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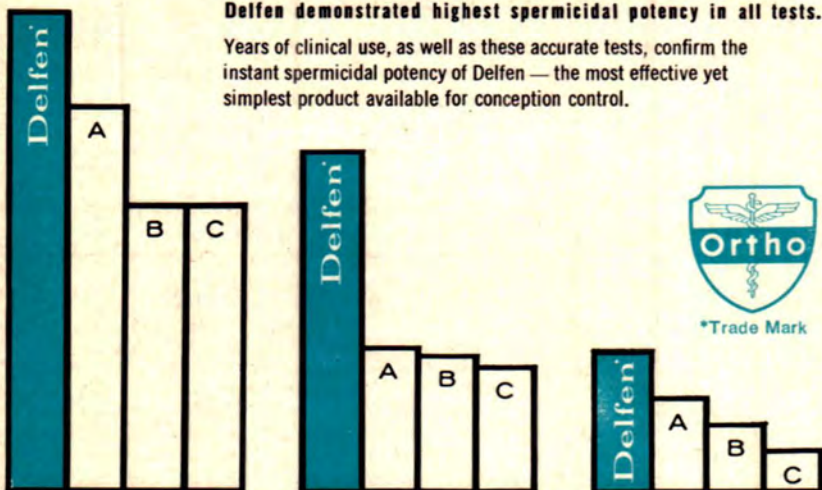
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Reference: (1) MacLeod, J.; Sobrero, A., and Inglis, W.: In Vitro Assessment of Commercial Contraceptive Jellies and Creams, J.A.M.A. 176:427-431 (May 6) 1961.

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# Cystic Fibrosis

SHIGERU SUGIYAMA, '64

## INTRODUCTION

Cystic fibrosis, also known as Mucoviscidosis and Fibrocystic Disease of the Pancreas, may be defined as a hereditary congenital disease characterized by dysfunction of many of the exocrine glands. Three main systems of the body are involved; the respiratory tract, the digestive tract and the sweat glands. The most obvious effects are susceptibility to all types of pulmonary diseases, morphologic changes in the pancreas with a deficiency of its enzymes and a high concentration of electrolytes in the sweat. The basic metabolic defect is unknown, but the secretion of an abnormal, viscid mucus by the mucous glands of the respiratory and the digestive tracts is a well known feature of the disease. In the majority of untreated cases, death occurs in infancy or childhood. However, a better understanding of this disease and its proper therapy and management has led to an increasing number of patients surviving to the second and third decades. As a result, this disease presents a challenge to the physician.

## HISTORY

In 1905, Landsteiner described pancreatic lesions in a case of congenital intestinal obstruction due to meconium ileus. Thus, attention was first focused on the pancreas, but it was soon realized that severe pulmonary involvement was present in almost all of these cases. In 1938, Dorothy H. Andersen analyzed all available case records and gave the first complete description of this disease. She noted that this was a relatively common familial disease. With clinical recognition and improved therapy, and particularly with the advent of antibiotics, the clinical picture and the life span of these patients was improved. More recently, abnormality of secretions of sweat and salivary glands, and cirrhosis of the liver have been recognized.

## ETIOLOGY AND INCIDENCE

Anderson and Hodges have claimed that Cystic Fibrosis appears when a recessive gene is present in the double or homozygous condition. This finding has generally been accepted and confirmed by Lowe, May and Reed.

It is estimated that one in thirty individuals of the Caucasian races carry this recessive gene. The likelihood of the occurrence of both parents being carriers is  $1/30$

$\times 1/30$  or one in nine hundred marriages. Statistically at least, of every four children of such parents, one will have the disease, two will be symptomless carriers and one will neither carry nor have the disease. The incidence of Cystic Fibrosis should be  $1/900 \times 1/4$  or one in 3,600 live births. Clinically, however, various reports indicate a greater incidence ranging from 0.7 to 2.03 cases per 1000 live births. This disease occurs mainly in the Caucasian races. It is seldom found in the Negro race and is excessively rare in the Oriental races.

## PATHOGENESIS

This disease affects a number of glands and organs in a variety of ways. It seems apparent that the abnormal function and structure of many tissues is probably secondary to abnormality of the mucus. It is now generally believed that the pancreas is damaged by obstruction of its ducts by abnormally viscid mucus. However, the abnormal salt loss in the sweat and parotid saliva has suggested that the basic defect does not lie only in the molecular structure of muco-protein of the body, but that the metabolism of a variety of exocrine glands is abnormal in some as yet unknown and more fundamental way. Efforts are still being made to find such a single primary basis for the disease.



## PATHOLOGY

The most consistent findings are pulmonary and pancreatic lesions, malnutrition and retarded growth. These are essentially the result of the underlying disorder which is believed to be the production of an abnormal mucus.

### (A) Respiratory Tract

The pathological findings of the respiratory tract vary in degree and number with the age at which death has occurred. Thick mucopurulent exudate which may contain cellular debris, leukocytes, necrotic bronchial epithelium, strands of mucus and masses of bacteria, commonly *Staphylococcus Aureus*, *Pseudomonas Aeruginosa* and *Proteus Vulgaris*, is found in the bronchi and alveoli. As a result, focal or segmental atelectasis, lobular pneumonia, enlarged tracheobronchial glands, chronic suppurative bronchitis, bronchiectasis, emphysema, multiple small bronchiogenic abscesses, pneumothorax, pyothorax and pyopneumothorax may be found.

### (b) Digestive Tract

1) *Pancreas*: Pancreatic lesions are rarely absent. The thick, abnormal secretion of the pancreatic acini and ducts is the cause of the obstruction. Initially there is dilatation of the acini and ducts, followed by atrophy of the acinar tissue and ultimate replacement by connective tissue. This eventually results in fibrosis of the entire gland. The Islets of Langerhans remain normal.

2) *Meconium Ileus*: Congenital intestinal obstruction due to an abnormal meconium is seen in 10-15% of infants born with Cystic Fibrosis. This meconium mass which is usually found in the terminal ileum may be gray, green or brown with the consistency of dried putty. It is composed of a homogeneous eosinophilic material which contains a few squames from the amniotic fluid, hyaline and an excess of abnormal thick gel mucoprotein. This abnormal meconium has been attributed to two factors: the lack of pancreatic digestion of

the meconium and the abnormal products of secretion of the intestinal glands.

3) *Liver*: Liver enlargement with some increase of fat deposition, and multilobular biliary cirrhosis with concretions in the small bile ducts have been reported.

4) *Other Gastrointestinal Changes*: All glands of the gastrointestinal tract may show an excessive mucus production with concretions in their ducts. The stomach is generally larger and more muscular than normal. Peptic ulcers have been reported in the older age group. Usually, the small and large bowels show a mild hypertrophy.

## CLINICAL FEATURES

The clinical features and physical findings vary, but in the majority of the patients chronic pulmonary disease, malnutrition and retardation of growth despite an excellent appetite, are common.

Most usually, the digestive and nutritional symptoms appear before the respiratory manifestations. In infancy and early childhood, failure to gain weight accompanied by a history of 3 to 5 massive foul smelling stools a day is noted. Balance studies have shown fecal loss of about half the ingested protein and fat and less wastage of carbohydrate. This has been attributed to pancreatic deficiency with poor absorption of food.

The failure to absorb fat-soluble vitamins associated with steatorrhea often occurs. Vitamin A deficiency can cause xerophthalmia and squamous metaplasia of the bronchial epithelium, Vitamin D deficiency can produce Osteoporosis and Rickets, Vitamin E deficiency may lead to muscle weakness and degeneration of the gastro-intestinal tract, and Vitamin K deficiency can cause excessive bleeding.

Rectal prolapse, which may be attributed to diarrhea or massive stools in wasted patients, has been frequently reported, while in older patients, peptic ulcers have been noted.



Besides meconium ileus of the newborn, a few cases of "late meconium ileus" due to impacted feces have been reported. In both of these situations, the clinical picture is that of bowel obstruction.

The respiratory infections are almost a constant feature of the disease. Persistent cough often initiated by acute rhinitis usually occurs before six months of age. Difficulty in relieving the tracheo-bronchial tree of its content becomes obvious, and the infection usually progresses to produce pulmonary complications. As a result, the following symptoms and signs may appear: chronic cough, audible respirations, decreased resistance to infection, barrel-shaped chest, intercostal and suprasternal retraction, cyanosis, tachypnea, clubbing of fingers and toes and respiratory acidosis.

Excessive salt loss in the sweat of these patients may cause heat prostration, and sometimes death.

## DIAGNOSIS

The diagnosis will only be made if the possibility of its occurrence is kept constantly in mind. Special attention in history taking should be given to the family history because of the inherited nature of the disease.

The physical examination should place special emphasis on the respiratory and the digestive systems.

Laboratory tests are extremely useful in diagnosis of the disease. Before 1949, the tests consisted mainly of analysis for enzyme content of pancreatic secretions. Tryptic activity is most usually tested. This can be done by placing a drop of duodenal juice on a gelatin covered photographic film. Lack of digestion of the gelatin indicates the absence of the enzyme. This test is adequate in 90% of the cases, but it is misleading in those patients in whom pancreatic function is partially preserved or even normal. Furthermore, duodenal drainage is both a time consuming proced-

ure and a very traumatic experience for the patient. This test is unsuitable for routine testing. Fat absorption tests and fecal fat analysis are equally unsatisfactory.

After the demonstration in 1948 by di Sant'Agnesse of an abnormal sweat electrolyte content, Shwachman introduced a test for content of sodium and chlorides on sweat collected by enclosing the patient in a plastic bag. Although this method is time consuming, cumbersome, and not entirely safe, it is a great advance since the sweat chloride content is abnormal in 99% of these patients. The normal range of chloride ions is 10 to 40 mEq/litre of sweat; in borderline cases of Cystic Fibrosis, the chloride values vary from 40 to 60 mEq., and in established cases, the values vary from 60 to 140 mEq., with a mean of 100 mEq.

In 1959, Gibson and Cooke introduced the Iontophoresis Method for inducing local sweating. This method has been tested by the author and the results were found to be comparable to the sweat bag method. This method is simple, convenient rapid and safe.

The X-ray findings of the pulmonary lesions, while fairly characteristic, and the pulmonary function tests, while almost always abnormal, only serve as an adjunct to the sweat test.

Four diagnostic criteria should be followed in arriving at a diagnosis. These are pancreatic deficiency, pulmonary pathology, abnormal sweat and a family history.

## TREATMENT

Early diagnosis is most important in the treatment to prevent irreversible changes in the pathology of the lungs and to ensure the growth rate of these patients. Since Cystic Fibrosis is an incurable but treatable disease, the role of the physician is of primary importance. He must maintain a careful and progressive clinical evaluation of the patient, a continuing and changing therapy to suit the patient's varying needs, and he must develop a good



patient-physician relationship. The chronicity of this disease demands the consideration of the psychologic factors, encouragement and support, and genetic counselling for both parent and patient. Without these objectives, the physician will fail in the best management of the patient.

The pulmonary lesion is due to the accumulation of abnormal viscid secretions in the tracheobronchial tree. Since this abnormality is genetic, it is a constant and lifelong process. This abnormal viscid mucus impairs the normal cleaning mechanism of the lung leading to obstruction, stagnation and secondary infection. Treatment by both physical and chemical means is directed to eliminate the obstructive lesion and improve pulmonary hygiene.

In the treatment of the obstructive pulmonary lesion, three aims or objectives must be considered: first to decrease the viscosity of the pulmonary secretions, secondly to improve drainage of the pulmonary secretion, and thirdly to control and prevent lung infection.

To decrease the viscosity of the pulmonary secretion, the patient breathes, for definite periods through the day, high-density water vapour mist. The aim is the deposition of particulate water in the bronchioles and the alveoli of the lung. 10% by volume of propylene glycol is added to the water vapour mist to stabilize the particle size and their deposition at these sites. Inhalation therapy by face mask is also used to deposit, in the tracheobronchial tree, decongestants and bronchodilators. Postural drainage accompanied by clapping with cupped hand all areas of the patient's chest, vibration of the chest, and the encouragement of the patient to cough and expectorate is most important. Breathing exercises and encouragement of full physical activity help to maintain pulmonary ventilation. To control and prevent pulmonary infection, regular sputum cultures are taken and the appropriate antibiotics are given systemically or by in-

halation. All this therapy requires very elaborate equipment and full cooperation from both parents and patient.

Provided adequate pancreatic enzyme replacement is given, there need be no strict limitation of diet. One should aim at a full diet, somewhat high in protein and somewhat low in fat. Vitamin supplements should be given to prevent deficiencies.

When rectal prolapse occurs, conservative treatment with the control of steatorrhea by proper dietary regime and adequate pancreatic extract replacement is usually sufficient.

The sweat gland defect can be controlled with adequate salt replacement in the diet, especially in hot water.

### PROGNOSIS

The fate of patients with Cystic Fibrosis is usually determined by the course of the pulmonary lesions. Pancreatic insufficiency affects the growth and state of nutrition, but rarely causes death. Therefore, all pulmonary lesions must be controlled by early diagnosis and proper therapeutic measures.

Whereas up to 10 years ago the diagnosis amounted almost to a death sentence, the prognosis of this disease has now greatly improved. However, the future of the individual patient is still unpredictable, especially in infancy. But, much can be done for the patient with Cystic Fibrosis. Many now live almost normal lives.

### Acknowledgement

Suggestions and assistance from Dr. G. H. Valentine, Assistant Professor of Pediatrics, are gratefully acknowledged. The author was able to serve as Research Assistant in the Department of Pediatrics in the summer of 1962 through the generosity of the Cystic Fibrosis Foundation of Canada.

