chance have made the right decision in grade thirteen; but, how many are there who, during first year Medicine, find they have made the wrong decision but are unwilling to admit it and start over? How many misfits get into the profession of Medicine in this way?

I think that when we say that Premed is to mature a person we mean to become convinced that Medicine is the right profession for this person. I have just shown how it is that Premed does not facilitate this maturation. How could one achieve this end? Two alternatives are apparent. The one is to be exposed to Medicine right from the beginning with no previous Premed; the other much better and more practical way is by a process of comparison and elimination. The first year student should be given the opportunity to select courses which he himself would like to investigate and not be tied down to a prescribed Premedical program. There is



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no other way any student can be expected to make an intelligent decision about entering Medicine as opposed to some other field of study.

Is the present Premed scholastic preparation for Medicine? From my point of view (i.e. third year), I would say that only two and one-half of the courses from two years of Premed were of any direct value in the first two years of Medicine; namely, Zoology 20, Psychology, and the definitions from Organic Chemistry. The rest of the courses are either totally unrelated to Medicine (e.g. English) or have the essential portions repeated in the Medical courses (e.g. Embryology, Physics).

I am not advocating the abolishment of university courses before entering medical school, but the advantages of a completely flexible curriculum have been pointed out above. Some schools recommend or even insist upon a broad educational background (i.e. a B.A. or B.Sc.). It may have been true 20 years ago that the only well-educated man in the community was the doctor and hence it was his responsibility to be community leader. But this is no longer the situation. An increasing part of the population is obtaining a university education, frequently to a level surpassing the B.A. of the doctor. At the same time, the strictly medical training required by the doctor has become greater as the trend to specialization continues. It is totally unrealistic to force a prospective doctor, who is certain of his goal, to obtain a degree before beginning his medical training. Even by third year, most medical students readily admit that they are getting

"fed up" with school as such, (this is the year one sees high school classmates graduated and gainfully employed and settled down in the community).

What then would be a more satisfactory means of maturing, preparing and selecting medical students? The freshman should not be required to enter any defined Premed course; i.e., he should be free to choose almost any combination of interesting subjects (including the biological sciences), and be spared the competition. In this way he will not be forced into a premature decision to aim for admission to Medicine. Admission to the Faculty of Medicine should be possible after one year and with only one or two required courses. One year for some students would be adequate preparation and would allow them to get on with the job of learning Medicine itself. Selection should be based on more than marks. High marks do not mean a successful doctor and low marks in unrelated courses do not mean a sure failure in medical school. An interview to assess the applicant and his reasons for seeking admission would help. A careful study of his general background and personality would help further.

This does not pretend to be a complete discussion of premedical training but represents only some thoughts on the subject as seen from third year Medicine. As this article was in preparation, the University of Western Ontario announced that changes in Premedicine would be revealed soon.

Gary Gibson, Meds '65



# Editorial

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The problem of article choice plagues every student publication. Although in continuous publication since 1930, the University of Western Ontario Medical Journal has not significantly increased its circulation. Competition from the deluge of journals containing news of more immediate discovery is only a partial reason. This journal cannot compete with historical, obstetrical, psychiatric, research, surgical, or other medical releases of special interest. Furthermore, student writing is frequently only student read. Alumni tend to subscribe by courtesy and read but hastily; or not at all. The unread article is a failure, though the exercise of authorship may be satisfied. Our role must be to present the general, the universal and the controversial, as the student is traditionally bound to be the critic of his milieu.

Uneasily but hopefully, the University of Western Ontario Medical Journal has printed this special alumni issue in addition to the four regular issues. The regular issues will be devoted to problematical areas of medical concern. This alumni issue is supplemented by interviews and biographies of selected graduates or staff members. Also included are some specially selected papers given to the school by her undergraduates. A complete documentation of this year's homecoming classes will be spread over the five issues. Each Journal will also have a section devoted to news submitted by our alumni.

The four regular issues will touch upon the fields of CONTRACEPTION, FRINGE MEDICINE, PROBLEMS OF AGEING, and THE RELATIONS AND INTERACTIONS OF MEDICINE WITH OTHER PROFESSIONS.

Textbook and exam-answer type of articles have long burdened this journal. If any advance towards maturity is seen this year, it is largely due to the patience and guidance of Dr. Valentine, our faculty advisor, and to the encouragement and help of the Dean, Dr. Meltzer and Dr. Walters. Special thanks are offered to Mr. Hartwell and his staff of the University Alumni Office and to the Alumni Association which has generously made this issue possible.

This is the Journal's first experiment in recording alumni classes. A disappointingly small amount of information was accumulated in return for exhausting work. There are undoubtedly omissions and perhaps inaccuracies. Please do not criticize too harshly, but rather resolve to help us to make further improvements.

J. H. C.



# Obituary

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ARCHIBALD JOHN GRACE, B.A., Sask., B.A.(Oxon.), B.M., B.Ch., *ibid*, M.A., *ibid*, M.R.C.S.(Eng.), L.R.C.P.London, F.R.C.S.(Eng.), F.R.C.S.(C), F.A.C.S.

Doctor Archibald John Grace died in Victoria Hospital at High Noon on September 7th, 1964. His untimely and insidious final illness lasted more than two years. His courage, his patience, and his fortitude during this trying period were characteristic of his life.

Doctor Grace was born in India of Missionary parents. He never relinquished his religious faith and beliefs. He remained an ardent Churchman throughout his busy life. He has passed on these beliefs and this faith to his singularly gifted family.

Many academic awards were bestowed on this great man during his undergraduate and postgraduate career, among these were silver and gold medals from his University and a Rhodes Scholarship. He qualified at Guys Hospital and took diversified and extensive postgraduate training in England and Canada before accepting the position as Associate Professor of Surgery in this University. For twenty-eight years he practiced and taught surgery in London, Ontario. He pioneered in many branches of surgery, but particularly in Thoracic surgery which was of special interest to him.

He was an ardent and stimulating teacher. Like many teachers he inspired respect in his students, but much more than that he also inspired affection. He had deep well waters of knowledge which he willingly shared. His enthusiasm was infectious and his energies unlimited. He fought against death when it approached his patients; all forces were mobilized; no time, nor effort was spared. He believed in the direct, early and radical attack. He rejoiced over his many victories; he mourned over his few failures.

Apart from his professional career he will be remembered for his personal qualities. He had a genius for friendship with colleagues, housemen, students and patients. He had a great sense of fun and believed sincerely that his work should be enjoyed. His ready wit and quick repartee made him excellent company.

Doctor Grace was also an ardent sportsman, actually refreshed and stimulated by demanding game of any kind. He could discuss with facility, photography, politics, religion or fishing. His interests were catholic in breadth, vast in dimensions, steeped in perfection.

He was a generous and kindly host. Many will have happy memories of friendly gatherings at his home where his gracious and talented wife assisted him so ably.

He will long be remembered. He will always be respected. We shall sadly miss his presence, for:

"His life was gentle and the elements so mixed up in him that Nature might stand up and say to all the world 'THIS WAS A MAN'".

*Requiescat in Pace*

D.W.B.J.



# The Onset of Labour

MARY ELLEN KIRK, '64

This paper was originally presented at the February 20, 1964 meeting of the Alpha Omega Alpha Society. Dr. Kirk graduated from Western with honours and was winner of the Reckitt and Colman (Canada) Ltd., prize in Obstetrics. She is presently doing her internship at the Toronto General Hospital.

## INTRODUCTION

On a practical level, it is highly desirable to know why labour starts in order that premature labours may be intelligently managed and that inductions may be safe and physiological. Pregnancy and parturition are physiological processes which are all too often regarded as a disease, simply because we do not understand what is happening. It is not at all surprising that there are numerous theories which attempt to explain the onset of labour. Nor is it surprising that no single one of these is adequate.

Most of the current theories fall into one of two main groups. The first group is concerned with factors which tend to terminate pregnancy. These theories consider the gravid uterus quiescent, having little inclination to spontaneous contraction. As term approaches, however, some compound or some mechanical stimulus attacks this quiescence; the uterus is stimulated to labour and the foetus is expelled. These are the *attack theories* for the onset of labour. The second group are the *defence theories*. The uterus is regarded as a contractile organ and the foetus as a foreign body to be eliminated. Spontaneous contractility of the uterus must be suppressed so that gestation may proceed to term. This suppression, or sedation, of a contractile uterus is effected by a defence mechanism which must be overcome at term as a pre-requisite for the onset of labour.

## THE OXYTOCIN THEORY

The Oxytocin Theory is an attack theory. Caldeyro-Barcia, chief of the service of Obstetrical Physiology in Monte-

video, is its most prominent advocate. Using fine-calibre polyethylene catheters inserted into the amniotic sac and micro-balloons placed directly into the uterine wall, he has shown that for each stage of normal pregnancy there is a consistent and reproducible relationship between the response of the uterus and the rate of infusion of oxytocin.

The uterine response to oxytocin, or the uterine activity, is measured in Montevideo units: the product of the height of the contraction times the number of contractions in a ten minute interval. Near term, infusion rates between two and eight mU of oxytocin per minute are required to raise the uterine activity to the values recorded in spontaneous normal labour. This is termed a physiological infusion rate. At mid-pregnancy, infusion rates eight times higher, or pharmacological rates, are required to produce the same effect.

As gestation proceeds, the uterus responds to increasingly smaller doses of exogenous oxytocin. At thirty-six weeks, the response to exogenous and, by inference, to endogenous oxytocin becomes maximal. During the entire last month of gestation, a very small amount of intravenous oxytocin will trigger labour. Shape, co-ordination, intensity, frequency, duration and tonus: all the characteristics of the contractions produced by oxytocin infusions, are indistinguishable from those recorded during normal spontaneous labour. The Smythe test depends upon this marked sensitivity of the uterus to oxytocin. If the myometrium responds with contraction to a small test dose of oxytocin, parturition is believed imminent, and amniotomy will likely prove a successful method for induction.



The onset of labour is attributed to an increase in endogenous release of oxytocin occurring during the last month of gestation, and not to any alteration in the uterine response to the hormone. This might be termed an 'auto-infusion'. It is a simple dose-effect relationship in which the attack becomes more concerted. Oxytocin is released from its storehouse, the neurohypophysis, when certain neuro-hormonal reflexes are stimulated. It has been demonstrated that stimulation of sensory fibres in the lower uterine segment and upper birth canal will fire nervous impulses which reach the supra-optic and paraventricular nuclei of the hypothalamus. Stimuli then travel along axons to the posterior pituitary and oxytocin release occurs, by the Ferguson reflex. In the last four weeks of gestation, the foetal head or presenting part exerts progressively more pressure on the upper birth canal and the neurohypophysis secretes more oxytocin. As with any oxytocin infusion, this will enhance uterine activity. Uterine activity further advances the presenting part, further stimulating maternal parts. The net result is a cyclic increase in endogenous oxytocin secretion and the onset of labour.

The Shirodkar operation may owe its success to preventing the patulous cervix from being stimulated by pressure from the presenting part, so that oxytocin is not released from the pituitary. Women close to term will frequently go into productive labour if minute amounts of oxytocin are administered, for example, with Syntocinon linguets. It is believed that this small stimulus may be just sufficient to trigger the above cycle, providing that the uterus is maximally receptive to oxytocic stimuli. Rupture of the membranes is also hypothesised to owe its success in inducing labour to the marked increase in oxytocin release. Another stimulus to oxytocin release is nicotine, a possible explanation for the increased incidence of premature labours in women who smoke heavily.

Plasma taken from pregnant women is capable of inactivating oxytocin; this activity is due to an aminopeptide enzyme,

oxytocinase. Until parturition, there is a continuous rise in plasma oxytocinase followed by a rapid decline in the puerperium. The role of this enzyme is controversial. If it does act to protect the myometrium from circulating oxytocin, its concentration would be expected to decrease *prior* to delivery. However, a decline of oxytocinase does not occur until *after* delivery. It is therefore hypothesised that the important variable is the concentration of the enzyme within the myometrial cell, and that circulating levels will not necessarily reflect the intracellular concentration.

On a cellular level, oxytocin has been demonstrated to lower the membrane potential of the myometrial cell and to increase the sensitivity of the cells to stimulation. Under oxytocin influence, the cell membrane becomes depolarized with an escape of potassium ions from the cell. As synthetic actomyosin does not respond to oxytocin stimulation, the primary effect of the hormone is believed to be, not on the myoplasm, but on the membrane. Oxytocin-altered membrane permeability makes the uterus highly sensitive to further triggering oxytocic stimuli. The frequency of spontaneous uterine contractions, the number of intrinsic stimuli capable of producing propagating contractions, and the force of contractions increases with more fibres participating in each contraction. The attack becomes so strong that expulsion of the foetus is inevitable.

In summary, Cladeyro-Barcia and members of the 'Oxytocin School' state that oxytocin is the primary factor in initiating labour. Oxytocin is released by reflex stimulation of the neurohypophysis and acts primarily on the membrane of the myometrial cell. The net effect is to increase uterine activity. Maximum uterine sensitivity to the hormone is attained by thirty-six weeks gestation and labour starts at term because of an increased endogenous release of oxytocin from the pituitary.

### PROGESTERONE-BLOCK THEORY

Csapo of the Laboratory of the Physiology of Reproduction, the Rockefeller



Institute, is the chief proponent of the 'Progesterone-Block Theory', a defence theory. He regards the uterus as an asymmetrical muscular bag comprised of two main functional portions: the placental and the anti-placental. Csapo believes that until the time of parturition, differences between these two portions prohibit effective uterine contraction.

One of the main functions of the placenta is to produce progesterone which has long been known to decrease the ability of the uterus to contract. The over-all effect of progesterone is to inhibit the uterus, to more or less sedate it. No change occurs in the actomyosin complex, but by some inhibitory mechanism the myometrium is rendered inert. The uterus is not myasthenic, but it is sedated. Progesterone produced in the placenta is released to the maternal venous sinuses and then drained by the uterine veins to enter the systemic circulation. Circulating progesterone is distributed to the myometrium and either this hormone or its metabolites permeates the myometrial cell. In the maternal sinuses, deep to the placental bed, progesterone is in direct contact with the muscle cells. The cells in the placental portion of the uterus are therefore more strongly influenced by progesterone than are cells in the anti-placental, systemically supplied, part of the uterus. This local increase in progesterone content constitutes the progesterone-block. This is believed to be the explanation for the relative paralysis of the muscle under the placenta. Until term, Csapo believes that this 'sedated' area is able to dominate the uterus and prevent it from functioning as a uniform muscle—as it eventually must do during labour. The cellular content of progesterone is the important factor in the defence mechanism, and systemic levels will not necessarily reflect intra-cellular conditions.