*Continued on Page 12*



# Genetic Counseling

HERBERT MANZ, '63

## INTRODUCTION

This field of medical practice, though based on scientific principles and biostatistics, is nevertheless an art which deals with human relationships between counselor and client and concerns itself with the hopes and fears of a sizable proportion of our population. It is found that of all new-born infants, 2-3% show some abnormality. Due to latency in appearance, this figure is doubled at 1 year of age. Of course, one must realize that not all of these unfortunate infants have their defect on a genetic or chromosomal basis. Environmental influences—such as infections, toxins, drugs, irradiation, endocrinopathy, etc.—during intra-uterine life can cause a certain proportion of these abnormalities.

## DEFINITION

In considering this topic, it is of value to define its compass. "Genetic" pertains to origin or beginning or having to do with birth; consequently the term deals with hereditary factors. "Counseling" is an interchange of opinion, or deliberation together, or consultation.

Genetic counseling, accordingly, is an aspect to medical practice in which someone qualified gives genetic advice to those who need it, so that a decision may be reached about the advisability of having future children who might have the same anomaly. Stated emphatically, it is not a birth control, planned parenthood or marriage licencing agency. Since its basis is purely scientific, it does not concern itself directly with religious or ethical precepts, though concepts may change in the future.

## STRUCTURE OF A GENETIC CLINIC

Such an institute should by choice be associated with a medical and university center and affiliated with a hospital. This arrangement facilitates detection of cases, investigation, diagnosis, treatment, research, and information and guidance.

Ideally, a heredity clinic would be staffed by a medical director, a human geneticist, a statistician, a physician, laboratory and research technicians, and a secretary. But probably even more important to the client, the counselor must be able to put the facts truthfully yet warmly; he must

quote chances or odds yet not force his opinion; above all, he must be human with a sincere devotion to helping the clients in their dilemma.

Financial support is made available usually from the medical school budget, supplemented by grants from government and voluntary agencies and, to a minor degree, from fees for services rendered. (None of the Canadian genetic counseling clinics charges a fee.)

## PROCEDURE OF INVESTIGATION

If parents are so unfortunate as to have a child with a gross abnormality, they will usually turn first to their family physician regarding the likelihood of a future pregnancy terminating in an identical abnormality. If he feels competent, he may counsel the parents himself, though more likely he will refer them to a heredity clinic and urge them to attend it with their child. On the basis of diagnosis, family history, and thorough knowledge of the pertinent literature, the genetic counselor can give sound advice.

1. *Diagnosis*: Often specialist opinion with cumbersome laboratory investigation is required to arrive at the correct diagnosis of some of the rare inherited conditions. For more reliable genetic prognosis, detailed analysis of minor differences in the phenotype from the classical description, age of onset of symptoms, and pattern and course



of the disease may be required to elucidate the mode of transmission and to assess the empirical risk.

2. *Family History*: With the lead subject or "propositus" as focus, inquiries are made regarding previous pregnancies of the mother and their outcome, her siblings and their children, and her parents. Then inquiry is made about her uncles, aunts, and cousins as to any relevant symptoms. Finally, it is of importance to know whether the parents are related as cousins or some other degree of consanguinity. A similar detailed history of the father's family is obtained.

3. *Background of Literature*: An individual family history only rarely will give adequate information for determining the mode of transmission of the particular condition. Not only must published pedigrees be collected but also assessed as to thoroughness of investigation and freedom from bias in selection. Moreover, there may be alternative modes of inheritance for the same clinical entity. Since some conditions are sometimes inherited, at other times caused by unfortunate intrauterine circumstances, the empiric risk figures are not precise, if the groups with different etiologies cannot be separated. The genetic counselor must accordingly assess the chances of the particular condition also on the basis of his judgment about the validity and thoroughness of investigation of published pedigrees.

#### EMPIRIC RISK FIGURES

These are "statements, based on experience rather than understanding of etiological mechanisms, of the likelihood that a particular condition will be present or develop in a particular individual under a particular set of circumstances".<sup>5</sup> Since older mothers deliver children with a markedly higher incidence of congenital malformations, assembly of statistics should consider only children born subsequent to

the birth of the first affected for a more accurate assessment of the statistical chances. It must be admitted that these are tentative values, subject to revision in the light of future experience. As a general, though not infallible rule, the less clearly the genetic mechanism of a defect has been delineated, the more favorable the prognosis appears to be.

#### HOW THE CLIENT SHOULD BE COUNSELED

At no time must the counselor decide whether or not future pregnancies should be initiated. People invariably resent such infringement on their privacy and freedom of choice. What is required is an explanation of the chances. People do understand, to a limited extent, answers given in terms of odds, though it must be admitted there is still much superstition surrounding probabilities expressed in a mathematical manner. If empiric risk figures, presented in terms of odds, are to be properly evaluated, some yardsticks are required against which to measure them. First, any random pregnancy has a chance of 1 in 40 of ending with some serious congenital malformation! Secondly, if the empiric risk for a subsequent child being similarly affected is not worse than 1 in 20, the client has really little to worry about.

As regards autosomal dominant inheritance, there is a chance of 1 in 2 that a subsequent child will be affected (of course, the isolated case might be due to a *new* mutation.)

With sex-linked recessive genes, laws of the mode of transmission are well known and genetic prognosis quite accurately predictable as regards males. It is the female relatives who are faced with a difficult decision, e.g., the sister of a hemophiliac has a 1 in 2 chance of being a carrier, particularly with a background of hemophilia in previous generations.



With regard to autosomal recessive genes, the parents can be informed that there is a 1 in 4 chance that any subsequent child will be similarly affected. Now it must be clearly stated to the parents that harmful recessive genes in the heterozygous state are by no means infrequent; it is only the affected persons who are rare. Thirdly, every person carries an estimated 7 or 8 recessive genes in the usually innocuous heterozygous form, which would prove either lethal or produce severe defects, if found in the homozygous state. The only difference between an affected homozygous person and everyone else is that he **knows he will pass on a particular, harmful gene to his children**, whereas the rest of us are quite certainly maintaining the pool of harmful genes, without knowing which particular genes are involved.

## PSYCHOLOGICAL FACTORS

Genetic counseling not only implies assessing risks and quoting statistics, but also dispelling guilt and combatting false notions. Clients who are affected or have affected children should be helped to live with their hard lot through rationalization of the problem, and to face courageously some added measure of risk.

It is of great value to explain to the client that intra-uterine development is an exceedingly complex and marvelous process. One must be amazed at how infrequently something does go wrong! However, unfortunate circumstances, which we are unable to control or even predict, sometimes result in a marriage in which both partners happen to be carriers of the same deleterious gene. And even then the 1 in 4 chance of homozygous recessive offspring need not come about, particularly when families are small.

The clients' minds might be plagued by questions such as, "Why did this unusual but painful accident happen to us?" One can only reply that though the particular abnormality is rare, it has to afflict some-

body. Much more difficult to console is the couple who have two or more children afflicted with the same or unrelated defects. Here, one points out, two or three independent pieces of bad luck may have coincided.

Further relief from anxiety comes from the fact that some inherited defects are curable or at least correctable. Advances in orthopaedics, biochemistry, cardiac surgery, endocrinology, and pharmacology have certainly alleviated some of the physical disabilities and functional incapacitations of congenital or hereditary anomalies.

It is also wise to assure the couple that it is not necessarily the wife or her family nor on the other hand the husband or his family who are to be held responsible, but that this misfortune happened to this particular married couple as a unit. This will often allay overt or covert resentments or self-accusations.

## FUTURE TRENDS

Eugenics, the science treating of the betterment of the human race, is gaining ever-increasing impetus. Negative eugenics concerns itself with the discouragement of matings between individuals representing types considered undesirable and uses the following methods: marriage restriction, segregation, and sterilization. Extermination is utterly untenable.

Positive eugenics is the other side of the coin and concerns itself with increasing the frequency of desirable traits by such means as regulation of immigration, subsidy to superior individuals with a premium on large families, education, promotion of genetic research, and improvement of environmental conditions.

Any improvement in human heredity is desirable and accordingly looms large in the public health aspects of the community. Such idealized traits as health, intelligence, moral character, and beauty are certainly not the lot of a large segment of any pop-



ulation group, and are therefore desirable. But marked improvement can by no means be expected in the near future.

A recent development has been the detection of carriers of some hereditary disorders before these are actually transmitted to the children. It is, for instance, possible to detect heterozygous congenital spherocytic anemia by a blood smear and hypotonic saline fragility test or epileptiform tendency by an electroencephalogram.

Theoretically, at least, parthenogenesis might be employed in the human race, or otherwise the rearing of "test tube babies", or perhaps even substituting desirable for undesirable genes in the germ cells.

Brilliant horizons beckon to anyone not frightened by the multitude and enormity of problems to be solved in that tremendously important subject, man's heredity.

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#### Appendix

A. Some pediatric conditions in which empiric risk figures for recurrence can be used. (Mechanism of transmission not accurately known, since environmental factors influence the genetic potentialities.)

Anencephaly  
Hydrocephaly  
Spina bifida (open)  
Cleft lip  
Cleft lip with cleft palate  
Clubfoot  
Congenital dislocation of hip  
Pyloric stenosis  
Congenital heart disease (certain types)  
Epilepsy  
Juvenile diabetes mellitus  
Mongolism (non-disjunction type)

B. Some pediatric conditions in which mechanism of inheritance is known and more precise probabilities for recurrence can be given.

Hemophilia A  
Hemophilia B (Christmas Disease)  
Hemolytic disease of the newborn (Erythroblastosis fetalis)

Sickle cell anemia  
Hypophosphatasia  
Albinism  
Cystinuria  
Galactosemia  
Phenylketonuria  
Glucose-6-phosphate dehydrogenase deficiency (Favism)  
Hepatolenticular degeneration (Wilson's Disease)  
Nephrogenic diabetes insipidus  
Childhood muscular dystrophy (Duchenne type)  
Myotonia congenita (Thomsen's Disease)  
Amyotonia congenita (Werdnig-Hoffmann's Syndrome)  
Infantile amaurotic idiocy (Tay-Sachs Disease)  
Juvenile amaurotic idiocy  
Laurence-Moon-Biedl Syndrome  
Achondroplasia (chondrodystrophy)  
Marfan's Syndrome  
Osteogenesis imperfecta  
Congenital nerve deafness  
Fibrocystic disease of the pancreas  
Mongolism (Translocation type)

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# The Children's Psychiatric Research Institute

London, Ontario

ROBIN S. SHEARER, '64

## INTRODUCTION

Because of the advances in medicine which have taken place over the past fifty years, many of the serious and crippling childhood diseases are now under control or can be prevented by various means. This has resulted fairly recently in stimulated interest in mental retardation by medical men. This, along with pressure exerted by parental groups, has resulted in the establishment of centres where these unfortunate children may be cared for and treated.

No truly large scale study has been undertaken to date to assess the number of mentally retarded children in our population. The figure which is often quoted is that of between 1 and 3% of the general population. Small studies have shown that the incidence varies with the age group being examined.

According to the American Association of Mental Deficiency all children having an I.Q. of less than 85 are considered mentally retarded. Because of the close watch which is kept on them it would be expected that the highest incidence of mental retardation might be found in the school age population. This, of course, does not mean that children below this age group are any less retarded, but by virtue of the fact that over 75% of mentally retarded children are only mildly retarded, their condition is much more likely to be spotted once they start attending a school and thus become exposed to direct comparison with other children by an experienced and unbiased observer—the teacher.

The Children's Psychiatric Research Institute in London is the first specialized clinic to be organized in Ontario for the diagnosis, assessment and therapy of children suspected of being mentally retarded, brain damaged, or mentally ill. In fact, this institute is one of the most up to date of its kind in North America. The clinic

serves 10 counties in South Western Ontario having a population of approximately 1,200,000.

The Institute was started in February 1960 and is financed entirely by the Mental Health Division of the Ontario Department of Health. The in-patient service began in February 1961. Several years of planning and waiting were put in before the Institute finally took shape. In addition to certain individuals who have been very keen on the formation of such a clinic for many years, three main groups were responsible for its origin:

1) *The Ontario Association for Retarded Children.*

This organization consists of parents and friends of retarded children and one of its aims is to improve the facilities for treatment and research in mental retardation.

ii) *The University of Western Ontario.*

Dr. Murray Barr and several associates have been doing cytogenetic and biochemical research connected with mental retardation for several years and drawing their patients from Orillia, some 200 miles north-east of London.

iii) *The Ontario Department of Health.*

The Mental Health Branch of this department has for many years been trying



to publicize the needs and lack of facilities for dealing with the serious problem of mental retardation.

Dr. M. B. Dymond, Minister of Health for Ontario, was eventually able to provide funds for the establishment of a clinic and the project was thus able to be commenced.

The Beck Memorial Sanatorium has for 50 years been an institute for the care of tuberculous patients. In recent years, due to the improved methods of treatment for these patients and the decreased requirement for hospital beds for this purpose, it has become more and more difficult to maintain the hospital as a financially sound proposition. In 1959 the Province of Ontario purchased the buildings and grounds from the Sanatorium. Many of the buildings are reasonably modern and the grounds are very spacious so that there is ample room for patient activity and any future development which might be considered.

In addition to the ideal conditions provided by the Sanatorium, this location was considered excellent because of its proximity to the University of Western Ontario Medical School and War Memorial Children's Hospital. This had the twofold advantage of providing teaching material for the medical students and research material for those working in this field. The potential to fill in a large blank in medical education, both at undergraduate and postgraduate levels, is now available and steps are being taken to utilize the Institute in this way.

Patients seen at the Institute are normally seen as out-patients first of all. In every case these patients are accepted only by referral from a physician or recognized social agency. This enables close contact to be maintained between the family and the Institute or the referring agency after the assessment or treatment.

The staff at the Institute are drawn from the fields of Psychiatry, Pediatrics, Neurology, Psychology, Social Work, Speech Pathology and Education. In addition to

the above, specialists in several other fields are available when consultation is felt necessary. The reason for the wide range of specialists on the staff is to enable the patient to be assessed from all possible angles so that an unbiased and accurate opinion may be obtained.

The term "mentally retarded" is often used to cover a wide variety of conditions. At this point it might be well to mention some of the illnesses which are included under this heading. These are seriously mentally retarded, physically handicapped, mentally ill, mildly brain damaged and children of normal intellect who are experiencing learning difficulties. Although children of all ages are seen at the Institute, varying from several months to young adults in their twenties, it is estimated that about 75% of those seen are under the age of 12 years.

Initially, contact is made with the patient's family by one of the social workers or a local public health nurse. From this, a history of any previous investigations, hospitalizations and other pertinent data is obtained. In addition, school reports are gathered together where applicable. A teacher from the Institute may be sent to observe the patient at school and observe him in his natural surrounding. This also enables the child's teacher to give a first hand report. There are certain obvious shortcomings to this procedure but it has been found very useful in the past.

One whole day is set aside for the patient's first visit to the Institute. He is accompanied by his parents and they are first of all seen by the social worker concerned and then by the physician in charge of the case. It is very important that a good understanding of the child's family and environment is obtained and especially the child's relationship with the parents. Following this the child is then examined physically and neurologically and the parents are interviewed together or separately by various members of the team concerned.



In addition to the above examinations the child is seen by a psychologist and speech pathologist and routine blood and urine tests are done. A series of other tests and examinations are also routine with each patient seen. These are: X-rays of skull and wrists, urine test for phenylketones, buccal smear for sex chromosome abnormalities, amino acid screening of the urine and cytogenetic studies. Complete chromosome studies are performed on all mongoloid children to provide data for the investigation of the Translocation Syndrome.

After the child has been evaluated by the team of examiners and the data has been worked up, the case is then presented at a staff conference. At the conference the following points are brought out:

- i) The pathological processes underlying and accompanying the suspected retardation.
- ii) The intellectual, social and emotional levels of functioning.
- iii) The family reactions to the child and his handicap.
- iv) The educational problems.

A diagnosis is arrived at based on the classification of the American Association on Mental Deficiency. Recommendations for treatment and management are then discussed and following this the doctor in charge of the case then arranges to see the parents again to discuss the recommendation of the team. Counselling and therapy may be advised for the patient and/or the parents and a follow-up of the patient is undertaken by the family doctor, by the referring agency or by the Institute staff.

Along with the out-patient service the Institute has 77 beds which are available for children who are recommended for closer investigation in a group setting. There may be any one of four reasons for a child to be admitted as an in-patient:

- i) To examine the child more closely.

- ii) To observe the child's reactions to a ward setting along with school and activity programs.
- iii) To provide special treatment.
- iv) To provide parent relief.

It must be emphasized that the Institute is not a home for retarded children and it is rare for a child to remain as an in-patient for more than a few weeks. Should the patient require permanent hospitalization he is sent to one of the several homes for these children in Western Ontario.

As already mentioned, one of the functions of the Institute is to supply research material, both in the form of patients and records. This research is moderated by the Research Advisory Committee of the University of Western Ontario under the chairmanship of Dr. Murray Barr. This research may be carried out at the medical school, War Memorial Children's Hospital, or at the Institute. At the present time the field of investigation includes Psychiatry, Cytogenetics, Biochemistry, Endocrinology, Pediatrics, Psychology and Social Work. teaching facilities are available and lectures and clinics are given by the departments of Pediatrics and Psychiatry. In addition to this a one year course is available for graduate students in Psychiatry and also for physicians interested in mental retardation.

The success of the Children's Psychiatric Research Institute is already assured and it is already making a very valuable contribution to medical science. In appreciation of this, the Institute and its staff have received several honours in recognition of their work. Last year the Institute won the bronze award of the American Psychiatric Association. Dr. Murray L. Barr was recently honoured with a Joseph P. Kennedy Jr. award for his work in connection with his discovery of chromatin material in human cells and its relationship to sex chromosomes abnormalities and mental retardation. Dr. Donald E. Zarfes, director



of the Institute, was also nominated for the same award. As a result of its success it is thought that the Institute will be used as a model for future establishments of its kind. In a recent brief to the Royal Commission on Health it was recommended that 15 such clinics be established across Canada.

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# The Diagnosis of Congenital Heart Disease

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## INTRODUCTION

Progress in cardiovascular surgical techniques has given impetus to the understanding and proper diagnosis of congenital heart lesions. Twenty years ago the differential diagnosis of congenital heart disease was merely of an academic nature. Today, the correct and early diagnosis of congenital heart disease has become a lifesaving measure. About 85 per cent of the congenital lesions encountered by cardiac specialists consist of one of the following: patent ductus arteriosus, atrial septal defect, ventricular septal defect, tetralogy of Fallot, tricuspid atresia, transposition of the great vessels, simple pulmonary stenosis, coarctation of the aorta and aortic stenosis. Stress is made in this paper in the diagnostic findings of the above lesions with a concise discourse of the clinical signs suggestive of congenital heart disease.

The congenital cardiac malformations are rare as a group and constitute an average of about two percent of all cases of organic heart disease. The frequency of congenital heart disease at birth has been placed, by some authors, at about three per thousand.

Several acquired factors have been described as causative agents for cardiac malformations; when the etiological factor is attributed to heredity, the cardiac defect may be alone or in conjunction with Mongolism, Marfan's and Turner's Syndromes.

In recent years significant progress has been made in the understanding of the nature and management of congenital heart disease. The scope of this paper does not permit a thorough classification of congenital heart disease. However, a glimpse of congenital heart disease as a clinical entity will be presented under the following headings:

I. Diagnostic clues of Congenital Heart Lesions

II. Most common types of Congenital Heart Lesions

## I. DIAGNOSTIC CLUES OF CONGENITAL HEART LESIONS

### A. General Observations:

1. *Cyanosis*: As a rule, in congenital heart disease, cyanosis is due to a shunting

defect which allows reduced hemoglobin to flow to the left side of the heart. This is in contrast to cyanosis which may occur peripherally due to low cardiac output as a result of pulmonary stenosis or mitral stenosis. Once cyanosis is recognized, it becomes important to exclude numerous extracardiac causes which may result in cyanosis by depressing the respiration and interfering with normal ventilation. Cyanosis due to cardiac shunting defect can be distinguished from that of pulmonary origin in that it is usually more severe, gets worse with stress and is only minimally reversed with inhalation of pure oxygen.

2. *Dyspnea*: In patients with congenital heart disease, laboured respiration occurs as a sign of obvious heart failure or high pulmonary blood flow. Dyspnea due to pulmonary disorders has to be differentially considered.

3. *Clubbing*: With long standing disturbance in oxygenation of the blood, clubbing is found in toes and fingers. The earliest manifestation is over the thumbs.

4. *Squatting*: The drawing up of the legs towards the chest results in an increased venous return and increased peripheral resistance which in turn increases the pulmonary blood flow to alleviate the dyspnea



## Congenital Heart

and cyanosis. This manoeuvre is classically observed in patients with severe tetralogy of Fallot.

5. *Edema and Ascites*: Right heart failure follows the same physiologic pattern of a "failing heart" due to other causes. However, this is a rare manifestation in childhood, unless the offending lesion is severe pulmonary stenosis. In contrast, rapid respiration and tachycardia are pronounced in the child with heart failure.

6. *Cardiac Enlargement*: In the absence of other causes, cardiac enlargement with an associate finding of a marked left chest prominence should lead one to suspect a congenital heart lesion with a large shunt.

7. *Murmur*: A congenital cardiac defect frequently manifests itself by a loud murmur; a thrill may or may not be present. This murmur tends to localize at the xiphoid process, the left sternal border or the second left intercostal space. Often, the onset of the murmur, as well as the character of the murmur, become prime diagnostic clues.

8. *Pulse*: Pulsation of jugular veins, liver and femoral vessels are diagnostic signs and should be looked for carefully. The disparity in the character of the radial and femoral pulse is the key to the diagnosis of coarctation of the aorta.

9. *Growth*: Generally speaking, patients with congenital heart lesions show evi-

dence of impairment in mental and physical growth, often directly related to the degree of insufficiency in circulation. Poor tissue oxygen supply gives rise to cerebral hypoxic spells and secondary polycythemia while pulmonary plethora leads to repeated upper respiratory infections.

### B. Specific Studies

When the diagnosis of a congenital heart defect becomes difficult, or confirmation is desired, roentgenography, electrocardiography, cardiac catheterization and angiocardiology become of extreme value. The results of these specific studies for the lesions to be discussed below will be briefly mentioned.

## II. MOST COMMON TYPES OF CONGENITAL HEART LESIONS

For purposes of brevity, the discussion of the congenital lesions of the heart will be limited to the nine most common types. The relative incidence of these individual lesions varies from author to author. However, 85 percent of the congenital cardiac defects encountered by cardiologists consist of these nine entities. An attempt is made in this paper to give the relative frequency of each lesion using a pool of values from four different authors (Abbot, Nadas, Wood and Ober & Moore). These lesions can be grouped into those that have a left-to-right shunt, a right-to-left shunt, or no shunt at all.

	Relative Incidence In Percent
A. Lesions with left-to-right shunt:	
1. Patent ductus arteriosus	11
2. Atrial septal defect	13
3. Ventricular septal defect	12
B. Lesions with right-to-left shunt:	
1. Tetralogy of Fallot	13
2. Tricuspid atresia	3
3. Transposition of the great vessels	10
C. Lesions with no shunt:	
1. Simple pulmonary stenosis	10
2. Coarctation of the aorta	10
3. Aortic stenosis	3
	—
	85



The reader may observe that, like any other classification of this nature, there is some degree of overlapping; unless otherwise mentioned, the discussion of each lesion will be limited to the dominant pathology as indicated.

#### A. Lesions With Left-to-Right Shunt

Since the pressure on the left side of the heart is normally greater than that on the right, the direction of the blood flow is from left to right. The pattern is sustained until heart failure occurs, when the direction of blood flow is reversed. The following findings are suggestive of the lesions in this group:

- a. Absence of cyanosis
- b. Poor growth and development
- c. Bulging of the precordium
- d. Mid-diastolic rumble at the apex
- e. Diffuse precordial impulse
- f. Cardiomegaly
- g. Pulmonary plethora

1. *Patent Ductus Arteriosus*: This lesion is one of the more common congenital heart defects and is due to a persistent communication between the aorta and the pulmonary artery. Functional closure of the ductus normally occurs soon after birth. The size of the opening of the duct varies from less than one mm. to ten mm. or more in diameter. The communication between the aorta and the artery may be direct, or the ductus may be several centimeters in length. Accordingly, the clinical findings directly vary with the size of the shunt and the pulmonary pressure and resistance.

On physical examination, the presence of a continuous machinery murmur during both systole and diastole, best heard to the left of the cardiac border, is characteristic of patent ductus arteriosus. The typical murmur is often accompanied by a thrill and has a late systolic accentuation and early diastolic fall, so that the second sound is enveloped in the murmur and can be recognized distinctly only at the lower precordium. In a typical case of this lesion, or even in one with complication, a wide

pulse pressure due to high systolic pressure and low diastolic pressure remains to be suggestive of the defect. It should be noted that in cases of pulmonary hypertension, or congestive heart failure, the characteristic findings of the murmur may be lacking. In uncomplicated cases of patent ductus arteriosus, oxygenated blood is being shunted into the pulmonary artery and therefore there is neither cyanosis nor clubbing.

Depending on the volume of blood entering the pulmonary artery, roentgenographic studies may reveal enlargement of the pulmonary conus, main pulmonary artery and its branches. There may be an engorgement of the pulmonary vasculature with or without a hilar dance; the left ventricle and atrium may be enlarged. Electrocardiographic studies likewise show left and right ventricular hypertrophies; small ducts show minimal changes in the tracing. Cardiac catheterization reveals an increased oxygen content and increased pressure in the pulmonary artery. The passage of the catheter through the patent ductus into the aorta establishes the presence of the lesion. Angiocardiography is of little value in the diagnosis of the defect but is of assistance in eliminating or detecting other lesions.

The treatment of choice is surgical ligation when the ductus produces cardiac enlargement and an impairment of function. Bacterial endocarditis due to streptococcus viridans is sometimes a complication of patent ductus arteriosus.

2. *Atrial Septal Defect*: This is a common-occurring congenital heart lesion which may be single or multiple; if single, it is either of the secundum or ostium primum type. If multiple, the associated abnormality may be a patent ductus arteriosus, a pulmonic stenosis or a ventricular septal defect.

The most frequent type is patency of the foramen ovale (secundum type). This comprises about 85 percent of atrial septal defects; it is often asymptomatic in child-



hood but progressive exertion dyspnea and heart failure become apparent in adult life. The secundum type is characterized by a soft systolic ejection murmur in the pulmonary area; the second heart sound is widely split, fixed and does not vary with respiration; the murmur is best detected after the first year of life. The electrocardiogram reveals a right ventricular hypertrophy with a right axis deviation in contrast to that of the primum type which has a left axis deviation.