Progesterone is thought to affect only the cell membrane. It causes an increased intracellular potassium, possibly by altering the rate of release of the bound ion, or perhaps by increasing the permeability of

the cell membrane to potassium. It is interesting to note that oxytocin has been demonstrated to have the opposite effect, namely, to decrease intracellular potassium. This correlates well with the philosophy of oxytocin as an attacker and of progesterone as a defender. A second effect of local progesterone dominance involves a strong calcium binding at the myometrial cell membrane, an effect which may lead to a relative excess of free magnesium. The progesterone-block might therefore be explained on the basis of a local magnesium anaesthesia. These ionic effects of progesterone: increased intracellular potassium, strong calcium binding, and free magnesium all act to decrease the spread of any impulses arising in the blocked tissue. The placental and anti-placental portions of the uterus are ionically different; these differences prevent synchronous action. These differences disappear near term, and the muscle of the uterus becomes a single functional unit.

If progesterone-blocked myometrium is electrically stimulated, only local activity occurs with little spread of excitation to adjacent cells. However, if poorly dominated myometrium, as in the anti-placental portion of the uterus, is stimulated with micro-electrodes or with oxytocin, the wave of excitation will spread over the uterus until arrested by the effectively blocked placental myometrium. If this blocked portion is relatively small, it is unable to resist contractile forces, and the whole uterus will contract. The progesterone block is therefore relative.

If it is the progesterone block which maintains a quiescent uterus, then what mechanism is responsible for converting the uterus into the powerfully contracting organ characteristic of parturition? It may be that the uterus becomes less able or unable to metabolize progesterone, permitting an escape from the progesterone block. Csapo's belief, however, is that a mechanical factor, uterine volume, provides the trigger for the onset of labour. As full term approaches, uterine volume



increases, stretching the myometrial fibres and increasing the amniotic pressure. A stretched muscle is more receptive to excitatory stimuli and also contracts more effectively. When a critical volume is reached, spontaneous uterine contractions increase in frequency and amplitude and labour begins.

Csapo contends that in cases of missed abortion, this critical volume is not attained because the intrauterine contents do not grow. There is therefore no stimulation to labour until placental degeneration and withdrawal of the progesterone block occurs. If the uterus becomes over-distended, as in polyhydramnios, the resting tonus is markedly increased and uterine contractions become ineffectual. Uterine activity will improve if this volume is reduced to its optimal value by amniotomy or amniocentesis.

One of the strongest arguments in favour of the local block theory is described by Csapo as "the embarrassing fact that human twins can be born some time apart from the same bicornuate uterus". For example, in one patient with a bicornuate uterus and a double cervix the first baby was born fifty-six days before the second. In another instance, a mildly toxic patient delivered a baby after seven months gestation. The toxæmia disappeared, and the second twin was born two months later. Cases such as these strongly suggest that oxytocin, which would be uniformly distributed throughout the circulatory system, does not precipitate parturition. It is assumed that the volume in one horn of a bicornuate uterus may reach the critical volume some time before the other, accounting for the interval between deliveries. In other words, parturition is triggered by *local* rather than by systemic factors.

In the normal gestation, volume-triggered contractile waves become increasingly forceful and progressively infringe upon the blocked portions of myometrium, until eventually the organ contracts as a whole. The defence is overcome by increased uterine volume. Although the endocrine

function of the placenta is diminished, the transport function is retained, permitting a narrow margin of safety essential for a live birth. In this manner, the myometrial cells lose their sedation and become responsive to the stimulation provided by increased volume. Uterine activity becomes auto-catalytic in that the cyclic increase in pressure may alter placental blood flow, with a gradual reduction of progesterone production and a weakening of the defence mechanism.

Legalized abortions in the Scandinavian countries provide human subjects for testing the validity of the progesterone block theory. If formalin, 50% glucose, or 20% saline are injected into the amniotic sac, the patient will go into labour and successfully abort after a relatively constant latent period. During this latent period, osmotically-induced haemorrhages and other degenerative changes occur in the placenta; the local block is destroyed and the defence mechanism is suppressed. Small infusions of oxytocin have no significant effect before the intra-amniotic injection, but after a day or so the uterus becomes highly sensitive to the hormone and oxytocin induces strong, effective contractions. If intramuscular progestational hormones are administered, the sensitivity to oxytocin is delayed for several days and the pregnancy is prolonged. This strongly indicates that progesterone is capable of protecting the gestation. As already mentioned, it is believed that in normal placentas the endocrine function declines before the transport function. Experiments are now being carried out in which hyper-osmotic dextran is injected intra-amniotically in patients judged close to term. The philosophy is that this procedure will overcome the progesterone block without causing adverse foetal effects, and may prove a useful means for inductions.

Csapo regards oxytocin as a substance capable of enhancing the intrinsic properties of uterine muscle. As the anti-placental portion of the uterus is not effectively blocked by progesterone, oxytocin infu-



sions will raise the amniotic pressure by causing a contraction of this non-sedated portion. He stresses, however, that until the volume is critical the uterus contracts asynchronously because the placental portion remains inactive. Therefore, although oxytocin infusions will induce uterine activity kymographically identical to labour, the uterus is not performing as it does during labour. The anti-placental portion of the uterus recovers from the progesterone block several weeks before the placental area, and oxytocin infusions may give rise to large changes in amniotic pressure long before term, by affecting the anti-placental portion only. If labour is induced prematurely with oxytocic substances, it is the rule that labour results only after a significant latent period of twelve to twenty-four hours. During this period, Csapo believes that damage is occurring within the placenta, damage which decreases progesterone production and reduces the placental block. The closer to term, the shorter this latent period. Labour results, not from an increased oxytocin stimulation, per se, but because of the decrease in progesterone block. Progress of the presenting part *after* the block is withdrawn will cause the release of oxytocin from the pituitary. Caldeyro-Barcia comments: "The role of progesterone is a matter of controversy." Csapo himself says that obstetricians may be put into two groups: the first group has never heard of progesterone and the block theory; the second group doesn't believe it.

A valid objection to the progesterone block theory has been the failure of systemic progesterone, even in massive doses, to delay the onset of term labour or to arrest premature labour once it has started. Large and well-controlled series have clearly shown this to be so. In reply to this argument, Csapo reminds us that the critical variable is the intra-myometrial concentration of progesterone. Experiments have been carried out in which gestational hormones are injected into the amniotic cavity and labour has been either arrested or delayed. If the progesterone is

injected directly into the myometrium, in human patients in early premature labour, the effects are even more dramatic. The contractions decrease in frequency and intensity and labour stops.

#### ADDITIONAL THEORIES

Altered haemodynamics and uterine hypoxia may be responsible for initiating labour. This theory may be rather loosely classified as an attack theory. As the uterus grows larger, it requires a greater blood supply and has an increased demand for oxygen. It has been hypothesized that the larger uterine vessels do not dilate and that relative haemostasis results in an accumulation of catabolites. Using radioactive  $\text{Na}^{22}\text{Cl}$  a decrease in effective uterine circulation has been demonstrated in women who deliver prematurely. Carbon dioxide has been shown, *in vitro*, to produce strong uterine contractions and either the stimulus of increased carbon dioxide or of decreased oxygen is believed by some to play an important role in inducing contractions *in vivo*. A contraction may be stimulated by a critical carbon dioxide level. With each contraction, about three hundred cc's of catabolite-laden blood is extruded from the near-term uterus into the maternal venous reservoir. Oxygenated arterial blood then flows in and the carbon dioxide or hypoxic stimulus to contract is overcome. The uterus then remains quiescent until carbon dioxide again accumulates to the critical level. With each successive contraction, more work is done, and more catabolites are produced. The period of carbon dioxide build-up therefore becomes progressively shorter, and the contractions occur closer and closer together. Some rather radical experiments have been performed in the past in which the uterine arteries, in the human patient, were ligated to produce anoxia and to initiate labour. This was once proposed as a method of induction. More recent studies in which the uterine arteries of pregnant rats were ligated indicate that the uterine ischaemia theory, while attractive, is not valid.



The foetus itself has often been considered as playing an important role in both the maintenance and termination of pregnancy. However, the rabbit foetus may be removed early in gestation and a wax dummy inserted in its place. Normal gestation, labour, and delivery still occur. In Rhesus monkeys, the foetus may be killed at mid-pregnancy by ligating the umbilical cord: provided that the placenta is not disturbed, the pregnancy is maintained. The foetus does not appear to play any significant role in either maintaining or terminating pregnancy.

### CONCLUSION

Much of our knowledge about the onset of labour is based upon evidence obtained from experiments with lower mammals. Some object that women are not the same as rabbits or monkeys but the general impression, however, is that pregnancy is controlled by a similar mechanism, regardless of the stratum in mammalian hierarchy. Certainly there are species modifications—special adaptations to allow for differences in uterus and placenta and foetal number—but there does appear to be some basic plan. Pregnancy is a very delicately balanced physiological process which terminates after a highly predictable interval. Perhaps this balance is tipped by a reduced defence, or perhaps by an increased attack. There are many promising theories supported by much experimental data. But, so far, there are no final answers.

As a concluding remark, I would like to emphasize that I have had to omit a great deal of pertinent information. Although I have tried to present fairly the theories most widely accepted, I have doubtlessly incorporated a considerable amount of personal (and probably quite unfounded) bias. I would also like to thank Dr. R. A. H. Kinch for his guidance in the preparation of this paper.

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# Class of 1919

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- Dr. Paul M. Andrus—Deceased  
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Dr. F. C. Ferguson, 776 Queens Avenue,  
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Dr. L. W. Pritchett—Deceased  
Dr. Arthur W. Smith—Deceased  
Dr. Earl M. Watson, 427 Regent Street,  
London, Ontario. After graduating as a  
gold medalist, at the University of Shef-  
field, England he returned to London,

Ontario in 1924 as instructor in medi-  
cine and founder of clinical pathology  
labs. at Victoria Hospital. In 1927 he  
got his M.Sc., in 1929 his F.R.C.P.  
(Edinburgh), in 1930 his F.R.C.P. (Can-  
ada) and in 1948 his F.A.C.P. In 1950  
he was nominated to the American  
Society of Clinical Pathologists. On  
June 30, 1960 he retired after 40 years  
of practice. On May 13, 1964 Dr. Wat-  
son was made an honorary member of  
U.W.O. Alumni Association. Of interest  
it was noted that Dr. Watson wrote an  
article for the 3rd issue of the first  
volume of the U.W.O. Medical Journal  
(February, 1931) titled "Fundamentals  
in the Diagnosis and Treatment of  
Diabetes Mellitus".

- Dr. H. I. F. Wiley—Deceased  
Dr. Charles M. Wortman, 40 Glen Road,  
Toronto 5, Ontario.

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# Reminiscences of Class of 1929

DR. LEWIS DEWITT WILCOX, M.D., F.R.C.P.(C.), '29

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The class of Meds '29 entered pre-medical school in 1923 in the old Huron College on St. George Street. The Arts subjects were taught in the central building, and botany was taught on the second floor of the barn at the rear. Physics and chemistry were taken in the old Medical School, at the corner of Waterloo and York Streets.

Chemistry was taught by Dr. A. Gunton, Miss Gertrude Rowntree and a Russian Count. The Professor and the Instructors all wore brown lab coats with acid burns suggesting the power of their subject.

Dull lectures were skipped by the students in the back row dropping out one of the windows, a distance of nine feet, onto the ground. But the courage of the act gave way to a sense of awful loneliness and it was never perpetrated twice by the same student.

Criticism of the apparatus used in the physics department annoyed Professor Allen, and we were told that the staff was doing its best with a tight budget and that thereafter only constructive criticism need be submitted.

The second year of the pre-medical course was spent with the first classes to occupy the new Arts & Science Buildings on the north campus. This did away with the need for travelling across town to attend different classes. Dean Fox was in command and Dr. K. P. R. Neville was the much beloved registrar. A. D. Robertson, as the teacher of comparative anatomy, was the man who most wielded the axe, and accounted for more failures than any other Professor. James Burns taught or-

ganic chemistry. Nelson Hart was in charge of the botany division. We met Dr. R. C. Dearle for the first time in physics.

Our first year in the Medical Course took us to the new Medical School on Ottoway Avenue, and the excitement of being under the shadow of Victoria Hospital made this move from the Arts environment a memorable change. All of our clinical work was taken at Victoria Hospital, except physical diagnosis which was taught on mental patients at Westminster Hospital. There was no clinical teaching at St. Joseph's in those days.

The Professor of Physiology, Dr. Fred Miller, was an outstanding world authority and his technician Stewart made the demonstrations unforgettable events. Dr. Paul McKibbon had been the Professor of Anatomy from 1916, and he was still at the head of this department when we came along. He had been made Dean of Medicine when Dr. Hugh McCallum died about 1920. He planned the new Medical School and he was responsible for molding a peculiar faculty in such a way as to give the school a class A standing.

Dr. J. W. Crane, was Professor of Pharmacology, and Rational Therapeutics. Dr. A. B. McCallum was the head of the Biochemistry Department. Dr. C. C. Macklin and Dr. Marge Macklin were in charge of Embryology and Histology. Dr. McKibbon had a nice political sense and because he was going to be asking citizens of London for financial help in the construction of the new Medical School, he pleaded with the Class of '16 to do away with their initiation ceremonies on the incoming class. However, the class disobeyed and the pres-



ident of the class was sternly reprimanded by Dean McCallum. In spite of the newspaper publicity of this hazing, the city was very generous, and paid through debentures the full cost of the New Medical Building.

Dr. McKibbon left for Ann Arbor in 1927. His place was taken by Dr. Crane who was acting Dean for a few months. He was replaced, without explanation, by the Board of Governors who had never consulted any members of the faculty, by Dr. A. B. McCallum. When Dean Fox asked the Board to explain its unprecedented action he was told that Dr. McCallum had more letters after his name than Dr. Crane! When we graduated, Dr. McCallum was still holding the office of Dean.