In the ostium primum type, the shunt is large and the load on the right ventricle is increased. In the usual case, the defect is such that oxygenated blood constantly flows into the right side and therefore there is no cyanosis. A fairly loud blowing systolic murmur is usually heard at the apex radiating to the axilla and again the pulmonic second sound is well split. In severe cases this may be followed by the diastolic murmur of pulmonary valvular insufficiency due to pulmonary artery hypertension. The precordium may be bulged with hyperdynamic impulse at the xiphoid area. The peripheral pulse is normal or diminished.

In both types, roentgenographic studies show considerable enlargement of the right ventricle, right atrium and the pulmonary conus; engorgement of the pulmonary vasculature with a striking hilar dance is also observed. Catheterization reveals an increase in pressure in the right atrium and right ventricle and the oxygen content of the blood in these chambers and the pulmonary artery is higher than normal. The shunt is definitely confirmed when a catheter is passed through the atrial septal defect into the left atrium and pulmonary veins. As in all left-to-right shunt lesions, the use of angiocardiology is valuable more in eliminating other defects than in detecting the lesions in this group.

The most frequent complications of large atrial septal defects are pulmonary congestion, chronic bronchitis, paroxysmal auricular tachycardia and increased blood volume; paradoxical embolism may occur

in some special cases. Surgical treatment has been successful in many instances; prophylactic measures to prevent complications of the lesion play a definite role in the medical management of patients with atrial septal defects.

3. *Ventricular Septal Defect*: The clinical manifestations of ventricular septal defect depend on the amount of shunt through the defect and on the pulmonary arterial pressure. With a small ventricular defect, the shunt is small and the pulmonary artery pressure is normal. The patients are asymptomatic and the only clinical findings are a murmur and a thrill on the left sternal border.

With a large ventricular septal defect, the peripheral pulse is normal or diminished; except in cases of diffused mixing of blood at the septal defect, there is normally no cyanosis. Cardiac enlargement, and increased left ventricular impulse, a to-and-fro motion of the precordium indicate the severity of the defect. A loud blowing systolic murmur accompanied with a thrill is heard at the lower left sternal border. The heart sounds are unusually loud with accentuation of the pulmonic second sound; a diastolic rumble around the apex is often found.

In both types, roentgenographic examination reveals a large pulmonary conus, a large left ventricle and pulmonary plethora. The electrocardiogram may show no change in a small ventricular septal defect, while ventricular hypertrophy with a complete or incomplete branch block is demonstrated when the defect is large. At catheterization the oxygen content of the blood in the right ventricle and the right pulmonary artery is increased; pressures are also elevated. Passage of the catheter into the left ventricle establishes the diagnosis.

In many instances, surgical correction has been successful. Patients with ventricular septal defect are prone to repeated attacks of pneumonia but usually respond favourably to sound medical management.



## B. Lesions with right-to-left shunt:

In contrast to those lesions with left-to-right shunt, the abnormality in this group of lesions results in the shunting of blood from right to left causing arterial unsaturation. The following findings generally characterize the lesions in this group:

- a. Cyanosis
- b. Clubbing
- c. Squatting
- d. Cerebral hypoxic spells
- e. Absence of forceful pulsation of the precordial impulse
- f. Presence of a short systolic murmur alone
- g. Absence of a rumbling apical diastolic murmur.

### 1. *Tetralogy of Fallot*:

This lesion is the most common cyanotic congenital syndrome of the heart. The tetrad of pulmonary stenosis, ventricular septal defect, overriding of the aorta and a right ventricular hypertrophy constitute the tetralogy of Fallot. The hemodynamics of the lesion are such that the systemic venous return to the right side of the heart is normal; during right ventricular contraction the outflow of blood through the stenosed pulmonic orifice is markedly resisted and results in shunting of blood into the aorta via the septal defect.

Physical examination reveals marked cyanosis of the lips, mucous membranes and the nail beds. It is practically always uniform, and persistent and aggravated by exercise; clubbing of the fingers and toes is equally noticeable. A distinct heaving precordial bulging due to right ventricular enlargement is usually observable. A systolic murmur and a thrill, when present, are usually elicited best at the pulmonic area; the second pulmonic sound is often single, loud and clear. Squatting is a frequent manifestation of this lesion. Depending on the severity of the defect evidences of impairment of mental and physical growth are noticeable.

Roentgenographic examinations show right ventricular enlargement with rounding and elevation of the apex, absent or diminished pulmonary conus and avascularity of the lung fields; the dextroposition of the aorta can be established by the characteristic displacement of the esophagus. Cardiac catheterization shows an increase in the pressure and oxygen content of the right ventricle. The passage of the catheter into the right ventricle and into the aorta via a ventricular septal defect demonstrates the anatomic defects of this lesion. Angiocardiography shows simultaneous outflow of the radiopaque media into the aorta and the pulmonary artery.

The occurrence of occasional arterial thrombi and secondary polycythemia are manifestations of this clinical entity. A common complication of the lesion is a formation of a brain abscess and should be judiciously looked for when a "Fallot patient" presents with neurological symptoms. Sound medical therapy consists in correction of hematological disturbances, prevention of cerebral hypoxic spells, prophylactic and therapeutic antibiotics and sustained emotional support. Surgical treatment consists of either shunting blood from a systemic artery into the pulmonary artery or completely correcting the involved defects.

### 2. *Tricuspid Atresia*:

This defect is characterized by the absence of direct communication between the right atrium and the right ventricle. It is accompanied by pulmonic stenosis or atresia and right ventricular hypoplasia. Consequently, blood in the right atrium passes into the left atrium via an atrial septal defect or patent foramen ovale. The pulmonary circulation is markedly reduced and depends on a ventricular septal defect, patent ductus arteriosus or well-developed bronchial arteries. Persistent cyanosis appearing in infancy is a manifestation of patients with tricuspid atresia. When the atrial defect is small visible pulsation of



the normal-sized liver is seen. A systolic murmur may be heard in the presence of a ventricular septal defect.

Roentgenographic examination demonstrates a small right ventricle, left ventricular hypertrophy and absence of the pulmonary conus and arteries. The electrocardiogram usually shows evidence of left ventricular hypertrophy with left axis deviation of the QRS complex. At catheterization the presence of an atrial septal defect with a right to left shunt is ascertained. An angiocardiograph reveals immediate opacification of the left atrium from the right atrium with little or no demonstrable filling of the right ventricle. The pulmonary artery usually fills from the aorta by way of a patent ductus arteriosus. Medical management is usually palliative and the treatment of choice is surgical correction by a shunting operation.

### 3. *Transposition of the Great Vessels:*

In its simplest form the lesion consists of a pulmonary artery and an aorta whose origins are the left ventricle and the right ventricle respectively; there is no abnormality in the position of the chambers. The resultant picture is that of two complete separate circulations; survival is impossible unless the pulmonary and systemic circuits are in communication. A patent foramen ovale or a ductus arteriosus, and atrial or ventricular septal defect connects the two circuits. At times, pulmonary stenosis is found with transposition of the great vessels.

During the first weeks of infancy, progressive cyanosis due to transposed vessels is second in incidence to tetralogy of Fallot; the cyanosis becomes more marked with physical stress and when the associated defect is a patent ductus, the upper portion of the body is more involved than the lower one. Dyspnea is always present and is minimally alleviated by squatting. Dilatation of the chambers of the heart increases with age and congestive heart failure is a common occurrence. There may be no murmur but if present, it usually is

a systolic murmur accompanied by a thrill which is best heard at the lower left sternal border.

Roentgenographic examinations show marked pulmonary plethora and absence of the pulmonary arc in the PA view, and enlargement of the right ventricle and atrium may be noted. Ordinarily catheterization via the aorta reveals increased right ventricular and pulmonary artery pressures; the oxygen content in these chambers and vessels is dependent on the associated malformation. Angiocardiography shows immediate opacification of the aorta from the right ventricle; there is little or no filling of the pulmonary artery.

Medical therapy is directed to the prevention of congestive heart failure; surgical treatment is still in the experimental stage but when applicable consists of a shunt procedure, creation of an atrial septal defect or total reversal of the venous connections.

### C. Lesions With No Shunt:

The individual lesions in this group have variable clinical findings; the locality and the severity of the lesions determines the clinical picture.

#### 1. *Simple Pulmonary Stenosis:*

With a narrow pulmonary valve, the right ventricle exerts a high systolic pressure in order to sustain the required pulmonary circulation. The symptoms found on physical examination vary with the degree of stenosis; in severe cases the findings are essentially those of congestive heart failure. Cyanosis when present, is peripheral in nature and is due to impairment of blood flow through the tissues.

The left anterior chest is felt to bulge during systole due to hypertrophy of the right ventricle. A high systolic murmur is elicited in the second left intercostal space, a systolic thrill is usually felt in the same space; the pulmonic second sound is frequently decreased in intensity. In extreme



cases, signs of tricuspid insufficiency such as pulsation of the jugular veins and liver may be noticed. An uncommon sequel of severe pulmonic stenosis is a right-to-left shunt through the foramen ovale resulting in central cyanosis. X-ray studies may show enlargement of the right chambers of the heart. Electrocardiogram reveals right ventricular hypertrophy with occasional right bundle branch block. On cardiac catheterization, the right ventricular pressure is increased while the pulmonary artery pressure is markedly reduced. Angiocardiography shows the site of stenosis with delayed filling of the pulmonary arteries. The defect is surgically correctable.

### 2. *Coarctation of the Aorta:*

The most frequent type of coarctation is the localized stricture of the vessel distal to the origin of the left subclavian artery and at or below the entrance of the ductus arteriosus.

On physical examination a high blood pressure is found in the upper extremities while pressure in the lower extremity may be lowered or normal. The presence of a weak, dragging femoral pulse in contrast to a strong and regular radial pulse is definitely suggestive of coarctation of the aorta. Auscultation shows enlargement of the heart; systolic murmurs are commonly discovered at the base of the heart or in the interscapular and axillary regions; palpable pulsations due to collateral arterial circulations may be present in the internal mammary, intercostal or cervical arteries. Again, this should be contrasted with the weak or absent pulsations of the femoral vessels.

Roentgenography almost always shows enlargement of the left ventricle with a reduced aortic knob. Notching of the ribs due to enlarged intercostal vessels is rarely found before puberty. An angiocardiograph localizes the site and extent of the stricture. Congestive heart failure is a common complication of coarctation of the aorta; ease of surgical correction is dependent on the degree of constriction.

### 3. *Aortic Stenosis:*

This abnormality is caused by congenital thickening of the valves and is commonly seen in males. Just as in acquired aortic stenosis, the clinical manifestations are determined by the severity of the obstruction. On auscultation a characteristic diamond-shaped systolic murmur with an accompanying thrill is heard at the second right interspace; the murmur is well-transmitted to the neck vessels and, except in infants is loud and harsh. With aortic stenosis an early aortic systolic click at the apex and aortic area is a frequent finding. In a severe aortic stenosis, due to delayed occurrence of the aortic closure, there is paradoxical splitting of the second heart sound. The pulse pressure is narrow.

X-ray film shows left ventricular enlargement and widening of the ascending aorta. Electrocardiogram may show evidence of left ventricular hypertrophy with flattened T waves. Angiocardiography and cardiac catheterization studies are used to ascertain the locality and severity of the lesion, which is surgically treatable. Heart failure, due to aortic stenosis in childhood, is a rare complication. Occasional syncope and sudden death have been observed. Subacute bacterial endocarditis is a frequent complication.

### Summary

In a patient with possible congenital heart disease, the presence of certain diagnostic signs such as cyanosis, dyspnea, clubbing, squatting, abnormal pulsations, edema, cardiac enlargement and murmurs should be carefully looked for. Once the existence of a lesion is ascertained, the nature and type of the disease should be defined. The differential diagnosis of the congenital cardiac malformations can be achieved clinically or with the assistance of roentgenography, electrocardiography, cardiac catheterization and angiocardiography.

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# Asphyxia Neonatorum

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Asphyxia literally means "stoppage of the pulse".<sup>1</sup> This is not the meaning of the term as used in the phrase "Asphyxia neonatorum". It is rather the name of a clinical syndrome manifested by:

1. Apnea, failure to establish normal respiration at birth. Frequently this is accompanied by:
2. Skin color which is blue to white.
3. Weak to limp muscle tone.
4. A slow heart beat, often under fifty per minute.
5. Covering of the infant by meconium.

The length of time after birth in which the term "neonatorum" may be used varies widely. Yohe<sup>2</sup> states that any baby which has failed to establish and maintain normal breathing within five minutes of delivery of the head, and in which it has been advisable to administer pure oxygen is considered to have had asphyxia neonatorum. If other signs, especially those of shock are present, the interval of five minutes may be shortened. Russ<sup>3</sup> states that "the presence of neonatal apnea may be stated to exist whenever the baby has failed to take a spontaneous respiratory movement within 30 seconds of severing the cord".

It is important to understand and recognize this syndrome for it precedes many stillbirths and neonatal deaths, and may have direct bearing on the production of retarded and brain damaged children.

Before studying the pathological physiology of this syndrome, it may be wise to review the normal fetal oxygen exchange mechanism and the normal change to the adult type.

## Normal Fetal Oxygen Exchange Mechanism:

### 1. *The Placenta.*

The placenta performs the functions of a fetal lung serving as the organ of trans-

fer from mother to fetus and of carbon dioxide from fetus to mother. Ramsey's studies<sup>4</sup> on the maternal circulation have shown arterial inflow and venous drainage scattered over the entire base of the placenta. Twenty to thirty spiral arteries lie perpendicular to the uterine wall spurting into the intervillous space; blood filters through the villi and gradually drains back through veins running parallel to the uterine wall. The venous outflow from the intervillous space is closed promptly at the onset of a uterine contraction while arterial blood continues to flow in until the spiral arteries are occluded by direct pressure, or indirectly by the myometrium. The hydrostatic pressure of blood in the space varies with the state of uterine contractility. In quiescence, the pressure is 5-10 mm. Hg., but at the height of a contraction, it rises to about 40 mm.Hg.

The fetal blood flows to and from the placenta through two arteries and one vein within the umbilical cord. The arteries delivering venous blood course through the chorionic plate into the villi, becoming smaller until they reach the capillary network of the terminal villi. The hydrostatic pressure within the fetal capillaries of the villi during uterine quiescence has been reported by Reynolds to be between 30 - 35 mm. Hg. With uterine contraction, fetal blood pressure rises so that it is always higher than the blood pressure of the intervillous space. If this did not occur, the chorionic villi would collapse and fetal blood flow through the placenta would cease. Hence transfer from mother to fetus takes place against a substantial pressure gradient.

Substances passing from maternal to fetal blood in the latter half of pregnancy must traverse:

1. The layer of syncytium ensheathing the villus.



2. The stroma of the villus.

3. The wall of the villus capillary.

These layers have a thickness of from 2-6 microns. At term the total absorptive area of the chorionic villi is about 15 square meters.

### 2. *Oxygen Transfer.*

Simple diffusion appears to be the mechanism involved in the transfer of oxygen and carbon dioxide, with the added difficulty that oxygen diffuses slowly through a wet membrane. Although arterial blood of the mother is 96+% saturated, blood in the intervillous space has an oxygen saturation of 60-70% since it is a mixture of arterial and venous blood, and a partial oxygen pressure of 30 mm Hg. Oxygen saturation of the umbilical vein is about 60% saturated with partial oxygen pressure of 20 mm. Hg.<sup>5</sup>

### 3. *Fetal Adaptation.*

The mechanisms by which the fetus adapts itself to its low oxygen tension include:<sup>6</sup>

a. High fetal cardiac output. Assali and his group inserted an electromagnetic flowmeter around the umbilical vein in human fetuses, then calculated the total cardiac output in utero, obtaining a figure of approximately 200 ml. per Kg. per minute. This is more than three times the cardiac output of an adult at rest.

b. The more favourable oxygen dissociation curve of fetal hemoglobin. The oxygen dissociation curve of fetal blood is shifted to the left; hence at the same oxygen tension, it will take up more oxygen and be more highly saturated than maternal blood.

Moreover, the dissociation curve is steep at low oxygen tensions, so that fetal blood rapidly loses oxygen to the tissues.

c. Increased oxygen capacity. The hemoglobin concentration of fetal blood rises until at term it is 18.0 gm. per 100 ml. The erythrocyte count increases to approximately 5.5 million per ml. at term.

d. The infant also has a number of mechanisms for obtaining energy without the use of oxygen.<sup>7-8</sup>

Thus, although fetal blood has a low saturation of oxygen, the infant is not necessarily existing in a state of cyanosis. The amount of oxygen lost by the umbilical venous blood in its passage through the fetus is probably plentiful for an organism resting in a dormant state of constant body temperature.

Confirmatory evidence of the lack of fetal hypoxia includes the finding that the lactic acid content of fetal blood is only slightly higher than that of the mother. Also, animal studies carried out by Misrahy and Assai in which oxygen polarographic electrodes were placed in the brain, liver and kidney of the fetus in utero as well as in the organs of the mother in guinea pigs, rabbits and cats, showed that after recovery from anesthesia, the available oxygen in the fetal tissues was not significantly different from that of the mother.

### 4. *Fetal Respiratory Activity*

It had been observed by many that characteristic rhythmic movements of the abdomen occurred in pregnant women. It was believed by some, but disputed by others that these were due to intrauterine respiration of the fetus.

Respiratory activity has been shown by Davis and Potter<sup>9</sup> to begin early in fetal life. In a group of women who required therapeutic abortion, a radio-opaque substance Thorotrast was introduced into the amniotic sac at times from 49 hours to 15 minutes before the fetus was surgically removed from the uterus. The lungs of all those that had been exposed to Thorotrast for 18 or more hours contained Thorotrast in greater concentration than in the amniotic fluid.

An objection to any respiratory activity before birth has been the suggestion that the presence of amniotic fluid would interfere with the establishment of respiration after birth. Potter states that this does not



matter; that respiration before birth is normally shallow, the lumina of the alveolar ducts are small and the area occupied by the fluid is only a fraction of the potential air space. Moreover, the fluid that is present can be rapidly absorbed through the rich capillary bed to the alveoli.

However, the fact of intrauterine respiration is disputed by many including Windle whose experiments indicate that it is the experimental hypoxia which induces aspiration.

#### 5. Onset of Breathing at Birth.<sup>10</sup>

What definitely establishes extra-uterine respiratory movement is as yet not known. The following theories have been put forward:

a. Physical stimulation. The handling of an infant at delivery, and its contact with air and rough surfaces provoke respiration through stimuli reaching the respiratory centre from the skin. However, it is objected that rough abdominal palpation, the application of forceps, and maneuvers at delivery do not initiate breathing as long as the fetus is in utero with placental circulation intact.

b. Compression of the fetal thorax occurring at delivery. Warnekros noted an almost conical compression of the thorax during the second stage of labour, and suggested that the expansion which follows the delivery of the shoulders may initiate the first inspiratory movement. This is objected to because babies born at Caesarean Section usually cry satisfactorily, and sometimes as quickly as babies born vaginally. However, since they do not cry regularly as soon as babies delivered vaginally, thorax compression may be an auxiliary factor in the initiation of respiration.

c. Carbon Dioxide Accumulation. During the interval between the interruption of the placental respiratory exchange and the establishment of pulmonary respiration, the partial pressure of carbon dioxide rises in the infant's blood. Since it is a recog-

nized respiratory stimulant, it would seem logical that its increased tension brings about the first breath. However, in studies by Eastman in which the carbon dioxide tension of the blood in infants was studied, it was discovered that respiration began just the same whether the tension of this gas was high or low. Hence, this hypothesis alone does not explain the onset of respiration.

d. Oxygen Deprivation. Barcroft believes the lack of oxygen is the cause of the onset of respiration. But Eastman states that nitrous oxide anesthesia to the mother renders the infant hypoxic, and yet there is no evidence that the infant makes violent respiratory movements. Studies of blood oxygen levels at birth show no relation between the concentration of this gas and respiration except that at high levels of oxygen, the infant breathes more readily, and with extremely low levels, it is apneic.

e. Intrauterine Respiration. It has been mentioned before that intrauterine respiration is believed to occur. Many authors including Eastman regard the onset of respiratory activity not as an event initiated abruptly at birth, but rather as a transition from the intrauterine type, and feel this is the most important factor in the initiation of respiration after birth.

Great effort is required by the infant<sup>11</sup> at the first breath to exert enough negative pressure on the chest for first lung expansion. Resistance to expansion comes from:

a) cohering bronchiolar and alveolar surfaces not yet separated by residual air;  
b) the stiffness, or compliance of the lung due to elastic tissue and smooth muscle of the pulmonary parenchyma. Negative pressure of up to 30 cm. of water may be required for first expansion. Once the alveoli have been expanded, far lower negative pressures are required to produce inspiration. Once breathing is established, a third type of resistance is present: the relatively small airways impose flow-resistance to easy movement of air.



Changes in circulation accompany the expansion of the lungs. The previously collapsed pulmonary vessels are now expanded causing a profound fall in pulmonary arterial pressure resistance; the blood in the pulmonary artery surges into the pulmonary vascular tree filling out the pulmonary capillaries, thus tending to maintain the alveoli open. Coincident with the fall in pulmonary pressure, there is a reduced systemic pressure because while blood pours into the lungs, there is a reduction in the return of blood to the heart. Within a few minutes, the lungs are filled, blood returns to the heart, and the level of the systemic blood pressure recovers.

#### Etiology of Asphyxia Neonatorum.

Eastman classifies the clinical picture of asphyxia neonatorum to be due to three primary causes:

- a. Narcosis
- b. Brain hemorrhage
- c. Hypoxia.

Varying degrees of asphyxia occur in all forms of delivery. However, the time required for recovery depends on the cause and duration of the asphyxia. James<sup>12</sup> carried out studies on the acid-base status of infants, normal and depressed, taking blood samples from umbilical arteries and vein, portal vein, right and left atria. His studies showed that the  $pO_2$  level did not correspond to postnatal vigor. The significant difference between vigorous and depressed infants lay in the pH,  $pCO_2$ , and  $HCO_3^-$  level. With a brief period of asphyxia, there was an increased  $pCO_2$ , little change in the  $HCO_3^-$ , and mild respiratory acidosis, (a pH fall to 7.25). This pattern was seen in the vigorous infant. But with prolonged asphyxia, a marked reduction in the  $HCO_3^-$  occurred, indicating that a metabolic acidosis had become superimposed on the respiratory acidosis. With the brief period of anoxia, there were increased attempts at respiration and the heart rate was accelerated. With in-

creasing anoxia, the effects of a low pH below 7.1 and high  $pCO_2$  in stimulating the respiration were decreased and the "O<sub>2</sub> crisis" or "reversal" took place suddenly. Respiratory efforts ceased, the heart rate slowed, blood pressure fell, general skeletal muscle relaxation occurred with flaccidity of the extremities including relaxation of the sphincter ani.

The clinical picture produced by narcosis, hypoxia, and cerebral hemorrhage is identical; the etiology of apnea of the newborn may in fact be compounded by two of them since the narcotized infant tends to become hypoxic, cerebral hemorrhage produces hypoxia, and the hypoxic infant is more prone to cerebral hemorrhage.

#### a. Narcosis.

It is known that every narcotic, analgesic and anesthetic agent administered to the mother crosses the placental circulation and exerts an effect on the newborn baby commensurate with the amount of time of exposure. In the group of approximately 80% of babies in modern America which are normal, when proper resuscitative measures are carried out using optimal oxygen mixtures and proper humidification, the infant mortality rate has not been shown<sup>13</sup> to be significantly different in any of the following categories of anesthesia:

- i. sedation and general anesthesia.
- ii. sedation and terminal conduction anesthesia.
- iii. Sedation and i.v. anesthesia.
- iv. No pharmacologic analgesia or anesthesia.
- v. Only continuous or intermittent conduction anesthesia.

However, the infant mortality rate is different in the remaining 20% of babies who have pre-existing abnormalities, are premature, are born through unusual presentations as breech, all multiple fetuses, or whose mothers have major systemic



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disease such as diabetes or respiratory disease. The mortality is significantly lowest in this large group when the babies are managed and delivered with the use of a properly administered conduction anesthetic that eliminates pain at the site of origin without being transferred across the placenta as a toxicologic deterrent.

### b. Brain Hemorrhage.

Intracranial hemorrhage may be produced by anoxia, or by mechanical trauma associated with subdural hematomas or dural tears. It is important in the present discussion in that it should be considered in the prevention and treatment of infants presenting with asphyxia neonatorum. The prevention of cerebral hemorrhage is of the utmost importance:

- i. reduction in the use of midforceps and difficult forceps manipulations.
- ii. The use of Caesarean Section for cephalopelvic disproportion.
- iii. Correct management of breech delivery.
- iv. Limitation of internal version and breech extraction.

Also in the treatment of infants with asphyxia neonatorum:

- i. The baby should not be laid too much head down to prevent compounding the hemorrhage;
- ii. If the anterior fontanelle is bulging, a lumbar puncture is indicated in order to relieve pressure.
- iii. I.M. administration of vitamin K may be indicated.

### c. Anoxia.

Etiology:<sup>14</sup>

Causes of Anoxia before birth:

#### I. Pre-Placental:

A. Decreased maternal blood flow to the placenta.

1. Maternal hypotension which may be due to
  - a. Shock and hemorrhage.

- b. Epidural, spinal anesthesia.
- c. Analgesia.

2. Vasoconstriction of maternal blood vessels
  - a. Hypertension
  - b. Toxemia
  - c. Diabetes.

In 1953, Browne and Veal<sup>15</sup> studied the transfer of  $\text{Na}^{24}$  from maternal to fetal circulations in various types of patients. They demonstrated the normal placental blood flow at 38 weeks to term to be about 600 ml. per minute and in chronic hypertension and pre-eclampsia, a reduction to about one-third of this figure. They concluded that since in all their cases the infant was born alive, that the healthy placenta must have a safety margin of more than 50% which in pre-eclampsia and chronic hypertension is seriously reduced.

#### 3. Uterine Contractions.

Caldeyro-Barcia has shown that with a strong uterine contraction, blood flow through the uterus and placenta is completely arrested.

- a. Tetanic contractions of the uterus which may occur with Syntocinon, Tocosamine.<sup>14</sup>
- b. Hypertonic uterine inertia with the tone 15 mm. Hg. or more above normal. Irregular, ineffective contractions are established with the production of prolonged labour and increased chance of fetal asphyxia.