The Clinical Pathological Conference was the exciting event of the week, and this was handled by Dr. H. H. Bullard and Dr. G. C. Hale. There were no protocols. Dr. Bullard was never a positive individual and left a great deal to our deductive capacities. However, he told us one story that lasted longer than any of his several descriptions of the inflammatory process. He told about an orderly in a London Hospital, by the name of John Bland Sutton. This man was working on one of the wards of Guy's Hospital at a time when the Professor of Surgery was giving a bedside clinic. The group of students around the bed were all utterly stupid, and the Professor, after asking for a simple reply to what he thought was a simple question, came to the last student who was worse than all of the others. In disgust, the Professor finally said "you men are all disgraceful, I am sure that even Sutton, the orderly, would know the answer to this question." Whereupon, he called Sutton over to the bedside and asked him the question which the students had missed and obtained a perfect answer. After the clinic the Professor took Sutton aside and told him he would like to pay for his tuition to Medical School. Sutton went through Medical School and became Brit-

ain's outstanding Surgical Pathologist, and was Knighted.

Dr. Hale was not a friendly person as far as the students were concerned, but he was very much respected, and he brought the teachings of McGill and the European Clinics to the Western Medical Students.

Dr. Hadley Williams as Professor of Surgery, used to hold his demonstrations in the Gartshore operating theater, which had just been erected. He was nervous and impersonal and far removed from the students. However, he was a dramatic teacher and was ambidextrous when using chalk so that he was able to draw both sides of the brain at once—a feat which has never been re-duplicated in these parts. While we were on the surgical service one man 34 years of age was operated on for exophthalmic goiter. This was the only thyroid operation we saw and the patient died as a result of post-operative bleeding. The most active junior members of the surgical department were Robert Johnston, Cameron Wilson, H. O. Foucar, Murray Simpson, E. D. Busby, George Ramsay, and Alfred Grant (who charmed us with accounts of clinics he had attended in New York).

Obstetrics and gynaecology were very well taught by Dr. W. P. Tew and Dr. F. R. Clegg, and we all left the school feeling that we were authorities in this department. Dr. Harold Little as Professor of Paediatrics was perhaps the best lecturer in the school of our day, and none of us carried any feelings of inferiority about this subject when we left Western.

The Department of Medicine had Dr. G. C. Hale as its Head and Dr. John A. MacGregor with Dr. F. J. H. Campbell and Dr. Roy Childs as the "junior members". Dr. Carl Cline did some of the teaching in neurology, and Dr. E. M. Watson was moving into the areas of haematology and metabolism. He was in charge of the entire clinical laboratory service.



Meds '29 at the time of graduation was made up entirely of students who lived within a 50 mile radius of London, with the exception of one man from Ohio. We had one young lady, namely Margaret Strang, and her presence in the group improved the general decorum, and marked us off very sharply from such a crude group as Med '28 for instance. Six of our twenty-five were so-called B.A., M.D. students. After graduation the class was quickly reduced to twenty-four with the death of Tom O'Hara while he was an Intern at Victoria Hospital from TB meningitis. When we had all finished our post-graduate studies, we ended up with twelve specialists and twelve generalists.

The choice of a hospital for internship was a very hit and miss business because our most illustrious teachers had trained in England or Europe, or they had been self-taught and had never been outside of London. This was unfortunate because there was no opportunity for discussing the advantages and disadvantages of hospital internships, and when one of our number went to the Brantford General Hospital he was told by the Senior Member of the Medical Department to take the job but not to listen to anything that anybody in Brantford told him.

When we left Medical School we had never been told that such a thing as coronary thrombosis existed. Bronchogenic carcinoma had not been mentioned, Pneumonia, diphtheria, scarlet fever, typhoid and syphilis were common, important subjects. Subacute bacterial endocarditis was one of the most tragic infections and it almost always affected wonderful young people and they all died. When we left school, the only treatment that seemed to carry any hope was intravenous mercurochrome and, of course, we all know that it didn't accomplish anything. Pernicious anemia was much more common than it is today and, although liver extract had not been developed, the value of liver in its treatment had been discovered two years

before we graduated. When we treated a patient with this kind of anemia, we had to order ground raw liver, flavoured with sauces or lemon juice and given to the patient in quantities that were always larger than he could handle, and always less than he required. The diagnosis of cancer was mostly clinical, because X-ray studies were still in a pretty crude state, and routine X-ray examinations were rather uncommon. There was no deep X-ray treatment, because the Roentgen unit had only been settled on in 1928. X-ray therapy consisted, then, in the treatment of skin cancer by giving small doses over prolonged periods of time. This led to atrophy of the skin and X-ray irritation with the development of subsequent cancer of the skin, which became worse and worse and caused much more trouble than the original lesion in many instances.

The surgery in those days, so far as our class was concerned, consisted in mastering the approach to the appendix, the gall-bladder, and hernia. Several of our members who did very well in life went into practice with these three tricks as their accomplishments.

We were a very youthful class at graduation; the youngest member was only 21. One out of the twenty-five was married in his final year. Dr. J. W. Crane had used the teachings of Dr. Osler in impressing on us the desirability of keeping our emotions on ice until the completion of our post-graduate studies.

A Hospital is a Shrine and Victoria Hospital in those days attracted a good many of our number for one or two years of early training. The Medical School has not really changed very much since those days except in so far as the contour of the staff personnel has changed. In any student period there will only be a few outstanding teachers and these are the influences which leave the greatest impact on the students.



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One of us has currently seen a patient with a skin rash and chills and high fever after two junior physicians had been struggling with it for four days. It was so easy to make a diagnosis of erysipelas at a glance. The experienced nurse making rounds after the pronouncement summed

it up very well by saying "these poor young lads have never had a chance to see the exciting things in medicine".

The Class of '29 has lived through the golden age of medical and surgical development.



# Class of 1929

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- Dr. Robert J. Bristow**, 21 Farley Place, St. Thomas, Ontario. Dr. Bristow is presently practicing surgery in St. Thomas.
- Dr. Gerald H. Jordan**, 4517 Cumberland Circle, El Paso, Texas. After graduation, Dr. Jordan studied at Johns Hopkins in 1934-35. He is presently a Governor of the American College of Surgeons, and a Fellow of the Texas Surgical Society.
- Dr. Frank S. Kennedy**, 53 Rollingwood Circle, London, Ontario. Dr. Kennedy obtained his M.Sc. from the University of Minnesota (Mayo Clinic) in December 1933 and his F.A.C.P. in April of 1934. Presently Dr. Kennedy is practicing Internal Medicine in London and is Clinical Associate Professor of Medicine at U.W.O. Medical School.
- Dr. J. Frederick Kenzie**, 31 Robie Street, Bath, New York.
- Dr. Carmen D. Kilpatrick**, 112 Delhi Street, Guelph, Ontario. Dr. Kilpatrick is presently a staff member at the Home-wood Sanatorium in Guelph, Ontario.
- Dr. Louis J. Loftus**, Quarantine Office, Immigration Building, Vancouver, British Columbia.
- Dr. Kenneth T. MacFarlane**, 3550 Cote des Neiges, Suite 500, Montreal 25, Quebec. Dr. MacFarlane is presently Associate Professor of Obstetrics and Gynaecology at McGill University and Chief of the Department of Obstetrics and Gynaecology at Montreal General Hospital, Montreal, P.Q. As well as being on the staff at six other hospitals in the Montreal area, he has an active private practice. Dr. MacFarlane has his F.R.C.S. (C), F.R.C.O.G. and F.A.C.S. He is a Founding Fellow, and Past Vice-President of the American College of Obstetrics and Gynaecology. He is also on the Executive Committee and is Honorary Treasurer of the Royal College of Physicians and Surgeons of Canada. He is a Past President of the Montreal Obstetrical Society and a Past President of the Canadian Gynaecological Travel Society. He is a member of the C.M.A., the Montreal Medico-Society and of the Society of Obstetricians and Gynaecologists of Canada. He is in AKK, AOA and Sigma X. Dr. MacFarlane is married and has 3 children. One son is now studying medicine at McGill.
- Dr. John A. MacLennan**, 13130 Riverside Drive, Tecumseh, Ontario.
- Dr. D. Stanley McHaffie**, Qualicum Beach, B.C.
- Dr. John J. McManus**, 26 East Street, St. Thomas, Ontario.
- Dr. Colin A. McPherson**, 15 Riddell Street Woodstock, Ontario.
- Dr. Gerald A. McTague**, 1539 Erie Street, E., Windsor, Ontario.
- Dr. Arthur R. K. Matthews**, 2233 Harlem Blvd., Rockford, Illinois. Dr. Matthews is a pathologist at St. Anthony's Hospital in Rockford.
- Dr. E. J. Murphy**, 1459 Atkinson, Detroit, Michigan.
- Dr. W. Walker Ollerhead**, 999 Maitland Street, London, Ontario. Dr. Ollerhead is an Orthopedic Surgeon in London and also an Instructor in Anatomy at U.W.O. Medical School.
- Dr. Cecil A. Osborne**—deceased.
- Dr. Frank D. Poole**, 347 Sunset Drive, St. Thomas, Ontario. Dr. Poole retired in 1949 and has since been an art dealer and manufacturer of picture frames.



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**Dr. Norman W. Roame**, 1 Vernham Avenue, Willowdale, Ontario. Dr. Roame studied surgery under Dr. Lester Dragstedt, Department of Surgery, University of Chicago. He has his M.Sc., F.A.S.C. and F.A.A.S. In 1941, Dr. Roame was appointed Urologist-in-Chief at the Toronto Western Hospital. A note of interest is that Dr. Roame was a charter member of the Osler Society.

**Dr. William J. Ross**, Orwell, Ohio.

**Dr. Herman C. Savage**—deceased.

**Dr. Winston A. Sutherland**, Waterford, Ontario.

**Dr. L. Dewitt Wilcox**, 719 Waterloo St., London, Ontario. After graduation as the valedictorian of his class, Dr. Wilcox interned in Brantford General Hospital (1929-30), was a senior at Royal Victoria Hospital (1930-32), and studied at Johns Hopkins Hospital, Baltimore. Dr. Wilcox is presently practicing Internal Medicine in London and is Clinical Associate Professor of Medicine at U.W.O. Medical School.



# Echinococcosis

RICHARD E. WYLIE, '64

This paper was originally presented to the Alpha Omega Alpha Society on January 23, 1964. Dr. Wylie graduated from Western with honours and is presently doing his internship at Victoria Hospital, London.

*"When the liver is filled with water and bursts into epiploon, in this case the belly is filled with water and the patient dies."*

—Hippocrates, 55th Aphorism, Sect. VII

Though Echinococcosis is a rare disease in North America, it is not uncommon from a world-wide standpoint. With the advent of modern means of transportation and increased immigration from areas where this disease is endemic, there is now a greater possibility of seeing Echinococcosis in Canadian hospitals.

## Case History

The following is a short history of a case seen by the author in St. Joseph's Hospital, Hamilton, in June, 1963.

Miss S. P., a ten year old Italian female, was admitted to the Children's Ward for investigation of vague abdominal pain in the right upper quadrant.

This patient, born in a small rural town in Italy, had come to Canada at the age of 5 years. At that time, her health was excellent and she remained well until the age of 8, when she was hospitalized because of the right upper quadrant pain. This pain began after trivial trauma in this region. No diagnosis was made and she was discharged. She continued to have occasional slight right upper quadrant discomfort. She was readmitted almost one year to the day after her first admission with the same complaint. Again after investigation, no diagnosis was made. The only finding on this second admission was a slightly enlarged liver. After this discharge, her right upper quadrant pain become more frequent and more intense. She was readmitted in June of 1963. At this time she complained of slight fatigue, right upper quadrant pain and occasional right shoulder tip pain. Her liver edge was palpable 4 - 5 cm.

below the right costal margin. X-ray examination showed the right diaphragm to be much higher than the left and the liver shadow to be markedly enlarged. Laboratory tests, including liver function tests, were within normal limits.

At this time, she was seen by a pediatric surgeon, who suggested the diagnosis of Echinococcosis. An intradermal skin test specific for this disease was subsequently performed, and was positive. The patient was operated upon and a single cyst 8 - 10 cm. in diameter was found sitting directly below the diaphragm, in the right lobe of the liver. The cyst was removed in a manner to be discussed later, and fourteen days post-operatively she returned home in excellent condition and at last report is still asymptomatic.

## Parasitology

Echinococcosis is a disease caused by the larval form of the cestode, *Echinococcus granulosus*, a parasite of the dog, wolf and other wild carnivorous animals. The adult form is 3-6 mm. long and  $\frac{1}{2}$  mm. in breadth and has 3 - 4 proglottids. The head, or scolex, has 4 suckers and a double row of hooklets on the rostellum. The adult is attached to the mucous membrane of the jejunum in the definitive host (dog) and takes eight weeks to mature and has a life span of five months. The distal proglottid contains several thousand eggs. This proglottid as it matures, separates from the main body of the worm, disintegrates and the ova are passed in the faeces of the dog.

These eggs, passed in the faeces, have a chitinous outer coat and can survive extremes of climate for long periods of time, before being ingested by the intermediate host. The main intermediate hosts are



sheep, cattle, reindeer, moose, caribou and other herbivorous animals which ingest the ova by eating grasses contaminated with dog faeces.

Man may become an intermediate host, in a similar manner, by ingesting contaminated food or water, by handling pelts of infected wolves, or by fondling or living in close proximity to infected dogs. When the ova are ingested by the intermediate host, the chitinous outer capsule is digested by the intestinal juices. The freed ova then penetrate the mucosa, enter the capillaries of the portal system and are carried to the liver. The ova are usually arrested in the liver, but may pass through the liver and lodge in the lungs, or even pass through the lungs and be distributed in other areas of the body by the systemic circulation.

At this point, undoubtedly many of the ova are attacked by mononuclear leukocytes and are destroyed; however, those that do survive grow into a spherical mass. In three weeks the larval worm becomes vesicular and can be seen by the naked eye. In three months it attains a diameter of five cm. and within five weeks has doubled that size. The surrounding tissue of the host reacts to this foreign growth by forming a membrane around the cyst, called the ectocyst or adventitia. This ectocyst varies histologically with the organ involved. In the liver, the ectocyst forms a hyaline membrane consisting of degenerated liver cells and masses of connective tissue cells and lymphocytes. In the lung, a layer of atelectatic lung forms part of the adventitia. The whole composite structure, consisting of the vesicle with its fluid, the endocyst and ectocyst is known as a hydatid cyst.

In certain areas of the original cyst, germinal layer cells may proliferate and form a mass of cells which is itself eventually vesiculated. This spherical mass, called the brood capsule, projects into the centre of the mother cyst and in this brood cyst 5-20 scoleces may develop. Brood

capsules may become detached from the inner wall of the cyst and form a fine sediment in the hydatid fluid, known as hydatid sand.

The scoleces of this hydatid fluid have two alternatives in their future role in this disease. First, in the intermediate host they may escape to other parts of the body by rupture of the cyst or by accidental opening of the cyst at operation, and thus establish secondary cysts. Secondly, after slaughter or death, the viscera of a diseased animal may be ingested by carnivorous animals, which are the definitive hosts of this parasite, thus establishing the continuity of the life cycle.

The rate of growth of a hydatid cyst and its eventual size are dependant on the organ in which it is contained. Some cysts attain enormous size and one has been reported containing sixteen litres of fluid.

### Pathology

A cyst of the lung grows quite slowly. As it increases in size and impinges on a bronchus, the allergic reaction between the wall of the cyst and bronchus brings about an erosion of the latter, and often, associated with a paroxysm of coughing, the contents of the cyst are evacuated by a rupture of the bronchial wall. The patient may then become asymptomatic with no signs of the disease persisting. However, the cystic cavity may become infected with a resulting lung abscess. A peripherally placed cyst of the lung may also rupture into the pleural cavity, seeding this cavity with scoleces and brood capsules. Infection may intervene causing empyema, but as a rule secondary Echinococcosis does not result.

Cysts of the liver grow very slowly and are often difficult to detect and are late to cause symptoms. The enlarging cyst may eventually cause erosion of a bile duct. If this results in the filling of the cyst with bile, the death of the larvae and eventual calcification of the cyst may occur. On the



other hand the contents of the cyst may escape to the exterior or, depending on the size of the bile duct involved, cause obstruction or cholangitis.

A cyst in any organ may also impinge on a vein. If the vein is small it usually thromboses with no sequellae. However, if the vein is larger, it may be eroded by the enlarging cyst. Eventually a communication between the cyst cavity and the venous system is created and scoleces may then be carried, as emboli, to other areas of the body. This process is called secondary metastatic echinococcosis.

The relative frequency of cysts in various organs in man is:

Liver	57 - 76%
Lungs	3.8 - 14%
Peritoneum	1.4 - 18%
Pleura	0.7 - 0.9%
Skin & muscle	0.7 - 9.1%
Spleen	1.2 - 9.1%
Brain	0.9 - 2.0%
Spinal cord	0.8 - 0.9%
Kidney	1.6 - 6.1%
Bones	0.8 - 9.1%

### Incidence

As stated before, Echinococcosis is a disease of world-wide importance. The countries in which this disease is common are Iceland, Australia, New Zealand, Arabia, Algeria, Tunis, Egypt, Abyssinia, Argentina, and Uruguay. The importance of this disease can be seen especially in sheep raising countries such as New Zealand. This country, with a population of 2,400,000 people has a sheep population of 48,000,000. In 1958 it was said that in New Zealand, the disease was more common per capita than in any other country of the world. The relative incidence of the pulmonary form of the disease in New Zealand may be obtained from a report by Barrie in November, 1962. He states that in reviewing routine chest X-rays, as many cases of hydatid disease of the lung were

found as cancer of the lung, and that the disease made up 25% of the pathological findings in this survey.

In Toronto in May of '63, Finlayson and Fergus reviewed the cases of Echinococcosis in the Toronto hospitals since 1932. They found 35 cases, all but three of which had occurred since 1949. In Victoria Hospital, London, there have been only two reported cases since 1946.

### Clinical Features

The symptoms of Echinococcosis may vary markedly because of the variation in the site and the size of the cysts. In many cases, even after many years, a simple hydatid cyst does not noticeably affect the host's general condition. Most of the centrally located cysts in the liver, lung or spleen are painless.

Cysts in the lung may present as a productive cough if a cyst impinges on a bronchus. Hemoptysis may occur following the erosion of a bronchus. A peripheral cyst, after rupture into the pleural cavity, may cause pleurisy, signs and symptoms of empyema or pleural effusion. The patient who has had a rupture of a cyst into a bronchus may remember the incident, and may state that he coughed up a copious amount of clear fluid in one paroxysm of coughing. After an episode as above, the patient may present with fever and malaise and other signs of a lung abscess.

The classical triad of biliary colic, urticaria and jaundice has been quoted as the symptom complex of hydatid disease of the liver. This triad however, occurs only with rupture of a cyst into the biliary tract. The urticaria seen here, and that seen with rupture of cysts in other organs, is an allergic reaction to the cyst contents. Secondary bacterial infection of cysts results in the destruction of the parasite with resultant painful hepatomegally and spiking fevers such as seen in patients with pyogenic liver abscesses.



Cysts in bones may present as pathological fractures, and those in kidney with flank pain, dysuria, and hematuria. Evidence of space occupying lesions or the history of focal epilepsy may be the presenting symptoms in central nervous system involvement.

### Diagnosis

Rarely, the diagnosis may be made from the history, such as in the case of a spontaneous rupture of a lung cyst into a bronchus. In many cases, a cyst in the lung is picked up in routine chest X-ray. Calcification in the wall of a liver cyst may also be seen on X-ray examination. The above findings are often quite suggestive of the diagnosis and the diagnosis may be confirmed with the following laboratory tests:

1. Eosinophil Count—Eosinophilia is a variable finding in hydatid disease, and its absence does not rule out the presence of a hydatid cyst. Eosinophilia over 4% is said to be present in 50% of cases, but the eosinophil count may vary from 0% to 46%.
2. Casoni Test—Tomaso Casoni in 1911 made use of the fact that patients with hydatid disease became sensitized to hydatid fluid to utilize the intradermal test which still bears his name. This test had been found to be effective in 84-90% of patients. The test consists of the intradermal injection of sterile, purified hydatid antigen. Within ten minutes there is an immediate response in the form of a raised wheal which fades after one hour. Six hours later a delayed response occurs consisting of a localized area of edema with transitory erythema. The test may give a false positive if the patient is jaundiced, syphitic, or has ever harboured a tape worm other than *E. granulosus*.
3. Precipitin Reaction—This test was developed by Fleig and Lisbomme (1907) using a serum precipitin reaction but is technically difficult to perform and is thus not of great diagnostic value.

4. Complement Fixation Test—This test is specific and relies on the presence of specific hydatid antibody in the serum of patients who have absorbed hydatid antigen. The test is useful in the follow-up made on treated cases because it eventually becomes negative, whereas the Casoni Test remains positive for many years even after the successful surgical removal of a cyst.

### Complications

The complications of this disease may be divided into two main groups—those due to pressure effects and those due to rupture of a cyst. The many effects of pressure become obvious when it is considered that these cysts may develop in any organ of the body and thus by their increasing size may obstruct or compress many vital structures.

The effects of rupture of a cyst are due to the dissemination of scoleces from the primary cyst to form cysts in other parts of the body, or due to the frequency fatal anaphylactic reaction to the contents of a cyst suddenly released from their previously well encapsulated surroundings. This may happen after some trauma to an affected organ, or accidentally during operation.

### Treatment

There is, as yet, no suitable means of treating this disease medically, and the only definitive treatment is surgical. In surgically accessible locations, the cyst is exposed and then evacuated with a needle, care being taken not to allow spill of the contents. After aspiration, 10% formalin solution is instilled in the cavity to kill the remaining scoleces. The cyst is then opened, loculated areas drained if necessary, the inner lining removed and the cavity closed.

At present prophylaxis remains the only answer to the eradication of this disease. The most practical and profitable area of attack is against the definitive host, which is the dog population of a community. In



areas where prophylaxis has been attempted by periodically deworming dogs, disposing of stray dogs, and disposing of organs of affected animals at abattoirs so that other dogs may not be infected, the results have been very promising.

In this paper, no mention has been made of *E. multilocularis*, a variant of this disease, differing in its lower incidence and in the fact that well encapsulated cysts are not formed. This has made even surgical treatment very difficult, and only very radical surgical procedures such as hemihepatectomy have given any hope of cure.

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# Class of 1934

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**Dr. Irvin Berney** is now residing at 74 Whiteoak Drive, South Orange, New Jersey. He interned at St. Francis Hospital in La Crosse Wisconsin, and took residences in E. E. N. & T. at Detroit Eye, Ear Hospital, Newark City Hospital and the Bronx Eye and Ear Hospital. He is now in Private E. E. N. & T. Practice in Newark, New Jersey.

**Dr. Charles Buchanan** is living at 223 Highland Road, London. After interning at St. Joseph's Hospital he was House Surgeon at the Manhattan Eye, Ear and Throat Hospital in New York in 1935-36. In 1937 he obtained the Diploma in Ophthalmology at Oxford University and in 1938 the Diploma of the American Board of Ophthalmology. In 1939 he married Jeanne Fulton, Reg. N. of St. Thomas. During World War II he was a Squadron Leader in the R.C.A.F. In 1944 he obtained the Fellowship of the American College of Surgeons.

**Dr. Archibald Denison** of 450 Central Avenue, London, interned at Brantford General Hospital following graduation. He has been a resident at Children's Hospital in Montreal and Birmingham (Eng.) Children's Hospital following which he obtained the degree of R.C.P. & S. During the war he was in the Royal Canadian Army Medical Corps. Dr. Denison is one of the few Paediatricians who has become a Fellow of the American Academy of Paediatrics. Presently he is Clinical Assistant Professor of Paediatrics at U.W.O.

**Dr. William Fraser** who resides at 1209 Richmond Street, London, interned at St. Joseph's Hospital after graduating from U.W.O. In 1936 he married Roberta Bridgette and they have three children. Dr. Fraser has spent eleven years in General Practice at Fordwich, Ontario

and for the past few years has been in practice in London. In 1959 he was appointed head of the Research Committee of the Canadian College of General Practice.

**Dr. A. Lyle Hutton.** "Hap" Hutton lives at 15 Maple Avenue, Brantford, Ontario. In 1936 he married Helen Myrick and they have two children.

**Dr. Louis Karmel** resides at 1144 Pelham Parkway, Bronx 61, New York, U.S.A.

**Dr. Earl Lamont** of 893 Main Street, E., Hamilton, Ontario interned for two years at Hamilton General Hospital and spent one year in Industrial Medicine at STELCO. In 1938 he married Dorothy McKellar of Hamilton.

**Dr. Charles C. Lee** is believed to live at 40 London Street, Tillsonburg, Ontario. In 1938 he married Orra B. Doke. During the war Dr. Lee served in the R.C.A.F., retiring as a Squadron Leader.

**Dr. Anthony Mascari**—1 Victoria Embankment, Nottingham, England.

**Dr. James Mattax** of 903 Highland Avenue, Carrallton, Kentucky, interned at the Toledo Hospital following which he was Resident in Psychiatry at Ogdensburg State Hospital. Until 1943 he was in General Practice in Warren, Ohio. During the war he saw service with the 11th Anboine Division of the U.S. Army in New Guinea and the Phillippines. Since then he has been in General Practice in Carrollton, Kentucky.

**Dr. Joseph B. McKay** resides at 639 Broadway Avenue, Toronto 17, Ontario. From 1934-38 he was Resident Pathologist at Belleville General Hospital and in 1939 became a member of the Ontario Associ-



—Class of 1934—

ation of Pathologists. In 1945 he obtained his Specialist Certificate in Pathology and Bacteriology.

**Dr. Donald Millen**—1206 Ouellette Avenue, Windsor, Ontario.

**Dr. Fred J. Milner**—270 Victoria Street, London, Ontario.

**Dr. George Pogorzelski** of 2126 Parade Street, Erie, Pennsylvania is married to Eleanore Plachta. Since 1935, Dr. Pogorzelski has been Chief of the Division of Anesthesia at St. Vincent's Hospital in Erie. He has spent four years in the U.S. Army. In the years 1958-59 he was the President of Medical Staff at St. Vincent's Hospital.

**Dr. Frank Riggall** resides in Prairie Croue, Arkansas. In 1949, Dr. Riggall became a Fellow of the Royal Faculty of Physicians and Surgeons of Glasgow. He also is a Fellow of the Royal College of Surgeons of Edinburgh and a Fellow of the Royal College of Physicians. In 1959 he passed the exams for the Arkansas Bar, and in 1962 he became a member of the Bar of the U.S. Supreme Court. In 1964 Dr. Riggall became a Fellow of the College of Pathologists of London. In 1960 he was elected City Attorney of Prairie Croue after completing fourteen years as mayor.

**Dr. Charles D. Russell**—389 Simcoe Street, N., Oshawa, Ontario.

**Dr. Edgar Sherrin** of 19021 W. McNichols, Detroit 19, Michigan, has been Chief of Staff of Mount Carmel Mercy Hospital in Detroit.

**Dr. David Stanley** resides at 29 Park Avenue, Tarrytown, New York. He spent 1934-36 at New York Medical School studying E.E.N.&T. Since then, he has practiced medicine at Jasper, N.Y., Vancouver, Washington, in the U.S. Army and Tarrytown, N.Y.

**Dr. Willard H. Stanley**—630 Brookside Drive, Oshawa, Ontario.

**Dr. Donald Steer** of 450 Central Avenue, London, obtained his M.Sc. from U.W.O. in 1946 and his Fellowship in the Royal College of Surgeons (Edinburgh) and since has been practicing in London.

**Dr. C. Stewart Ward** of 890 Clearview, London was the first Western Mustang player to throw a forward pass in a Senior Intercollegiate game in London. He interned at Victoria Hospital, spent four years in the R.C.N. and has been in General Practice since.