4. Decreased pressure gradient between uterine arteries and veins. The supine position has been shown to be associated with compression of the mother's inferior vena cava by the heavy gravid uterus. Pressure in the femoral vein may be raised from 108 to 239 mm.  $\text{H}_2\text{O}$  by this mechanism<sup>15</sup>



B. Decreased maternal oxygen.

1. Maternal anesthesia when oxygen intake is reduced.
2. Maternal breath holding and straining during vaginal delivery.

## II. Placental

A. Abruptio Placenta. This is the commonest cause of anoxia that can definitely be identified. At any time during the last trimester, especially in women with pre-eclamptic toxemia, detachment of part or all of the placenta occurs from the uterine wall. If the area is small, the remaining portion of the placenta may be sufficient to oxygenate the fetal blood and the fetus may suffer no ill effects. If a large part is separated, death occurs quickly.

B. Placenta Previa. The anoxia occurring with placenta previa is a result of premature separation of the placenta as in abruptio placenta. Attachment of the placenta over part or all of the internal cervical os does no harm to the fetus until the cervix begins to undergo changes incident to labor and delivery.

C. Postmaturity?

## III. Post-Placental.

A. Cord lumen compression. The cord may be looped several times around the neck, or an extremity, or it may have a true knot. Prolapse of the cord between the head of the fetus and the maternal pelvis will cut off circulation almost immediately. After rupture of the membranes uterine contraction may compress the cord against the body of the fetus.

B. Chest compression. Severe chest compression may interfere with return of venous blood from the head and may cause extreme congestion of the brain with distention and rupture of small blood vessels.

C. Cord thrombosis.

### Causes of Anoxia After Birth:

1. Causes of intra-uterine anoxia.
2. Diminished space for pulmonary expansion as diaphragmatic hernia, pleural effusion.
3. Lack of space for oxygen in the alveoli because the lumina are filled with

solid material as leukocytes in intra-uterine pneumonia, or squamous epithelial cells and other debris following excessive intrauterine respiration.

4. Tumor compressing the trachea or obstructing the larynx.
5. Hypoplasia or other malformation of the lungs.

### Pathology of Anoxia:<sup>17</sup>

In a study by Clark and Anderson of the brains of 67 infants who died in the perinatal period, certain types of lesions appeared to be closely associated with certain clinical problems: infants who died with prolapsed cord had pallid brains in which microscopic lesions were hard to demonstrate; the brains of infants born after abruptio placenta showed extreme vascular congestion, especially in the parietal and occipital white matter with multiple hemorrhages. Extreme fetal distress in utero seemed to produce a distinctive and fairly selective necrobiosis of neurones in the lateral portion of the thalamus.

Courville has been most convincing in his support of the idea that a number of chronic diseases which make their appearance during infancy and early childhood have their genesis in fetal asphyxia. He believes that these diseases included cortical scars, atrophic lobar sclerosis, cerebral hemiatrophy, chronic progressive degeneration of the cerebral gray matter, and demyelinating diseases of infancy and childhood.

### Diagnosis of Intrauterine Anoxia:

1. Fetal Bradycardia. Slowing of the fetal heart occurs during normal intrauterine contractions. It has been shown by Reynolds<sup>18</sup> that stress induces vagal tone in the fetus with slowing of the heart, and that such induced efforts may last from a few minutes up to a half hour.

Hon<sup>19</sup> has studied fetal heart rate patterns continuously during labour and delivery using electronic techniques to determine the significance of the fetal heart rate in fetal distress, the importance of transitory and moderate bradycardia, and



the significance of tachycardia. The "physiological" heart pattern is V-shaped at the contraction, slowing onsets 10 to 15 seconds after the beginning of the contraction, is of short duration, and returns to normal while the contraction is still present. The "cord compression" pattern is U-shaped, slowing onsets immediately after the onset of the contraction and persists up to 40 seconds after the contraction is over. The "hypoxic" pattern shows slowing toward the end of the contraction and persists beyond the end. It is associated with frequent and strong uterine contractions and is thought to be due primarily to hypoxic fetal myocardial depression.

Hon concluded that profound and prolonged fetal bradycardia associated with irregularity appears to indicate fetal distress. Sustained fetal tachycardia, that is, over 160 beats per minute, may be the earliest sign of mild fetal hypoxia but does not appear to warrant immediate removal of the fetus from its environment. Fetal heart rate patterns which show marked beat-to-beat arrhythmias are of no clinical significance if the average fetal heart rate is in the normal range.

2. Meconium. The presence of meconium, particularly if the thick "pea soup" variety, is considered as a warning of possible fetal difficulty in a vertex presentation, but does not of itself constitute grounds for the interruption of labour. The escape of meconium is due to relaxation of the sphincter ani muscle induced by anoxia, or increased vagal tone with stress.

3. Fetal Movement.<sup>20</sup> The occurrence of tumultuous fetal movement is said to indicate the presence of fetal distress. Diminished or absent fetal movement is often recorded prior to fetal death in utero when the fetal heart can still be heard. It has been concluded that the wide variation in pattern of fetal movements during normal pregnancy markedly detracts from the value of alteration of fetal movements as a sign of fetal distress.

#### Treatment of Anoxia:<sup>21</sup>

1. Prophylaxis. Watch those predisposed to fetal distress: hypertensives, pre-eclampsics, diabetics, prolonged labour, prolapsed cord, pitocin-stimulated labours, post-mature patients.

Use moderate narcosis using local anesthesia whenever possible.

2. Diagnose fetal distress: Watch the fetal heart that remains below 100 beats per minute throughout the interval between contractions, and the fetal heart which does not return to normal within 30 seconds after the end of the contraction; watch for thick meconium in the amniotic fluid.

3. Carry out a vaginal examination to rule out a prolapsed cord if there is fetal distress. Give 100% oxygen to the mother to raise her oxygen tension. Start an intravenous drip of 10% glucose in water since it is known that the infant has mechanisms for obtaining energy without the use of oxygen.

4. Deliver at once by the best obstetrical means. If the head is down and the cervix is fully dilated, or the breech is down and the os fully dilated, deliver vaginally. If not fully dilated, carry out a Caesarean Section.

If just bradycardia is present, give oxygen, glucose drip and observe closely. If just meconium, watch closely and deliver before another 24 hours. If meconium in a postmature patient, deliver at once.

5. Evaluate the infant to determine the need for resuscitation. A useful aid is the Apgar scoring system: a score of 0 indicating a severely depressed baby, while a score of 7 - 10 indicates it to be in excellent condition.

Immediately after birth while the infant is still being held head down, suck out the excess mucus from the mouth and pharynx with a soft rubber ear syringe.

6. If the infant does not begin to breathe within 1 minute, or appears severely shocked, resuscitation should be undertaken.<sup>22</sup>



a. Maintain the infant in a heated crib where it is easily accessible, the head can be lowered and oxygen, suction and other necessary equipment are at hand.

b. Promote drainage of the upper respiratory tract by placing the baby in a thirty degree head downward position.

c. Administer oxygen. When oxygen is administered at pressures of 16-20 cm. of water, this stimulus initiates a gasp in about 85% of cases.<sup>23</sup> The lungs may be expanded by intermittent positive pressure normally exceeding 15 cm. of water after the possibility of obstruction has been eliminated.

d. If there is no effort at voluntary respiration, and the infant's heart continues to slow, direct endotracheal intubation should be begun immediately by an expert.

e. Nalline 0.2 mg. may be given intravenously into the umbilical vein for narcosis due to morphine or Demerol if these narcotics have been given to the mother in large amounts within 4 hours of delivery.

f. Antibiotics should be administered to minimize the danger of pneumonia.

g. After resuscitation, the infant should be placed in an incubator with maintenance of body temperature, humidification, and oxygen not to exceed 40% concentration.

#### Sequelae to Asphyxia Neonatorum:

The most serious result of asphyxia is undoubtedly death of the fetus. Less definite effects are difficult to determine. The only changes ordinarily ascribed to anoxia are cerebral and it is usually impossible to be certain that other changes in the central nervous system such as gross hemorrhage or malformation may not have been co-existent and responsible for the major symptoms. In general, it is said that infants who survive a period of anoxia may or may not show the effects of anoxia in later life. If a brief period of anoxia was present, no ill effects may follow. If more prolonged, neurologic injury may occur producing the picture of cerebral palsy, mental retardation, epilepsy, blindness, deafness and behavior disorders.

The only way to have definite information about the effects of anoxia in the human being is to set up an extended longitudinal study beginning with large groups of pregnancies; newborns at birth classified as to their responses to the birth process. These children should then be followed for many years until they are evaluated as either normal or abnormal adults or, in the case of death, careful autopsies are performed on the central nervous system. For even though an infant seems to be normal after anoxia disappears, it is not possible for several years to be sure that no handicap has been produced.

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# Surgical Emergencies of the Newborn

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## INTRODUCTION

Conditions that create surgical emergencies in newborn infants, mainly congenital malformations of the alimentary tract, are rare. However, recent advances in pre- and post-operative management, anesthesiology, and surgical technic have improved mortality figures so considerably that diagnosis has become of utmost importance. This paper will consider the diagnosis of some of these anomalies in order as they appear, from birth until the first few days of life.

### 1. OMPHALOCELE

An omphalocele is a translucent sac, lined by amniotic membrane and peritoneum, protruding from the anterior abdominal wall at the base of the umbilicus at birth and containing intestines, liver, and possibly other abdominal organs. The intestines have failed to return to the abdominal cavity in embryonic life due to spatial disproportion or a primary defect in the anterior abdominal wall. The wall of the sac is thin and avascular and hence prone to perforation, drying, necrosis and infection. Evisceration and peritonitis are logical sequelae. In 20% of cases the sac ruptures before birth or during delivery. Delay in treatment allows swallowed air to inflate the intestines, making reduction more difficult.

Diagnosis is obvious at birth. Fifty-nine per cent have associated congenital anomalies, especially malrotation of the midgut, but many are of minor importance.

### 2. MALFORMATIONS OF ANUS AND RECTUM

Arrest at various stages of development of the primitive gut can result in various types and degrees of ano-rectal abnormalities: (1) anal stenosis, (2) membranous imperforate anus, (3) imperforate anus with a rectal pouch ending blindly some distance above it, and (4) blind rectal pouch with a normal anus and lower rec-

tum. The third type is the commonest (90%) and is usually associated with fistulae to the perineum, the male urinary tract, or the female genital tract. Excessive fusion, failure or development of the urogenital septum, and failure of anal migration have been incriminated. Forty per cent have other abnormalities.

The diagnosis should be made by the obstetrician at delivery or by a nurse when she attempts to obtain the rectal temperature. However, diagnosis may be missed at this stage and signs and symptoms that vary with the type and degree of malformation follow. Most (75%) have complete obstruction and present with abdominal distention, failure to pass stools, and failure to feed or vomiting. Fistulae may follow decompression and passage of some stools but with difficulty.

Diagnosis is made by thorough inspection and examination and confirmed by x-ray. A dimple or small perineal ridge may be seen in the third type. With imperforate anal membrane the meconium stains the membrane and causes it to bulge when the baby strains or cries. Fistulae may evade detection, especially those communicating with the urinary tract. Microscopic examination of the urine may be helpful. Local probing often delineates perineal and vaginal fistulae.

Radiography is performed with the infant inverted to allow colonic gas to reach the distal end. A lead marker is taped to



the anal dimple to determine the extent of the gap. It must be remembered that thick meconium may not permit replacement by gas and that gas may not be present in the rectum before 15-20 hours of age. An I.V.P. using the umbilical vein should be carried out since the urinary system is abnormal in one third of cases.

### 3. ESOPHAGEAL ATRESIA

In most instances (90%) the esophagus ends as a blind, dilated pouch in the upper thorax, the distal esophagus connecting with the trachea to form a tracheo-esophageal fistula. Five per cent have an atretic or stenotic length of esophagus only. Pure tracheo-esophageal fistula, esophageal atresia with a fistula between the upper esophageal segment and trachea, and fistulae between the trachea and both upper and lower segments comprise the remaining 5%.

In the early hours of life, the child drools because saliva and mucus cannot be swallowed. Feeding and inhalation of mucus produces coughing, gagging, and often temporary cyanosis and respiratory distress. Tracheo-esophageal fistula can give rise to abdominal distention when the infant cries.

Thus, drooling and dysphagia in a newborn infant warrant further investigation. A stiff rubber catheter should be passed down the child's esophagus. Firm resistance 3-4 inches from the lips means esophageal obstruction. Then, under fluoroscopic control, 1 ml. Gastrografin should be injected through the catheter to delineate the pouch and demonstrate a proximal fistula, if present. Air in the stomach and intestine will prove the presence of a distal tracheo-esophageal fistula.

Early diagnosis before pneumonitis sets in is important. Other serious malformations (30%), prematurity (20%) and hydramnios in the mother may be associated.

### 4. CONGENITAL DIAPHRAGMATIC HERNIA

In infants the hernia usually involves either the postero-lateral portion of the dia-

phragm (foramen of Bochdalek), the left side more commonly. Much rarer sites are the esophageal hiatus and the retrosternal portion (foramen of Morgagni). The affected pleural cavity contains intestines, a portion of the colon, and depending on the side involved, part of the liver or stomach and spleen. In contrast to hiatus and retrosternal hernias, most postero-lateral hernias have no pleural sac, the pleural cavity is more completely filled, and important symptoms usually appear early.

The lung on the affected side is completely collapsed, the heart and mediastinum are pushed to the opposite side of the chest and the contralateral lung is partially compressed. Thus, severe respiratory distress with dyspnea and cyanosis may appear soon after delivery. Vomiting may also be a symptom. On examination, respiratory excursion of the affected side lags and the abdomen is flat or scaphoid. The apex beat is displaced to the contralateral side and the affected side is either hyperresonant or dull on percussion depending on whether the intestines contain fluid or air. Auscultation reveals distant breath sounds and sometimes bowel sounds may be heard.