**Dr. John Weinstock**—32 Giles Blvd., Windsor, Ontario.

**Dr. Andrew Williamson**—Deceased.

**Dr. Alexander Winter**—98-50 67th Ave., Rego Park 74, New York, N.Y., was in General Practice in New York City from 1935-42, following which he spent five years in the U.S. Army. From 1946-47 he was a Fellow in Roentgenology at Goldwater Memorial Hospital and from 1947-52 Attending Radiologist at Metropolitan Hospital in New York. Since 1952 he has been Attending Radiologist at Queens General Hospital.



# Physicians, Patients and Placebos

DAVID M. P. THOMSON, '64

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This paper was originally presented to the Alpha Omega Alpha Society on November 21, 1963. Dr. Thomson graduated, cum laude, and is presently taking his internship at the Montreal General Hospital.

Throughout the history of medicine, man has searched for drugs to assuage his discomforts and his agonies and yet he seems never to have completely made up his mind how he really felt about them. Associated with his search, there inevitably has been a wealth of magic and a close connection between drug treatment and healing by suggestion. Layman and physician alike have vacillated between almost magical belief in the efficacy of drugs and the other end of the scale—therapeutic nihilism. On the one hand, man undertakes the quest for a life-giving elixir or "a sweet oblivious antidote" and then, upon learning that "therein man must minister to himself" he, like Macbeth, bids physicians to "throw physic to the dogs" for he'll none of it. As time moves on and it is found that each new pharmaceutical discovery has promised more than actually delivered, then, each new generation of physicians has stood and watched disconsolately the waning power of a medication earlier endowed with great promise.

Davidson compares the introduction of new drugs to "the launching of pharmaceutical sputniks" into the therapeutic heavens.<sup>5</sup> He further suggests that these sputniks "often return promptly to their launching sites." He submits that these multi-coloured satellites may orbit for years, sustained by two powerful forces: medical ignorance of the placebo effect and the dissemination of this ignorance—doubtless unwittingly by the drug industry.

Lasagna outlines necessary conditions for the unwarranted success of some new drugs:<sup>11</sup>

1. A new drug must be essentially non-toxic.
2. No effective standard for comparison.
3. The drug must be allegedly useful for some disease or symptom, which is hard to evaluate, or has a high rate of spontaneous or placebo-induced remission.

Gold has made several statements which will probably be challenged because they are drastic.<sup>4</sup>

Firstly, although placebos are scarcely mentioned in the literature except for the last few years, they are administered more than any other group of drugs. Secondly, although few doctors admit that they give placebos, there is a placebo ingredient in practically every prescription. Thirdly, the placebo is a potent agent, and in its action can resemble almost any drug.

Let us trace the history of the word placebo. It is the first person singular, future tense of the Latin infinitive "placere", to please. The word placebo is equivalent to the phrase, "I shall please." The first use of the word dates back to at least the 13th century, appearing in the "Vespers for the Dead" in the Roman Catholic service. It is then found in Chaucer and Scott suggesting servility. It is defined as "commonplace method of medicine in the 1787 edition of Quincy's *Lexicon* and in the Philadelphia Medical Dictionary published in 1808.

A satisfactory definition of placebo is: a preparation containing no medicine (or



no medicine related to the complaint) and administered to cause the patient to believe he is receiving treatment.

We can divide placebos into three classes. The first is the pure placebo, e.g., the lactose tablet. These lactose tablets have been found to be more effective, if they are coloured either pink or blue, or better still, mottled. Then there is the impure placebo. This is the adulterated placebo, the false placebo, the bastard placebo, you might call it. It is adulterated with a drug which might have some pharmacologic action.

Whereas the patient is deceived by both "pure" and "impure" placebos, the physician may be deceived by the impure variety, attributing to them unwarranted therapeutic properties. The modern clinician-scientist feels uncomfortable in the use of sugar-pills of his frock-coated and bearded predecessor. He, instead, prescribes impure placebos and eases his conscience in the vain hope that some benefit may ensue. Weiss suggests that neurotic patients exhaust their physician's supply of placebos and then get themselves a new doctor.

For the third group there is the universal pleasing element which accompanies every prescription. You cannot write a prescription without the element of a placebo. It carries weight, the weight of two or three thousand years of medicine. The fact that it is signed by a doctor, that it has required a doctor to write out the prescription, that the prescription has to be taken to a drug store to be filled out, that the patient has to pay for it, that it has, perhaps a bad taste; these things are placebo elements in a prescription.

Of course, the history of placebos goes back, way beyond Hippocrates. They are the most ancient of drugs and we are safe in saying that in older times and in backward communities at the present, about 90% of the drugs which are given are placebos.

The history of medical treatment, although concordant with scientific progress

in general, is at the same time incredible. In ancient Egypt, according to the Ebers Papyrus, in 1500 B.C., patients were often treated with medication such as lizard's blood, crocodile dung, the teeth of swine and fly specs. Few treatments of specific value are found in all the pages of Hippocrates. In ancient Babylonia gastric complaints were treated by pouring burning juice of cassia over the patient. In the 17th century Paul of Aegina outlined the use of blood in treatment, e.g. owl blood for dyspnea. In 1827 in France thirty-three million leeches were imported for bleeding because domestic supplies were exhausted.

Consider the treatment by the physicians of his day that Charles II endured. A pint of blood was extracted from his right shoulder and one-half pint from his left shoulder, followed by an emetic, 2 physics, and an enema comprising 15 substances; the royal head was then shaved and a blister raised; then a sneezing powder, more emetics and bleeding, soothing potions; a plaster of pitch and pigeon dung on his feet, potions containing 10 different substances, chiefly herbs; finally 40 drops of extract of human skull, and the application of bezoar stone; after which his majesty died.

Despite the ignorance and superstition physicians must have benefitted their patients because they continued to be held in high esteem.

One may ask how physicians maintained their positions of honor and respect throughout history; in the face of thousands of years of prescribing what we know to-day to be useless and often dangerous medication? Indeed! this would have been a major accomplishment of the physician were it not for the fact that despite the uselessness of the drugs and procedures; physicians nevertheless did help their patients. One must conclude that potent placebo effect which characterizes the history of medical treatment is related in some as yet unelucidated way to the doctor-patient-relationship.



The extraordinary power of placebos merits special discussion. Its size and pervasiveness can best be illustrated by quantitative data from experimental studies.<sup>2</sup> In 15 different studies involving more than a thousand subjects, placebos satisfactorily relieved on the average  $35 \pm 2.2\%$  of subjects. The great power of placebos provides one of the strongest supports for the view, that drugs that are capable of altering subjective responses and symptoms; do so to an important degree through their effect on the reaction component of suffering.

Beecher, in studies of severe post-operative pain extending over a number of years, found that 30% or more of these individuals got satisfactory pain relief from a placebo.<sup>1</sup> This becomes more impressive when one realizes that Lasagna and Beecher found that the average effectiveness of a large dose of morphine 15 mgm/70 kg. body weight relieved only 75%. Thus of the average pain relief produced by a large dose of morphine in treating severe pain nearly half must be attributed to a placebo.<sup>3</sup> In another study, evidence was presented that placebos are more effective the greater the stress. This is supported by further observations that placebos are less effective in studies of experimental pain than they are when the pain arises in pathology. They are found to be ten times as effective in relieving pathological pain over experimental. Pathological pain produces more anxiety or stress.

Approximately the same high level of 35% effectiveness was produced whatever the subjective state under examination; pain of angina (26-38%), seasickness (58%), cough (40%), common cold (35%), and tension and anxiety (30%).

In a study of 199 patients with headache, 120 got relief from placebos.

Hillis in studies of inhibition of the cough reflex obtained an effect with placebos as great as that observed with 0.03 Grams Codeine.

Diehl investigated the ability of a vaccine to prevent colds. He found a reduction in the number of yearly colds of 55% among those given vaccine and 61% among a control group who received injections of isotonic Sodium Chloride. Besides these beneficial effects, placebos were held responsible for many untoward effects e.g. insomnia and dizziness.

The "placebo reactor" still remains to be positively identified. There is a great deal of disagreement about placebo reactors; whether they even exist is disputed. Wolf denies the existence of a "placebo reactor" and considers the placebo effect unpredictable and even variable in the same patient; a fundamental point, for Lasagna feels that reactors should be excluded from double-blind studies.<sup>12</sup>

Prior to the study of Lasagna no previous attempt had been made to investigate the distinguishing personality characteristics of the placebo reactor.<sup>10</sup> Lasagna concluded that the reactor is a recognizable type but only with the aid of an intensive interview, plus psychological testing. It was clear that the placebo reactors did not belong to the lunatic fringe of the population, they were neither whiners nor notable incompetents, neither male or female, neither young nor old. Their average intelligence was the same as that of the non reactors.

Some of the personality characteristics which differed in the reactor and non reactor were as follows. Reactors on the whole tended to be more expansive, cooperative and uncomplaining, regular church goers, and slightly less educated. They used drugs more frequently e.g. aspirin and cathartics.

On psychological testing, reactors were more anxious, more self-centered and preoccupied with internal bodily processes. They are individuals who seem more dependent on outside stimulation than on their own mental processes. Their instinc-



tual needs are greater and their control over social expression of these needs is less strongly defined.

Non reactors are far more rigid and emotionally controlled than the "average" for their age and background.

It may be postulated, that in stressful post-operative situations, placebo reactors behave in immature, dependent and yet more outwardly responsive fashion and thus receive considerable relief of pain through comfort received from attentive nursing care and from their confidence in the effectiveness of drugs. On the other hand, the non reactors, withdrawn and rigidly clinging to intellectual processes are less comforted by the care received, evidently more critical of drug effect.

Many authors regard the placebo effect as a direct expression of the doctor-patient relationship.

Wolf points out that the placebo as a symbol of the doctor says in effect "I will take care of you."<sup>19</sup> The person reacts to suggestion because what is suggested to him becomes reality. A whole body of knowledge, experience and wisdom is epitomized in that little pill for the patient.

Michael Balint points out that by far the most frequently used drug in general practice is the doctor himself, and that this is a drug without directions as to dosage form or frequency of administration, without allergic responses or undesirable side effects. Yet, this is an extremely powerful drug and those who use it relieve more suffering than has yet been recorded for the most powerful drug in the pharmacopeia.

Whereas the suffering patient looks to his doctor for comfort, the physician, in turn, is dependent upon his suffering charge. A recovery from illness, besides helping the patient, bolsters the physician's morale.<sup>18</sup> Dichter in a study of the medical personality notes that the physician's personality is a major factor in every cure.<sup>6</sup> But Dichter suggests that the physician is almost narcissistic in his self regard, citing

the example of one doctor who said, "When I get a good drug, I feel almost like God." Perhaps, herein lies an explanation of the average physician's weakness for unproven drugs and his prompt rejection of drugs that fail him. Therapeutic failures threaten his self image; therapeutic catastrophes shatter it. Perhaps more than compassion motivates the humble physician and perhaps with each prescription he treats himself as well as his charge.

Failure is an essential part of research but physicians do not like to fail. In practicing clinical research, there is an obvious conflict of loyalties which is not shared in purely medical work. Therefore, they avoid controlled clinical research and report primitive clinical trials with never-ending optimism.

Feldman noted that among some researchers their therapeutic success bore a statistical relationship to their enthusiasm for drug therapy. Those who were enthusiastic about the drug seemed to be far more successful than their psychotherapy-oriented colleagues.<sup>8</sup>

A few writers have made a random analysis of segments of the medical literature for evidence of clinical control. Faulds concluded that claims for the success of a treatment are closely associated with absence of the means whereby these claims can be scientifically substantiated.<sup>7</sup>

For example, one researcher undertook an exhaustive review of the literature relating to a "shut-gun" tranquillizer. The conclusions reached were that carefully controlled drug studies were a conspicuous rarity (1 out of 37 clinical reports); and that the value of the tranquillizer was nothing more than an expensive placebo. The one double-blind controlled study showed that the drug performed as the other investigators had said but so did the control placebo.

In the U.S. in 1958 an estimated 50 million prescriptions were written for tranquillizers. In the first nine months of that year, one manufacturer of a popular



tranquillizer sold 30 billion tablets. The Doctors' desks are covered with brochures expensively indicating in carefully scientific jargon that the door of the corner drugstore is the gateway to Nirvana. The eager and gullible public puts its physicians under pressure to supply happiness pills, while the latter all too often succumb to the discovery that here is an effective agent for getting the patient out of the office and the doctor out on the golf course. At some levels the ataractics have become not a new instrument, but successors to the vitamins as a facile substitute for it.<sup>9</sup>

With all this fanfare one would think that the professional literature would be full of studies of the tranquillizer in minor stress states. One learns with amazement that the enormous popularity of these drugs is unsupported by any weight of independent professional opinion.

There isn't any good evidence that, in mild dosage for mild disorders, the tranquillizers have any more beneficial action than could be provided by placebos. However, their placebo effect probably produces relaxation and sedation. To millions of people who have to be a bit numb to stand their own company this is enough. It may be concluded that in mankind's naive but age-old search to get happiness out of a bottle; the tranquillizer will rate as being a good deal more expensive than placebos and a good deal less honest than whiskey.

The epitome of unscientific candour is reported by Rose in one tranquillizer study he reviewed. This worker, obtaining 65% improvement in his study, concluded, "more would have got better, if it had not been for their neurotic need to remain sick."<sup>14</sup>

Physicians, to some extent, in one form or another recognize the widespread existence and potent influence of placebo effects. However, there is a marked tendency for them to recognize placebo effects more easily in the work and practice of

others than in their own work and practice. This is illustrated by the finding that three times as many physicians are of the opinion that they used placebos less frequently than their colleagues.

Shapiro, "believes that if we keep the thought that perhaps our treatments are only placebos we will appear as wise 100 years from now as do the compilers of the *Paris Pharmacologia* of a century ago: who said, "What pledge can be afforded that the boasted remedies of the present day will not, like their predecessors fall into disrepute and in their turn serve only as a humiliating memorial of the credulity and infatuation of the physicians who recommended and prescribed them."<sup>13,15</sup>

Shapiro states "that scientific medicine truly began only 7 or 8 decades ago and therefore, we are led to the inescapable conclusion that the history of medical treatment for the most part until relatively recently is the history of the placebo effect."<sup>15</sup> Although in the last few decades we have developed many scientifically proven and useful drugs e.g., antibiotics, the number of non-scientific and unproven medications are far greater and are continuing to grow. Unfortunately, through drug company promotion and the incompetent investigations of clinicians who enthusiastically postulate drug actions and in turn carry out many greatly successful clinical trials—uncontrolled of course!—these drugs take on the guise of scientific medications. Not until we recognize the potent placebo effect, and study and evaluate therapeutic efficacy in the light of the methodological principles stemming from this knowledge, will our faith in current nostrums, differ from that of our forebearers, who avidly digested crocodile dung, blood, and moss from the skull of executed criminals."<sup>16</sup>

This paper has not been presented in any spirit of iconoclasm. What we have attempted to do is to indicate that, in our opinion, a more critical attitude is needed towards various treatments. Some of these



will prove, in time, to have intrinsic but not specific value.

We realize that we have left much unsaid, but I fear to go further. Like Burton in his "Anatomy of Melancholy," "I shall urge these cavilling and contumelious thoughts no further, least some physician deny me physic when I'm ill." In other words, I am well persuaded by physic and when my time comes, I want either my tranquillizer or my stimulant, but I want it administered by a doctor wise in medical lore.

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# Class of 1944

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**Dr. Murray R. "Gus" Abell.** In 1944-45 he interned at St. Michael's Hospital in Toronto. In 1945 as a Captain in the Royal Canadian Army Medical Corps he married Ruth Summers who was a graduate in B.Sc.N. In 1947 he spent some time at Crumlin Military Hospital and then went to Westminster Hospital, London. He is now Professor of Pathology at University Hospital, Ann Arbor, Michigan.

**Dr. A. W. Banghart**—Deceased.

**Dr. John V. Christie**—Deceased.

**Dr. Harry A. Collins** lives at 538 Dundas Street, London, Ontario. After graduation, he interned at Victoria Hospital. Since then he has been in General Practice in Arkona, Ontario and London.

**Dr. R. Robert Dickson** now resides at 13 Marlene Drive, St. Catharines, Ontario. He interned at the Kingston General Hospital following which he was a Fellow in Pathology at Queen's University. In 1948 he was a Fellow in Medicine at the McGregor Clinic in Hamilton, following which he was Assistant Resident in Medicine at Westminster Hospital and Fellow in Medicine at the Lahey Clinic, Boston, Mass. In 1955, he obtained his certification and has been in Internal Medicine at St. Catharines. Besides his graduate work he found time to marry Kae Adams and they now have three children.

**Dr. Charles G. Drake** of 1545 Gloucester Road, London, interned at Toronto General Hospital, following which he was a Fellow in Neuroanatomy at U.W.O. A National Research Council Fellowship enable Dr. Drake to study physiology. In 1946, he married Ruth E. Pitts. In 1947 he studied physiology at Yale Uni-

versity before returning to Toronto General to study Neuro-surgery. He is now Assistant Professor of Surgery at U.W.O.

**Dr. J. Malcolm Edworthy** of Kamloops, B.C. interned at Kingston General Hospital following which he spent a year in the R.C.N. During 1947, he was in Internal Medicine at Kingston General Hospital. He then spent five years in General Practice in Kamloops, B.C., before going to Toronto Sick Children's Hospital to study Paediatrics. From Toronto he went to Bellevue Hospital in New York City and then back to Kamloops, B.C., in Paediatric Practice. In 1944 he married Margaret Bocking.

**Dr. John Eydt**—28 Searle Street, Hamilton, Ontario.

**Dr. Phillip Fleisher**—1178 Burr Street, Fairfield, Conn. U.S.A.

**Dr. Robert Gammie**—Hespeler, Ontario.

**Dr. Walter G. Harding**—R.R. 1, Preston, Ontario.

**Dr. John M. Howes** is at Shaughnessy Hospital, Vancouver where he is doing Post-Graduate work. In 1945, he married Elizabeth Galbraith.

**Dr. Allen C. Johnson** resides at 349 Shadowlawn Avenue, Pittsburg, Penn., with his wife the former Shirley Dresser also of Meds '44. Shirley interned at Toronto East General Hospital following which she was a Resident at Sick Children's Hospital in Toronto. In 1951 she was Certified in Paediatrics. In 1963, she received a Master's degree in Maternal and Child Health at the University of Pittsburgh and is now Assistant to the Director of Health Department for the city of Pittsburg.



Allen also interned at Toronto East General and then spent one year in the R.C.A.M.C. and then took his M.Sc. in Biochemistry at U.W.O. From 1949-50 he was Resident at Lahey Clinic in Boston and then he was with the University of Toronto, Department of Pathology. In 1964 he graduated in Hospital Administration at the University of Pittsburgh and appointed Administrator of Presbyterian University Hospital, Pittsburgh, Penn. and Assistant Professor of Medical and Hospital Research at the Graduate School of Public Health at the University of Pittsburgh.

**Dr. Siegfried J. Koegler** is now at the Children's Psychiatric Research Institute, London. He is also an instructor in Paediatrics at U.W.O.

**Dr. Harold O. Kreimer**, 300 Toke Street, Timmins, Ontario.

**Dr. R. B. Marchildon** is the the Medical Director at the Cartier Co., Port Cartier, Quebec.

**Dr. Robert McCubbin**, 436 Lake Street, Wilmette, Illinois, U.S.A.

**Dr. Orville R. Newton** of Box 446 Strathroy, Ontario interned at Hamilton General Hospital. In 1944, he married Elva P. Waters, Reg. N. Since leaving the R.C.A.F. he has been in General Practice in Strathroy.

**Dr. Jack S. Nichols**, 742 King Street, W. Kitchener, Ontario. Dr. Nichols interned at Montreal General Hospital and has an Obstetrics and Gynaecology Practice in Kitchener.

**Dr. K. Eric Rogers** resides at 292 Oakdale Avenue, St. Catherines, Ontario He was in the R.C.A.M.C. after interning and then did Graduate work at St. Michael's in Toronto, at Civic Hospital in Ottawa, Peter Brent Bringham Hospital in Boston and St. Mary's Hospital in London,

England. He also did research at Harvard Medical School. After being awarded his F.R.C.S.(C) he entered Surgery Practice in St. Catherines.

**Dr. T. Hanson Ross**, Hanover, Ontario.

**Dr. Kenneth W. Runnals** of 847 McIntyre Street, West, North Bay, Ontario interned at Victoria Hospital following which he spent a year in the R.C.A.M.C. In 1946, he entered the Ontario Hospital Service and now is Superintendent at the Ontario Hospital, North Bay.

**Dr. C. Borden Sanders** resides at 62 Pine Street, Welland, Ontario. He is married to Jean McKenzie, Reg.N. He spent 1946-51 in Graduate work in London and Toronto and obtained his F.R.C.P. (C) in 1951. Since then he has been in practice in Welland, specializing in Internal Medicine.

**Dr. Frank Shapiro**, 36 Wilson Street, Hamilton, Ontario.

**Dr. Jack Siddall** of 8763 Crest Drive, Burnaby, B.C. attended University of California Medical School as a Resident Fellow in Ophthalmology. In 1949 he married Dorothy S. Sproule in Edmonton. In 1950 he obtained his Certification.

**Dr. Lloyd G. Stevenson.** Immediately following his graduation, he married Jean Campbell, who is also a graduate of U.W.O. Dr. Stevenson interned at Oshawa General Hospital for 1 year following graduation, during which time he also worked on the biography of Sir Frederick Banting. For 1 year following his internship, Dr. Stevenson and his wife resided in England and it was during this time that their eldest son, Peter was born. In 1946, Dr. Stevenson returned to U.W.O. as an Associate Professor, lecturing in The History of Medicine. It was in 1946 that Dr. Stevenson's book 'Sir Frederick Banting'



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was published. Dr. Stevenson remained at U.W.O. until 1954, when he went to McGill University as Medical Librarian and Professor of History of Medicine. During the years Dr. Stevenson was at Western he received a Master's degree (1946) and subsequently a Ph.D. (1949) from Johns Hopkins University. Prior to their leaving London in 1954, the Stevenson's 2nd son, Hugh, was born. In 1958, Dr. Stevenson became Dean of the Faculty of Medicine at McGill University, remaining in this capacity until 1963. In 1963, Dr. Stevenson went to Yale University as Professor of History of Medicine. While at McGill University in 1961, Dr. Stevenson received a Doctorate of Letters degree from U.W.O. In addition to "Sir Frederick Banting", Dr. Stevenson is the author of "Nobel Prize Winners in Medicine and Physiology 1901-1950" which was published in 1953 and "The Meaning of Poison", published in 1959. Dr. Steven-

son's busy life allows him little time for hobbies. His chief interest aside from his work is in reading.

**Dr. Friel Stewart**, 310 Ouellette Avenue, Windsor, Ontario.

**Dr. J. Douglas Struthers**, 14 Chapman Street, Port Dover, Ontario.

**Dr. Arthur H. Sussman**, Suite 24, 345 Bloor Street, West, Toronto, Ontario.

**Dr. Ward Van Patter** of 9125 View Avenue, Seattle 7, Washington, interned at Montreal General and then took a Ph.D. in Surgery from the University of Minnesota.

**Dr. Cecil A. Wallace**, Box 71, Elora, Ontario.

**Dr. James K. Whittal**, 6521 27th Street, N.E., Seattle 15, Washington, U.S.A.



# Tissue and Organ Transplantation: Problems and Progress

D. MICHAEL GRACE, '64

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This paper was originally presented at the November 21, 1963 meeting of the Alpha Omega Alpha Society. Dr. Grace graduated, cum laude, from Western and was the recipient of many awards indicative of his high achievement as a student including the Howard Ferguson Trophy, the Medical Alumni Gold Medal, the Roche Scholarship, and the Poulenc Award and Gold Medal. He has also won a Rhodes Scholarship. Dr. Grace is presently taking his internship at Victoria Hospital, London.

In recent years there has been amazing progress in the field of tissue and organ homotransplantation. Workers in many branches of medicine and related sciences are working on this promising subject and the immunological problems which it has raised. A number of seemingly successful kidney transplants have been carried out in humans between identical twins, and with a lesser degree of success between relatives and unrelated subjects. The human liver and lung have been transplanted and there is considerable work on transplantation of the heart and other organs in experimental animals. At present more research is necessary in order to understand the true nature of the immune response, for this response must be modified if organ homotransplantation is to be successful.

First some of the basic definitions and concepts in this field should be reviewed. An autograft is tissue transplanted from one site to another in the same animal. This procedure is often used to study the techniques of transplantation and the effect of denervation on organs such as intestine and lung. A homograft is tissue transplanted from one animal to another of the same species. In homotransplantation a distinction should be made between homostatic and homovital grafts. Homo-

static grafts like bone and blood vessels act only as scaffolds which are infiltrated by the recipient's cells. In homovital grafts like the kidney, donor cells survive and continue to function in the body of the new host.

Some of the earliest work on renal homografts was performed by Carrell in 1902. Later, work on homotransplantation was carried out by Williamson and Ibuka in the 1920's. These workers showed that kidneys were always rejected when transplanted between dogs. This situation was contrasted with the continued function of kidneys transferred from one site to another in the same animal.

In 1944 and 1945, Medawar working in London, England, reported his studies on skin homograft behaviour in rabbits. He developed the concept that homograft rejection is the result of an immune response in the host against antigens of the graft. For his work Medawar shared the 1960 Nobel prize in medicine and physiology with Sir MacFarlane Burnet.

Medawar described primary and secondary responses to transplanted skin. The primary response occurs when the recipient of the transplant is not sensitized. There is a lag period of some days before the graft is rejected. During the first few days



vascular and lymph channels enter the graft. Nuclear amino acid complexes are carried to the regional lymph nodes where cells proliferate in response to the antigenic stimulus. These cells are carried by the blood to the homotransplant site where they appear to be responsible for rejection. Circulating antibodies have been described but their role in graft rejection is probably secondary to the activity of sensitized cells. After five or six days the graft is infiltrated with lymphocytes, plasma cells, and eosinophils. Vascular dilatation occurs with stagnation of blood and thrombosis of the vessels. Interstitial edema and hemorrhage follows and there is finally necrosis and loss of the graft.

This rejection occurs despite complete perfection of technical details and despite the absence of infection. It occurs for whole organs transplanted by the anastomosis of blood vessels, for skin or minced tissue acquiring blood supply by outgrowth of small vessels, and for direct intravenous transplantation of homopoietic tissues.

A secondary or accelerated immune response occurs in sensitized animal. A great variety of cells from the donor will sensitize the recipient so that a subsequent graft is rapidly rejected. Removal of lymph nodes delays the primary response but does not hinder the secondary response. Some workers think that there is a similarity between the homograft reaction and that which occurs in delayed skin reactions such as the tuberculin reaction. In both there are perivascular infiltrates of mononuclear cells and similar infiltrates are found in autoimmune disorders like Hashimoto's disease.

The exact nature of the immune response is the subject of considerable research and controversy. It is known that the immune system of the newborn animal is poorly developed. Cells from an embryo mouse can be injected into a newborn mouse of a different strain. Some of these cells persist in the host and so it appears that host and donor cells become tolerant of each other. The result is a mouse which

has two sets of genetic characteristics and is thus called a chimera. This mouse will later accept grafts from the original donor. It is not known yet if this tolerance is a property of individual cells or of selective clonal elimination as advocated by Burnet.

There is an interesting result if adult spleen or lymph node cells are injected into a newborn mouse. The mouse does not grow and develops a diffuse dermatitis and diarrhea. There is enlargement of the spleen and lymph nodes, atrophy of the thymus and blood dyscrasias occur. This process was called runt disease by Billingham and Brent who first described it in 1957. It is postulated that runt disease is due to the effect of graft antibodies on the defenseless host and hence the effect is called a graft versus host reaction. A picture similar to that of runt disease was observed by Trentin in adult animals subjected to massive irradiation and bone marrow homo-transplants. This disease was called secondary or homologous disease. Again this may be an example of a graft versus host reaction.

Recently there has been considerable work on the role of the thymus in immunity. Miller in London has shown that thymectomy has little effect on adult rodents except to decrease the level of circulating lymphocytes. Mice thymectomized at birth are normal for a few weeks and then die of a wasting disease which is similar to runt disease. These mice are deficient in blood lymphocytes and in lymphoid tissues and they are unable to produce antibodies against foreign antigens. Thus many of these mice are unable to reject skin homografts from other strains of mice. Immunity is re-established if a thymus is grafted into the young mouse, but homografts are accepted from the thymus donor.