Radiography or fluoroscopy establishes the diagnosis but often the condition is so urgent that time is not permissive. The affected pleural cavity contains intestines and viscera whose shadows are continuous with those of the abdomen. The unaffected side has a poorly expanded lung since the heart and mediastinum are shifted in that direction. Barium studies are usually unnecessary and are dangerous.

### 5. INTESTINAL OBSTRUCTION

A diagnosis of intestinal obstruction should be suspected in any infant that vomits bile-stained material, is distended (although vomiting may decompress the bowel), fails to pass meconium in the first 24-36 hours or whose mother had hydramnios. High small bowel obstruction is



typically characterized by epigastric fullness and usually persistent vomiting. In contrast, in low small bowel obstruction persistent vomiting is delayed and generalized distention is prominent. With colonic obstruction, distention is marked and vomiting is late. In general, the higher the obstruction, the earlier signs and symptoms appear. Partial obstruction is characterized by vomiting but distention is minimal. The value of Farber's test for distinguishing partial and complete obstruction is questionable.

Radiological findings are of prime importance in diagnosis. Plain films allow conclusions to be reached as to the site of obstruction from the number and position of distended loops and fluid levels. Barium enema can distinguish large and small bowel and can provide information as to the patency and position of the colon. Oral administration of barium is inadvisable except in the rare, incomplete high intestinal obstructions.

#### (a) Duodenal Obstruction

##### (i) *Atresia and Stenosis*

These are due to failure of recanalization in embryonic life. Half of intestinal tract stenoses and one fifth of atresias are duodenal. Serious stenoses, which constitute the majority, are seen early and present like atresias. Mongolism and congenital heart disease are frequently associated.

The symptoms are those of high small bowel obstruction. Vomiting, usually with bile staining, is progressively more frequent and intense as subsequent feedings are taken. Normal meconium stools are usually not passed. Epigastric distention is noted unless vomiting has decompressed the stomach. Peristaltic waves may be seen crossing the epigastric area. The infant is often restless and febrile and may be shocked and dehydrated.

Roentgenologic examination reveals a dilated duodenum and stomach (the "double bubble"). Barium by mouth is not recommended and colonic studies are unnecessary.

##### (ii) *Annular Pancreas*

Annular pancreas is due to failure of the tip of the ventral pancreatic anlage to rotate with the duodenum. A band of pancreatic tissue surrounds the duodenum and may cause complete or partial duodenal obstruction. If complete, the signs, symptoms and x-ray findings are like those of duodenal atresia. Diagnosis of partial obstruction may not be apparent in the first few days of life. Vomiting is less severe and x-ray shows small bubbles of air distal to the distended stomach and proximal duodenum.

##### (iii) *Malrotation of Midgut*

This condition is more properly failure to complete the normal process of rotation and fixation of the bowel after the temporary omphalocele of the midgut (that portion of the bowel supplied by the superior mesenteric artery). The result may be: (1) incomplete rotation of the cecum with peritoneal bands running across and obstructing the duodenum and/or (2) a rudimentary mesenteric attachment near the origin of the superior mesenteric artery with a resulting tendency to volvulus. The latter causes obstruction at the upper end (duodenum) initially, and then at the lower end (mid-transverse colon). Infarction and gangrene are apt to occur.

Duodenal obstruction presents near birth with the signs, symptoms and x-ray findings described above. With midgut volvulus, generalized distention results from gas collecting in the closed loop. Stools may be bloody but scanty. With infarction and gangrene, signs of peritonitis and shock are seen. Signs and symptoms may be intermittent as the bowel twists and untwists.

Plain films may or may not show a gas-filled and dilated stomach and duodenum, with no gas or only small bubbles in the rest of the intestine. Barium enema shows the cecum to be in its incompletely rotated position in the left epigastrium. Barium swallow demonstrates dilatation of



the stomach and proximal duodenum and only a small amount of barium passes the obstruction.

#### (b) Jejunal-ileal Atresia

Most atresias occur in this area. They are thought to be due to failure of recanalization or vascular accident. Malrotation is frequently seen but other severe anomalies are rarely associated.

The symptoms are of low small bowel obstruction. Vomitus is bile-stained and normal meconium is not usually passed. Abdominal distention is marked and generalized and intestinal patterning is seen. Radiography shows distended loops of small intestine with no air beyond the atresia. Barium enema may be of some value.

#### (c) Meconium Ileus

Meconium ileus is one aspect of cystic fibrosis which is considered elsewhere in this symposium. Pancreatic enzyme deficiency and thick gastrointestinal secretions account for thick and sticky meconium which causes obstruction usually in the lower ileum. No meconium is passed when obstruction is complete but partial obstruction may allow the passage of a quantity of black, sticky meconium after a rectal examination or enema. Vomiting is progressively more frequent and more copious and the vomitus becomes darker. Abdominal distention is generalized and intestinal loops may be seen or felt through the abdominal wall. Firm rubbery masses may be palpated within the intestinal loops, especially in the right lower quadrant.

Radiography reveals gas and fluid-filled loops of intestine which vary greatly in size. Inspissated meconium flecked with air bubbles gives the characteristic "ground glass" appearance. Gross considers the combination of hard abdominal masses and the characteristic radiographic findings diagnostic.<sup>9</sup> The diagnosis is supported if there are affected siblings or if other systems show evidence of cystic fibrosis.

#### (d) Hirschsprung's Disease

Hirschsprung's disease is a congenital absence or atrophy of the parasympathetic ganglion cells of Auerbach's plexus in the distal colon. The deficiency almost invariably includes the internal anal sphincter and may involve the rectum and lower sigmoid (70%), the rectum only (15%) or the rectum and other parts of the colon up to the ileum (15%). Normal peristalsis is prevented causing physiologic obstruction. Gas and feces accumulate causing dilatation and hypertrophy of the proximal segment.

Obstruction may be complete, partial, and/or recurrent and thus symptoms vary in severity, but the most severe forms are seen most frequently in the neonatal period. The classical picture is a history of progressively obstinate constipation, the passage of no or only small meconium stools, and abdominal distention with or without vomiting. Palpation demonstrates massive accumulations of gas and hard fecal material in various parts of the abdomen. Peristaltic waves may be seen or heard. Rectal examination reveals a clean anus and usually empty rectum and a palpable fecal mass just above the spastic recto-sigmoid junction. Often, this may cause passage of the greyish mucus plug (suggestive of obstruction), masses of soft meconium and flatus with temporary relief of symptoms. A small enema can produce the same results.

Plain films often show a markedly distended colon containing large amounts of gas or mottled fecal material. Barium enema demonstrates the typical contracted distal segment and either a funnel-shaped widening or an immediate dilatation of the proximal segment. Rectal biopsy, revealing aganglionosis in the distal segment, is diagnostic. However, this procedure is not as easy as is said<sup>6</sup> and interpretation by the pathologist is difficult.

#### (e) Meconium Plug Syndrome

Meconium plug syndrome is a low intestinal obstruction due to a solid plug



of meconium in the rectum, sigmoid or descending colon, possibly due to a deficiency of trypsin (a liquefying enzyme). Symptoms are abdominal distention and vomiting. Normal meconium is not passed and bowel loops may be seen and palpated. Rectal examination may yield meconium with subsequent relief of symptoms.

On plain films there is a generalized gas pattern and marked dilatation of the entire bowel. Barium enema reveals a long, smooth, ribbon-like, distal colon and dilatation at and proximal to the point of obstruction.

The conditions resemble and must be distinguished from meconium ileus and Hirschsprung's disease. Differentiation is based upon the fact that symptoms may be relieved by digital examination, barium enema or dilute hydrogen peroxide enema. Furthermore, repeated barium enemas indicate increasing calibre of the distal colon and analward migration of the mass.

#### (f) Duplications of the Alimentary Tract

Duplications are cystic or tubular structures of variable size and shape usually not communicating with (80%) but firmly adherent to any part of the alimentary canal. The three alimentary tract layers form the walls and fluid is secreted in accordance with the type of mucosa. They may be sequestrations, diverticulae or sites of aberrant recanalization. Dilatation causes partial obstruction of the adjacent gut. Distention of the structure causes pain. Pressure on vessels produces necrosis, sloughing and bleeding of adjacent intestine. Gastric mucosa produces erosion and hemorrhage.

Non-communicating thoracic duplications give rise to respiratory symptoms and signs (coughing, cyanosis, dyspnea) or hemoptysis or hematemesis when lined by gastric mucosa. Other rare thoracic duplications communicating with intestine can cause intermittent cardiorespiratory symp-

toms due to gas or exsanguinating hemorrhage, melena and anemia when lined by gastric mucosa.

The more common intestinal duplications produce partial or sometimes complete obstruction by extrinsic pressure. The symptomatology varies with the site.

Barium studies may permit a positive identification of the lesion but a correct pre-operative diagnosis is seldom made.

#### CONCLUSION

Prematurity and the presence of multiple anomalies greatly increase the operative risk in surgery of the newborn. Because the cough reflex of newborn infants is impaired, post-operative pulmonary complications account for a large percentage of deaths. However, approximately 80% of full term infants with one abnormality survive and most become perfectly normal children. Thus early diagnosis and definitive treatment are of paramount importance.

#### SUMMARY

The importance of early diagnosis of congenital abnormalities, mainly of the alimentary tract, which are incompatible to life but amenable to surgery, is stressed. The diagnosis of some of these conditions is discussed.

All figures quoted are from Gross, "The Surgery of Infancy and Childhood".

I wish to thank Dr. D. G. Marshall for his help in the preparation of this article.

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Continued from Page 19

The clinical and laboratory findings of the most common types of congenital heart disease have been discussed within a framework of three main groups.

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2. The data on the frequency of congenital heart defects given by the following investigators, Abbot, Nadas, Wood; and Ober & Moore.

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# Parenteral Fluid Therapy

JAMES E. CALLAGHAN, '63

## INTRODUCTION

"Reviews of fluid therapy like water are everywhere".<sup>1</sup>

A bewildering array of different methods based on surface area, weight and calorie requirements have been suggested for calculating the amount of fluid to be administered. The use of both British and Metric systems has been a further complicating feature. Admittedly, no single method is perfect but it is advisable to adopt one arbitrarily at the outset and use it to avoid confusion. It will be the purpose of this paper to provide a brief review of the basic principles underlying the rationale of fluid therapy and to present a method which has been found useful in the treatment of pediatric patients. No attempt will be made to discuss the many specialized situations which may require modification of this basic outline.

## BASIC PHYSIOLOGY:

In the interest of brevity, a review of these facts is presented in point form.<sup>4</sup>

1. Total Body Weight is
  - 70% Water
  - 50% Intracellular
  - 20% Extracellular
    - 5% Intravascular
    - 15% Interstitial
2. Chemical Constituents of Water in Body Compartments
  - (a) Cations (+) K and Mg are mostly intracellular  
Na is mostly extracellular
  - (b) Anions (—) Phosphate and Protein are mostly intracellular  
Cl and HCO<sub>3</sub> are mostly extracellular
3. Units of Measure
  - (a) Milliequivalent (mEq.) =  $\frac{1}{1000}$  equivalent weight  
Equivalent weight =  $\frac{\text{atomic weight}}{\text{valence}}$   
Atomic weight =  $\frac{\text{molecular weight}}{\text{valence}}$   
The equivalent weight is that weight of an element which will combine or react with one molecular weight of hydrogen. It is a unit indicating combining or reacting ability.
  - (b) Conversion of Units — This is useful when the laboratory reports electrolytes in milligrams.

$$\text{mEq./litre} = \frac{\text{mg./100 ml.} \times 10 \times \text{valence}}{\text{atomic weight}}$$

Some Common Ions	Valence	Atomic Wt.
Na	1	23
K	1	39
Cl	1	36
Ca	2	40

## Diagnosis of the Dehydrated Patient

The problem of treating the dehydrated patient, from whatever the cause, revolves around the question of how much electrolyte and water to administer. There is no exact solution to this problem for any particular patient, nor is there any single laboratory test which will easily and quickly provide the answer in the clinical situation. A combination of history, physical examination, laboratory data and personal experience are required. Much of the following outline will be in point form for the sake of brevity and clarity.

## HISTORY

The clinical evaluation of the patient is of the utmost importance and the value of a brief history is not to be underestimated. In it the following points should be considered.

1. Intake
  - Quantity
  - Kind: water, electrolyte, protein, drugs
2. Output
  - Quantity
  - Kind: urine, vomiting, diarrhea, sweat, drainage



### 3. Balance

Weight change

### 4. General Medical

Age

Cardiovascular, respiratory, renal or central nervous system disease.

A word might be said here regarding the assessment of kidney function since in the calculation of fluid therapy the ability of the kidneys to regulate fluid balance is of paramount significance. In dehydration urinary output should normally decrease. The usual volume of urine in the face of clinical evidence of dehydration should be a warning of kidney malfunction. Likewise, a history of kidney disease prior to the onset of the dehydration would be an important consideration.

## PHYSICAL

The physical signs of dehydration are of even greater significance than the history. The clinical differentiation between hyper-, iso-, and hypotonic dehydration is by no means clear<sup>2</sup> While in certain instances the delineation between these states may be of importance, in most cases, restoration of the circulating blood volume and adequate kidney function will permit the body to regulate its own electrolytes from the supply provided. Consequently, this subject will not be dealt with here.