In adult mice the thymus is necessary for the re-establishment of immunity in a radiated animal. A mouse which is subjected to radiation and thymectomy is permanently unable to reject homografts. How-



ever if the thymus is left, immunity may be re-established in the radiated mouse. Thus it appears that the thymus is necessary for the development and re-establishment of immunity, and thus has a role in the rejection of homografts.

The most important cell in transplant rejection appears to be the sensitized small lymphocyte. Billingham has shown that skin homograft sensitivity can be transferred to tolerant rats by inoculating lymphocytes from sensitized animals. It has been demonstrated in humans that skin homografts between mother and child usually last longer than those between father and child. This may be due to the occurrence of cell transfer between fetus and mother. Apparently white cells, but not red cells, are important in homograft transplantation for the important antigens are carried in the nuclei. Further immunological studies of nucleic acid function are necessary in order to solve the problem of homograft rejection.

Recent studies indicate that humeral factors may be important. Lymphocytes in chambers with cell-impermeable walls, still accelerate skin graft rejection when transplanted subcutaneously. These cells probably gave off some factors which speed up the rejection of the homograft. Thus the exact role of the sensitized lymphocyte is still in doubt.

In homograft transplantation the immune response may be modified in two ways:

1. By performing transplants between genetically similar animals such as inbred strains of mice or identical twins.
2. By depressing the production of immunity with irradiation, steroids, and chemicals such as antimetabolites.

The first factor then for successful homograft transplantation is genetic similarity between host and donor. In identical or monozygotic twins, tissue can be permanently grafted from one twin to the other. From a biological point of view this is a special form of autograft since the two subjects are genetically identical.

In animals homografts of many different organs have been carried out, but homograft transplantation in humans has been limited almost entirely to the kidney. The kidney has provided some of the most precise information on graft function because its excretory products can be accurately evaluated. A number of human kidney homografts have been carried out between identical twins and recipients who were in terminal renal failure have now lived four or five years, and have even given birth to children.

For successful homograft transplantation between unrelated subjects, every effort must be made to achieve the highest degree of tissue compatibility possible. This has been done first of all by matching blood groups and subgroups. Different tissue typing techniques have been introduced in an attempt to match the antigens of host and donor more accurately and thus slow the rejection of a homograft. A leucocyte agglutination method has been used to compare the response of recipient and donor white cells to a standard serum. In another test, lymphocytes of a prospective graft recipient are injected intradermally into a potential donor, and the local reaction graded in severity. The best donor is the one with the least reaction.

Chances of homograft survival are higher if the subjects are antigenically similar. However the immune response must still be suppressed for subjects other than identical twins. Natural suppression of the immune response has been observed in uremia, generalized malignancy, and in hypogammaglobulinemia.

Experimentally many substances have been used to prevent the rejection of homografts. Prolonged homograft survival has been produced using steroids, anti-metabolites, and irradiation. Steroids have prolonged the survival of skin homografts but high doses are necessary and the graft is rejected when medication is stopped. For kidney transplants, steroids have usually been used in conjunction with anti-metabolites.



The use of antimetabolites was stimulated by the work of Damashek and Schwartz who described the immunosuppressive effect of 6-mercapto-purine in 1959. In 1960 Calne and Zukoski reported increased survival of renal transplants using chemotherapy. Antimetabolites used since then include purine analogues like 6-mercapto-purine and Imuran, folic acid antagonists like methotrexate, and antibiotics like actinomycin C and D. In spite of the use of these drugs, the results of kidney transplants between other than identical twins are not good. Deaths occur due to kidney rejection, renal failure, drug toxicity, or septicemia following complete suppression of the immune response. Usually the kidney recipient does not live more than a few months, although rare cases have lived 6 months to one year or more. Murray in Boston has a patient who is alive and well 5 years after receiving a kidney from a non-identical twin.

Antimetabolites seem to provide the best method of suppressing the immune response because the dosage can be easily altered. Imuran has been the most successful of these agents during the last several years. Whole body radiation has been tried but there is a great danger of infection because of complete suppression of the immune response. Bone marrow transplants have been attempted in radiated humans but in general these have functioned poorly and have been rejected. Recently however there was a successful bone marrow transplant in France.

Because of these various difficulties, renal transplantation remains a dangerous procedure which should be reserved for patients in the terminal stages of renal failure. Centres carrying out homotransplantation must have a source of healthy kidneys, excellent surgeons, specialists on renal function, and extensive laboratory facilities in order to assess kidney function in the graft recipient.

Work is also being done on the transplantation of other organs. The first human liver transplant was performed in

Denver in May of this year in a patient with extensive carcinoma of the liver. The patient died after 23 days with thrombosis of the inferior vena cava. There were few signs of liver rejection. More human liver transplants have been performed since with temporary success and the human lung has been transplanted also. Transplanted parathyroids have functioned for a short time and nerve homografts have been used successfully to bridge large nerve deficits.

In animals the scope of homotransplantation has been wide. Workers have performed auto and homotransplantation of lung, liver, heart, kidney, endocrine organs, limbs, and multiple visceral structures. Monkey kidneys have been transplanted to humans with short-term success.

Cardiac homotransplantation has not been very successful because of the immune response and because ventricular fibrillation often occurs in the denervated heart. Workers in various centres, particularly the Department of Artificial Organs of the Cleveland Clinic, have gone one step further and are devising artificial hearts. It is now possible to imagine a plastic heart, remotely controlled and electronically regulated being used in humans in the near future.

The immune response is the greatest barrier to successful homotransplantation and may never be surmounted. However there are also lesser obstacles. One concerns the effect of denervation on organ function and more experimentation is needed in this area. Another is related to the storage of organs so they remain viable. Cooling and freezing has been tried as well as perfusion with hypothermic solutions using a pump oxygenator. At present homotransplantation must be carried out quickly by several teams of surgeons to achieve success and the best source of organs is a living patient. A third problem is moral in nature. Should the future health of a kidney donor be risked for the dubious results now achieved with kidney homografts?



Although many more questions remain to be answered and many more problems must be solved, the progress in this field is now rapid. It is possible that in the future, worn out or diseased organs will be replaced at will and that new years will be added to the human life span which has already doubled in the past century.

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# Class of 1959

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- Dr. James Bain**, 9 Kingsford Crescent, London, Ontario, interned at St. Michael's Hospital, Toronto. He is married with one son and one daughter. He is now a resident in Anaesthesia at Victoria Hospital in London, Ontario.
- Dr. Hugh W. K. Barr**, 26 Underhill Drive, Apt. 401, Chloisters of the Don, Don Mills, Ontario, interned at Toronto General Hospital. He served a residency in neurosurgery here and in England. He is married with three children.
- Dr. Peter R. Boyer**, 20211 Rosemount Avenue, Detroit, Michigan, interned at Hotel Dieu, Windsor. He is now practicing in Detroit and is married and has one son.
- Dr. Lawrence A. Burk**, 654 Viscount Ave., London, Ontario, interned at Victoria Hospital. He is now married and has four children.
- Dr. Edward L. Burrton**, 38 Woodstock Rd., Golder's Green, London, N.W. 11, England, interned at Vancouver General Hospital.
- Dr. Peter Cardillo**, Maumee Valley Hospital, 2025 Arlington Avenue, Toledo 9, Ohio, interned at St. Joseph's Hospital, Flint, Michigan.
- Dr. Noel Chant**, 18 Spruce Street, Apt. 2D, Galt, Ontario. He was married in July 1963.
- Dr. Edward M. Dundas**, 6867 Parkway Circle, Dearborn Heights, Michigan, interned at Grace Hospital, Detroit. He served a general practice residency at Oakwood Hospital, Dearborn. In 1961 he succeeded his father in general practice.
- Dr. Gene Gordon Essert**, 11677 N.E. Glisen, Portland, Oregon, interned at Hotel Dieu, Windsor. Then he served a residency in psychiatry at the Lafayette Clinic, Detroit and at the same time worked on a Ph.D. in Psychology at Wayne State University. Now he is in private practice as a psychiatrist as well as consultant to Lane County Mental Health Clinic in Eugene, Oregon, Consultant to Clark County Mental Health Clinic in Vancouver, Washington, Consultant to the Oregon State Board of Education in Vocational Rehabilitation and Clinical Instructor in Psychiatry at the University of Oregon.
- Dr. Bruce Feaver**, Box 1420, Kapaskasing, Ontario. He is in general practice and married with 2 children.
- Dr. Marie Jeanne Ferrari**, 12946 Riverside Drive, Tecumseh, Ontario, interned at Montreal General Hospital. She did post-graduate work at Memorial Hospital for Cancer and Allied Diseases, New York. Present activities not known.
- Dr. Norman Fretz**, 2275 Victoria, Windsor, Ontario.
- Dr. Paul Galway**, 1242 Stanton Road, Ottawa, Ontario.
- Dr. William Gedz**, 176 Galloway Road, West Hill, Ontario.
- Dr. Roy Gillick**, 1639 Louise Blvd., London, Ontario. Now in general practice.
- Dr. Ross Gillman**, 480 William Street, London, Ontario.
- Dr. Ronald Kimber**, 34 Cottonwood Drive, Don Mills, Ontario.
- Dr. William A. Kindree**, Ontario Hospital, Owen Sound, Ontario. He did Post-graduate work at the Ontario Hospital, St. Thomas; Ontario Hospital, London;



- Huron Road Hospital, Cleveland, Ohio; Hotel Dieu, Windsor. He was married in 1959.
- Dr. Alexander Kolibac**, Columbia Hospital of Richmond County, 2020 Hampton Street, Columbia, South Carolina, interned at Hotel Dieu, Windsor. From 1959-61 he was at Hotel Dieu, Windsor. He was Resident in Orthopaedic Surgery at Columbia Hospital from 1961-64. He is presently at the Austin Moore Clinic, Columbia, South Carolina.
- Dr. Robert Linton**, 31 Ardaven Place, London, Ontario, is presently Resident in Anaesthesia at Victoria Hospital.
- Dr. Marvin Lipton**, 1726 Caravan, Dallas, Texas, interned at Mount Zion Hospital, San Francisco, California. He was at the U. S. Army Hospital, Orthopedic Department, Fort Hood, Texas, in 1962.
- Dr. Thomas Lofft**, Department of Psychiatry, University of Michigan Medical Centre, Ann Arbor, Michigan, interned at St. Michael's Hospital, Toronto. From 1960-61 he was at the Department of National Health and Welfare. In 1961 he did Post-graduate work in psychiatry in Ann Arbor.
- Dr. O. Earle McCutcheon**, 4271 Emerson Street, Riverside, California.
- Dr. Gene McDonald**, 30 Drew Avenue, Galt, Ontario, interned at St. Joseph's Hospital, London, Ontario. He is now in general practice.
- Dr. and Mrs. A. Robert McKay** (nee Berta Taylor), 15905 San Juan, Detroit 38, Michigan. Interned at Detroit Memorial Hospital. They now have a four-year-old daughter.
- Dr. William Manax**, c/o University Hospital, Department of Surgery, Minneapolis, Minnesota, interned at Baylor Hospital, Texas.
- Dr. Gordon Martyn**, 23119 Edsel Ford Street, Clair Shores, Michigan, interned at Harper Hospital, Detroit.
- Dr. Robert J. Mason**, 2775 Academy Drive, Windsor, Ontario, interned in Denver, Colorado. He did his residency in psychiatry at U.W.O. and received his certification. In November 1963 he became director of the Ontario Mental Health Clinic in Windsor. This is to be incorporated into a new I.O.D.E. Community Psychiatric Hospital which, along with a 50 bed neurosurgical unit, will be part of a new 350 bed general hospital in Windsor.
- Dr. Carl Moore**, 22 David Street, Dundas, Ontario, interned at Hamilton General Hospital. He is married with one daughter.
- Dr. Frank T. Murdock**, 4669 Oak Street, Vancouver, B.C., interned at St. Joseph's Hospital, London. He practiced at Hagersville, Ontario until 1961. His present activities in British Columbia are unknown. He is married with 2 daughters.
- Dr. Steve Radin**, 97 Euclid Avenue, London, Ontario, interned at Victoria Hospital and is studying for his fellowship in surgery this year. He was married in June, 1963.
- Dr. H. Campbell Robinson**, 1140 Baseline Road, London, Ontario, interned at Toronto General Hospital.
- Dr. Ted Roman**, 4532 Melrose Avenue, Montreal 38, Quebec, interned at Toronto General Hospital. He spent a year or two in Vancouver. He is now resident in Obstetrics and Gynaecology at Royal Victoria Maternity Hospital, Montreal. He was married in 1960 and now has one daughter.
- Dr. Otto Salonen**, 100 Hinton Avenue, Port Arthur, Ontario, interned at Hotel



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Dieu, Windsor. He is presently in general practice and is married with 4 children.

**Dr. Howard Searle**, 2347 Edgewood Blvd., Berkley, Michigan, 48075, interned at St. Michael's Hospital, Toronto. He is married and has one son.

**Dr. George Sennewald**, 4814 Terrace Drive, N. E. Seattle, Washington, interned at General Hospital, Pontiac, Michigan.

**Dr. Hugh A. Short**, 227 Lloyminn Avenue, Ancaster, Ontario. Interned at St. Joseph's Hospital, London.

**Dr. Theodore Stiller**, 4940 Coronet, Apt. 4, Montreal, Quebec, interned at Montreal General Hospital. He is presently resident in Othopaedic Surgery. He is married with one child.

**Dr. F. Rance Smeeton**, 2815 Avendale Court, Windsor, Ontario, interned at Victoria Hospital. He is now in general practice in Windsor and married in June, 1960.

**Dr. Keith Smith**, St. Luke's Hospital, Cleveland, Ohio, interned at Montreal General Hospital. He is now serving his residency in Pathology at McGill.

**Mrs. Leslie Somlo** (Agnes Marta Beer), interned at Montreal General Hospital. She is now serving her residency in Medicine at Queen Mary Veterans Hospital.

**Dr. Donald Stevens**, 66 Forest Glen Road, Newmarket, Ontario, interned at St.

Joseph's Hospital, London. He did Post-graduate work in Montreal and is presently in practice in Newmarket.

**Dr. John P. Sweeney**, 43 Piccadilly Street, London, Ontario, interned at Victoria Hospital. He is presently studying for his fellowship in surgery. He is married with two sons.

**Dr. Martin Taylor**, 11 Arrowstock Road, Willowdale, Ontario, interned at Toronto East General Hospital. He is now in general practice in east Toronto and is married with two children.

**Dr. Henry Thut**, 15 Havill Street, Galt, Ontario, interned at Hamilton General Hospital. He is now in general practice in Galt and is married with two sons.

**Dr. Nicholas Vasiloff**, Department of Anesthesia, U.C.L.A. Medical Centre, Los Angeles 24, California, interned at Hamilton General Hospital and has studied at the following centers before joining the staff at U.C.L.A. Medical Centre:

1960-61: Southern California Permanent Medical Group, Pasadena.

1961-62: Los Angeles.

1962: Department of Paediatrics, Los Angeles County General Hospital.

**Dr. Francis Wm. Walker**, 29 Giles Street, Oxford, England, interned at St. Joseph's Hospital, London. He served his residency at Victoria Hospital and in England in Anaesthesia.

**Dr. David F. White**, 20 Killerton Avenue, London, Ontario.



# Letters From Other Years

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1924—**Dr. Archibald A. Bond** of 7520 Altama Road, Jacksonville, Florida spent over 25 years in Kenya, East Africa as a medical officer. In 1953 he was forced to retire on account of failure of health.

1940—**Dr. Owen D. Cousins** has recently been assigned as executive officer of the 819th U. S. Army Hospital Centre, Orleans, France. He has been in France since 1962. He entered the U. S. Army in 1941. He is married to the former Evelyn Burleson of Muskogee, Okla. and has a daughter Anne, 11.

1946—**Dr. A. R. Bainborough** after graduation obtained his M.Sc. degree in Pathology from McGill University. At present he is Pathologist at Lethbridge Municipal Hospital and St. Michael's Hospital and President Elect of the Canadian Association of Pathologists.

**Dr. W. J. Wills** is residing at 815 Fleming Avenue, Ottawa, 8, Ontario. After graduation he interned at Hamilton General Hospital and went into General Practice at Peterborough from 1947-49. In 1946 he married Charlotte Godby, Reg.N. In 1949 he joined the R.C.A.F. as a Medical Officer, and has served at numerous postings since. From 1953-54 he took a Senior Internship in Pathology at Hamilton General Hospital and then became a Resident in Pathology at Ottawa General Hospital and then Research Fellow in Pathology at the University of Ottawa. In 1962 he obtained his Certification in Pathology and the following year the degree M.Sc. in Pathology. He is now a Wing Commander and is Assistant Pathologist at the National Defence Medical Center. He and his wife have four children.

1947—**Dr. Lebert Harris** is now residing at 15W 72nd Street, New York, N. Y. He is a practicing psychoanalyst in New York City and is a consultant to the Department of Surgery of Long Island Jewish Hospital. He also lectures to internes and residents in psychosomatic medicine.

**Dr. P. G. Skelton** can be reached at 201 Caspen Hall, Department of Pathology, State University of New York at Buffalo, Buffalo 14, New York. In 1952 he obtained his Ph.D. degree from the University of Montreal. In 1961 he was appointed Professor and Chairman of the Department of Pathology at the State University of New York. He is a member of the Pathology Study Section of the U. S. Department of Health, Education and Welfare. He is the 1964 President of the Erie County Heart Association. He has also received the NIH grant for studying the Pathogenesis of Experimental Hypertension.

1948—**Dr. R. S. Morphy**, 216 McDonald avenue, Belleville, Ontario. Dr. Morphy interned at Hamilton General Hospital and also was a Senior Intern in Surgery there. He was Assistant Resident in Urology at Shaughnessy Hospital, Vancouver and then spent one year at Vancouver General Hospital. In 1953 he was Certified in Urology. He then spent eleven months in London in practice and since 1954 has been in Belleville, on the consulting staff of the Belleville, Picton and Trenton Hospital. In 1951 he married Vera H. Whittergham, Reg.N. and they have four children.

**Dr. Martin H. Humphrys** has been in General Practice in St. Mary's for the past 12 years. Following internship he



spent 2 years in London, Ontario and then went to St. Mary's where he is in group practice with four other U.W.O. graduates: Dr. Wm. Davis, Dr. Don Munro, Dr. J. Mackney and Dr. J. Hiscock.

1949—Dr. David G. Sim can be reached at 452 Main Street E., Hamilton, Ontario. He interned at Hamilton General Hospital and then obtained his Diploma in Psychiatry from the University of Toronto in 1953. He obtained his Certification in 1955, while on the staff of the O. H. Hamilton. Since 1956 he has been in Psychiatric Practice in Hamilton. He is on the staff of Hamilton Civic Hospital and on the courtesy staff of St. Joseph's Hospital and Chedoke General Hospital. He is consulting psychiatrist to the Ontario Reformatory, Guelph. He married Lila Dennis in 1949 and they have three children.

1950—Dr. J. S. W. Aldis, c/o Seccombe House, 443 Mount Pleasant Road, Toronto 7, Ontario. Dr. Aldis writes that he has been editor of *Modern Medicine of Canada/Medicine Modern du Canada* and *Applied Therapeutics* for eight months now. He suggests hopefully that Seccombe House is considering offering an award for the best medical journal in Canada.

Dr. R. E. Schenck resides at R. R. 2, W. 7th Street, Portland, Indiana. He interned at Methodist Hospital in Gary, Indiana and then entered a General Surgery and Orthopaedic Residency at Methodist Hospital in Indianapolis. He is now in Private Practice in General and Traumatic Surgery in Portland, Indiana and at present is Chief of Surgery at Jay County Hospital at Portland and is Deputy County Coroner.

Dr. Hugh J. Williams resides at 5 Sunset Lane, North Oaks, St. Paul 10, Minnesota. From 1951-56, Hugh was in General Practice in Morocco, Indiana. He then proceeded to obtain his Fellowship in Radiology at the Mayo Clinic

and his M.Sc. (Radiology) from the University of Minnesota. At present he is Radiologist at Children's Hospital, St. Paul and C. T. Miller Hospital also in St. Paul, and Clinical Instructor in Radiology at the University of Minnesota.

Dr. Raymond H. Prince of 4280 Western Avenue, Apt. 3, Montreal, recently completed a study of the management of psychiatric disorders in Nigeria and is currently assisting the Cornell Group in its Sterling County Study. He also is Lecturer in Psychiatry at McGill University.

1951—Dr. A. S. Norris, 5425 S. W. Burton Drive, Portland, Oregon. Since 1957 Dr. Norris has been Associate Professor of Psychiatry and Director of Psychiatric Out Patient Clinics at the University of Oregon Medical School, Portland, Oregon. Prior to that he held the post of Associate Professor of Psychiatry at the State University of Iowa Medical School. He has been active in research, especially "Capillary Morphology, its Role in Mental Illness" and various other clinical projects, including psychosomatic Gynaecology and Obstetrics. In 1946 he was elected Fellow of the American Psychiatric Association.

1952—Dr. E. Q. Harrison is in Ophthalmology Practice at 366 Central Avenue, London. In 1957 she obtained her Certification in Ophthalmology. She is married to Tibor B. Alexander of London.

Dr. George L. Clarke of 309 Lancaster Street, W., Kitchener, Ontario, interned at Kitchener-Waterloo Hospital. He then was Senior Intern in Medicine and Surgery at Colonial Hospital P.O.S. J/dad. From 1954-58 he was in general practice in Kitchener. He then entered a Residency in Obstetrics and Gynaecology at St. Joseph's Hospital, London and at Victoria Hospital. From 1960-61 he was Senior Registrar in Obstetrics and Gynaecology at University College



Hospital, Jamaica. In 1962 he obtained the M.R.G.O.G. and the Canadian Certification.

1953—**Dr. Gerald Swartz** resides at 5555 Main Street, Williamsville 21, New York. He is presently doing Ophthalmology in Buffalo with special emphasis in Retinal detachment.

1954—**Dr. Nancy Alexander** interned at Victoria Hospital and then spent another year at St. Thomas Elgin General Hospital, following which she was in General Practice in St. Thomas. In 1962 she began a psychiatric residency and is presently a psychiatric resident at O. H. St. Thomas.

**Dr. Michael Dietrich** of 112 Altadore Crescent, Woodstock, Ontario, interned at the Kaiser Foundation Hospital in

Oakland, California. He then was Resident in Pathology at Henry Ford Hospital in Detroit, Michigan and Hotel Dieu Hospital, Windsor, Ontario. Following this he spent 4½ years at Hotel Dieu Hospital and 1½ years at Wayne County General Hospital, Eloise, Michigan. Presently he is Director of Laboratories at the Woodstock General Hospital, Woodstock, Ontario. (He was certified in Pathology in 1959).

**Dr. J. D. Campbell** of 214 6th Avenue, S. W. Calgary, Alberta is practicing Otolaryngology at the Calgary Associate Clinic.

**Dr. W. E. Keil** after interning spent six years training in medicine and psychiatry. He obtained his certificate in 1960 and is now Director of the Department of Psychiatry and Clinical Assistant Professor of Psychiatry at U.W.O.



# Letter To The Editor

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Dear Sir,

I have read with interest the article entitled, "A View of Pre Medicine", written by Mr. Gary Gibson, in Volume 34, Number 3, May 1964 issue. A thoughtful paper of this nature is obviously the result of considerable study and work, and the author is especially to be commended in view of the fact that this article was produced in the face of a very heavy study schedule.

There is contained in the article, however, some reasoning, and conclusions which, I would suggest, are open to question. Perhaps I might make comment, without fear of academic bias, on some of the statements which Mr. Gibson has made.

I think one would have to take issue with the collegiate misconception that a curriculum, or curricula in general, is arbitrarily established by any individual, be it the Dean of a Faculty, or his delegate, or even by a Curriculum Committee. Undergraduate curricula are arranged after much study and deliberation, and are arrived at by more or less general agreement among a group of highly competent, and highly interested persons. The results of much experience are considered in deciding what to teach, how to teach it, and with what end result in mind. The desired end product inevitably must be considered in the establishment of a curriculum, and in a dynamic profession, such as medicine, this obviously increases the difficulties attendant thereon.

In addition, one must be clear in his mind, that there is a vital and profound difference between training and education, between a trained person and an educated one, and between a Training or Trade

School, and an Educational Institution. The Trade School is concerned with producing skilled tradesmen or craftsmen, and the Educational Institution is concerned with producing an educated person. While there are many differences between trained and educated persons, the central difference is that a trained person can act, and an educated person can think.

While the complete Doctor must be a skilled craftsman and technician, he must demonstrate additional, and perhaps more profound capabilities. It is difficult to see how these latter abilities can be adequately developed save on the framework of a truly liberal education. It is perhaps understandable that the great mass of technical knowledge which he must absorb has made the medical tyro, and perhaps all Doctors, more parochial in his outlook; but it is lamentable that it is evidently doing so at the expense of his education in the humanities and the arts.

Sadly, Mr. Gibson singles out English as a subject whose abandonment he would evidently favour, to be replaced by a course say in Cellular Micro-biology. Certainly, imperfect and inadequate communication between individuals is one of the pressing problems of the day, and the profession of medicine is anything but remote from this difficulty. Having been witness to, and experienced considerable difficulty in the field of inter-personal communication, it would be my suggestion that, rather than removing English from the curriculum, it be continued throughout the medical school years. Cogent and lucid self expression is vital to the successful practice of medicine.

One can generate a considerable amount of sympathy for Mr. Gibson, labouring as he is under a very heavy schedule, and



being besieged with mountains of technical information. It should be pointed out to him, however, and to undergraduates in general, that, beyond the final set of examinations, is a hazy world of great responsibility and challenge, and of perpetual examination, for which all his undergraduate training and all his liberal education will never fully prepare him.

The medical profession, in spite of an ever increasing degree of technical capability, does not at the moment enjoy a particularly high degree of public esteem. There are, of course, many reasons for this and many reasons which are only remotely related to the undergraduate curriculum. I think it is true, however, that it will be difficult for the medical profession to resume a role of leadership, and high respect, in the community, if the

level of liberal education among Doctors is lowered.

Mr. Gibson suggests that, with the level of education in the population at large increasing, that the medical profession can afford to leave community leadership and responsibility to others. I suggest that quite the opposite is true; that as the level of general education rises, the Doctor will have to be an increasingly well educated man, in order to remain a relevant and influential force in the community.

The problems attendant upon the practice of medicine are many and varied indeed. It is gratifying to see an undergraduate giving some concern and some consideration to these matters.

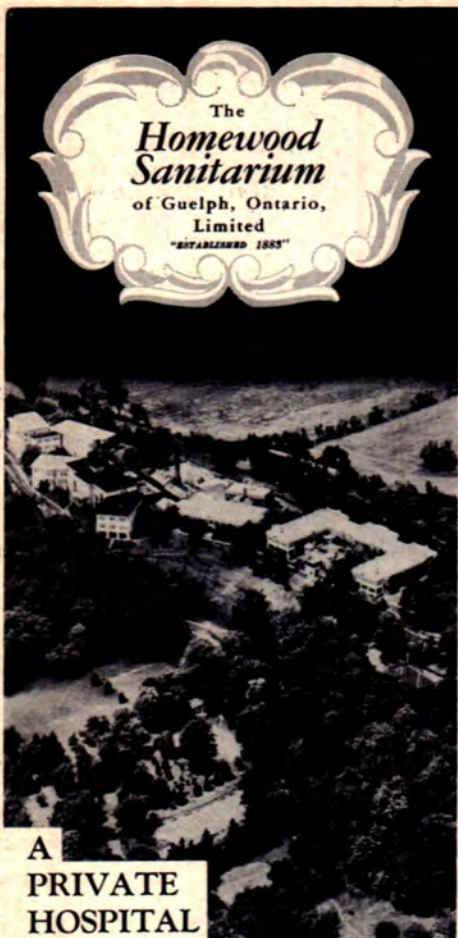
Your very truly,  
Andrew T. Hunter, M.D.  
London, Ontario.



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