The following are the most significant signs of dehydration:

#### 1. Skin

Colour\*—gray

Temperature—cold or hot

Turgor—loose

Feel—dry

2. Mucous Membrane—Dry

3. Eyeball—Sunken and/or soft

4. Fontanelle—Sunken

5. Psyche—Lethargic or hyperirritable

Coma=very severe dehydration

6. Pulse\*—Rapid

7. B.P.\*—Low

\*Signs of Shock

Estimation of the degree of dehydration from which the volume of deficit therapy can be calculated is something which only experience can teach. There are, however, some useful and simple criteria in addition to the above that give a rough estimate of the degree of dehydration.

- 1) Weight: A decrease in weight is useful if the weight before the onset of dehydration is known. With infants, a recent figure is more likely to be obtainable than with older children.
- 2) Skin Turgor (Pinch Test): This simple test is used arbitrarily as a rough estimate. The skin over McBurney's point is pinched up and released. With a stop watch or other timing device, the interval for the skin to flatten out is noted.  
0.5 - 1.0 sec. = mild dehydration  
1.0 - 2.5 sec. = moderate dehydration  
2.5 + sec. = severe dehydration

In summary, to estimate the degree of dehydration and provide a rough figure for judging initial deficit therapy, the following outline may be considered:

- 1) Mild Dehydration (0-5% body weight or 0-50 cc./Kg.): Pinch test 0.5 - 1.0 sec.: minimal signs of dehydration.
- 2) Moderate Dehydration (5-10% body weight or 50 - 100 cc./Kg.): Pinch test 1.0 - 2.5 sec.: definite signs of dehydration; shock.
- 3) Severe Dehydration (10 - 15% body weight or 100-150 cc./Kg.): Pinch test 2.5 + sec.; definite signs of dehydration; shock; coma.

## LABORATORY

No laboratory data are so essential that adequate therapy cannot be started in their absence. Any or all of the following pieces of information may prove useful in forming a baseline for later evaluation of the results of therapy:

#### 1) Urine

volume and specific gravity

Sugar, acetone, albumin

Sediment



## —Parenteral Fluid Therapy—

- 2) Whole Blood  
*Hematocrit*  
*B.U.N.*
- 3) Serum or Plasma  
Electrolytes - Na, K, Cl  
Proteins  
CO<sub>2</sub> Combining Power
- 4) Electrocardiogram

Of these tests the BUN bears special mention as an indication of renal function. A rising BUN once therapy has been instituted, would mean either renal disease or continuing circulatory insufficiency.<sup>6</sup>

### TREATMENT OF THE DEHYDRATED PATIENT

After the diagnosis of dehydration has been made, the next step would be the institution of therapy. Considerable difference of opinion exists among various authors as to the best approach. For instance, Oliver, Graham and Wilson<sup>5</sup> have rejected computing fluid requirements using surface area on the grounds that it is awkward and that there are insufficient measurements available for infants and children. On several points, however, most authorities do agree. The best evidence of proper fluid therapy is the patient's response and the best measure of the degree of hydration is weight. Thus, all children on parenteral fluid therapy should be weighed daily. The aim of all therapy should be alleviation of the underlying cause of the dehydration and prevention of its recurrence.

Planning for parenteral fluid therapy should be considered under three categories each with a specific aim in mind.

- 1) Deficit Therapy—to make up the amount of fluid lost in dehydration. This aims first to restore the circulating blood volume, thereby treating shock and reinstating adequate electrolytes so that the kidney can restore the normal physiologic balance.
- 2) Maintenance Therapy—to provide sufficient fluid and electrolytes for natural losses via the lungs, skin, kidney and bowel.

- 3) Replacement Therapy—to keep up with abnormal losses occurring during therapy, such as through diarrhea, or vomiting.

With the foregoing principles in mind, it is now possible to proceed to the actual calculation of the amount of fluid to be given.

- 1) Deficit Therapy
  - a) Water: The amount is determined by the clinical estimation of the degree of dehydration (see Diagnosis - Physical).
  - b) Electrolytes:  
Na 8 mEq./100 cc. H<sub>2</sub>O required  
Cl 6 mEq./100 cc. H<sub>2</sub>O required  
\*K 6 mEq./100 cc. H<sub>2</sub>O required.  
\*see note on administration of K to follow.  
For hypotonic dehydration, give more electrolyte and conversely for hypertonic dehydration give less electrolyte.
  - c) Carbohydrates and Vitamins are given as required.

- 2) Maintenance Therapy
  - a) Water: The amount is determined according to the caloric requisite at different weights of patient allowing 1 cc. H<sub>2</sub>O for each calorie required, i.e.  
Calories required /24 hours  
1-10 kg. patient allow 100 cal./kg.  
10-20 kg. patient allow 1000+50 cal./kg.  
20+ kg. patient allow 1500+20 cal./kg.  
Rationale behind allowing 1 cc./cal.:  
For normal metabolism each 100 calories burned requires  
67 cc. H<sub>2</sub>O for urine formation  
50 cc. H<sub>2</sub>O for insensible loss and respiration  
117 cc. /100 calories total  
But each 100 calories burned liberates 15-20 cc. H<sub>2</sub>O (17 cc.) Thus 100 cc. H<sub>2</sub>O are required for each 100 calories burned ∴ 1 cc. H<sub>2</sub>O for each calorie.



b) Electrolytes:

Na 3 mEq./100 cc. H<sub>2</sub>O required  
Cl 2 mEq./100 cc. H<sub>2</sub>O required  
\*K 2 mEq./100 cc. H<sub>2</sub>O required  
\*see note on administration of K to follow.

c) Carbohydrate and Vitamins as required.

3) Replacement of Abnormal Losses Occurring During Therapy

Initially this amount can only be roughly estimated. As therapy proceeds a more accurate determination can be obtained by charting the volume of fluids lost by the various routes, as urine, vomitus, diarrhea, perspiration or gastric suction.

**Rate of Administration:**

To replace the deficit and restore circulating blood volume, a fairly rapid rate of 15-20 cc./kg./hour may be used for the first one to two hours. Once therapy has been started, however, a *position of flexibility must be taken*. The patient must be carefully watched—the younger the child, the closer the scrutiny—and adjustments made as needed. Once the deficit has been restored, the maintenance dose is continued remembering that the dose as calculated above is the amount required in 24 hours. Replacement of abnormal losses during therapy is done as required.

**Example:**

In the treatment of dehydration in a 10 kg. child, the following steps would be followed:

1. Diagnosis: From the history, physical examination, and possibly some laboratory aids, the degree of dehydration is determined to be roughly 10% or 1000 cc.

2. Calculation of Amount of Fluid to be Administered:

a) Deficit Therapy - to replace 1000 cc. fluid

1) H<sub>2</sub>O requirement = 1000 cc.

2) Electrolytes

Na 8 mEq./100 cc. = 80 mEq.

Cl 6 mEq./100 cc. = 60 mEq.

K 6 mEq./100 cc. = 60 mEq.

3) Carbohydrate may be given with the water as 5% glucose + Vitamins.

b) Maintenance Therapy - to maintain 10 kg. child for 24 hours

1) H<sub>2</sub>O requirement = 1 cc./calorie  
Calorie requirement = 100 cal./kg  
or 1000 cal.

∴ H<sub>2</sub>O requirement would be 1000 cc.

2) Electrolytes

Na 3 mEq./100 cc. = 30 mEq.

Cl 2 mEq./100 cc. = 20 mEq.

K 2 mEq./100 cc. = 20 mEq.

3) Carbohydrates and Vitamins as above.

c) Replacement of Abnormal Losses Occurring During Therapy

This amount will be determined by the charted information regarding fluid loss.

3. Administration:

The fluid calculated for deficit therapy would be given rapidly 15-20 cc./kg./hr, at first to restore circulating blood volume and kidney function. After 1-2 hours the rate is slowed and maintenance therapy is adjusted to the response of the patient.

**Administration of Potassium:**

Potassium is usually included in parenteral fluid therapy to replace deficits and also to avoid them. To avoid dangerous potassium intoxication Darrow<sup>3</sup> suggests that the following rules should be followed:

1) Restore circulation and renal function by replacing deficits of water and other electrolytes partly or completely before adding potassium.

2) Do not give more than 40 mEq./litre in I.V. solution.

3) Give the daily requirement of K over as long a period as possible—not less than 6 hours.

4) Potassium is almost always contraindicated in renal insufficiency and untreated adrenal insufficiency.

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# Legal Cross-examination: The Inside Story

FRANK RIGGALL, M.A., M.D., LL.B.

Forewarned is forearmed. In this explanation of the cross-examining lawyer's job I hope to rid the witness-box of some of its discomforts for doctors who might be called as witnesses. Such riddance will aid the cause of justice because it is difficult for an anxious, uncomfortable, harassed, and confused doctor-witness to put his facts clearly.

All doctors cross-examine their patients. After taking the history, which equals direct examination in a law court, the doctor cross-examines the patient to clarify the history by bringing out items forgotten, glossed over, or suppressed. Above all, he seeks to fit the story the patient tells into the framework of anatomy, physiology, and pathology upon which all medicine and surgery rest. Of course, the most penetrating, revealing questions come from the doctor who keeps his knowledge tools sharp and so it is said that a doctor is known as much by his questions as by his answers. After all, a doctor who knows his job simply does not ask questions about rickets in the case of an ailing baby five months old.

Lawyers are taught that cross-examination is a great tool for probing after truth and they believe the teaching with a fervor that would credit a prophet. A lawyer has an advantage over the cross-examining doctor because the lawyer often has months to formulate his questions while the doctor must cross-examine on "the occasion fleeting". However, busy doctors cross-examine more than do busy lawyers; so perhaps matters equalize.

A doctor is engaged to cure or improve his patient's condition of health. A lawyer is engaged to cure or improve his client's condition at law. Legal stratagems except-

ed, there are only three things a cross-examiner can do and knowledge of this fact is important for the doctor-witness.

First, on cross-examination the lawyer can try to bring out facts omitted, forgotten, or glossed over in the direct examination taken by the opposing counsel. One example lies in eliciting actual relationship or long time friendly contact of a doctor-witness to one of the parties in the case. Another example is eliciting failure to make certain laboratory tests or to take x-rays.

Second, by cross-examination a more favorable look might be had at facts brought out on direct examination. The lawyer might show that his client did all that a reasonably prudent man could be expected to do; or that a dark night made identification difficult; or that authorities differ in opinions on the matter in question.

Third, it is the lawyer's duty to imitate St. Thomas and doubt everything the doctor says. Advancing his client's case often demands derogating or contradicting the testimony of medical witness. When this stage is reached it is very important for the doctor-witness to know that there is rarely anything personal in the questioning. (Indeed, experienced lawyers know that it may be bad for a client's cause to show personal bias or enmity against a witness. Judges and jurors have sympathy for abused under-dogs.) The doctor-witness should tell himself that the lawyer is merely fulfilling a duty he owes to the court, the client, and himself, and that he would be guilty of a dereliction of duty if he left any stone unturned which might aid his client's cause.



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In turn, it is the doctor's duty as a witness to be such master of the fact, the theories, and the opinions that he does his best to counter the derogations and doubts raised by the cross-examiner. This means he must keep his medical knowledge of the tripod up to date from reliable sources. The latest editions of the doctor's favorite textbooks are a good beginning. He should freely admit the existence of other views and say they do not agree with his teachers, reading, and experience though they may well fit the criteria of their proponents. Remember that judges of appellate and supreme courts often disagree upon the same set of facts so that law reports are replete with major and minor opinions. And remember further that as Time rolls on the minor opinions sometimes oust the major ones.

(In medicine, a classical example of this is "A New Theory of Vision" promulgated in 1706 by Berkeley when that philosopher and theologian was 21 years old. The good bishop defended that theory against many attacks for the rest of his life. It was not until 250 years later that the Oxford University anatomists demonstrated the extraocular muscle spindles which proved the truth of Berkeley's theory!)

The doctor-witness who keeps his knowledge tools sharp rarely needs to fear the lawyer who has read up on the anatomical, physiological, and pathological tripod. Medical books written for lawyers are simplified versions of medical students texts. The knowledgeable post-graduate doctor knows, or should know, the fairy tales contained in many student textbooks, which have to be dogmatic and simplified.

Cross-examiners, like doctors, come in all grades of ability! Fuzzy, rambling questions usually betray a fuzzy rambling type of mind but beware of the able lawyer who assumes this disguise to lull witnesses into complacency. Able cross-examiners use short, incisive questions couched in simple words, a method resembling that

of the able surgeon who approaches his objective with sure, bold strokes. In any case, never forget that the cross-examiner is always an opponent.

If the medical witness is asked a two part question, he should ask the cross-examiner to separate the parts. Almost always such questions are of opinion and not of fact. If the cross-examiner refuses to rephrase such a question into its component parts, the witness should say that he has no opinion on the question. If the witness answers a two part question with a yes or no, a contradiction might later confound him.

Questions that are not thoroughly understood should not be answered. There is nothing in law that compels a witness to answer a question that he does not understand. Ask the cross-examiner to explain the question or to rephrase it. Never be afraid to say that a question is not clear. A witness is sometimes asked to answer questions by a straight yes or no. Factual questions can be answered so, but it may be impossible to adequately answer yes or no to an opinion question. In such cases, the witness should tell the judge he cannot properly answer the question yes or no and ask if he might be allowed to qualify his answer. Almost always a judge will agree. It is the duty of the court to bring out all the facts in connection with the case and to always seek and obtain the truth so far as possible. If the judge does not agree to such a request, he may ask the lawyer to reframe or withdraw the question. No honest, able, truthful witness trying to be impartial has anything to fear from a diligent and upright judge.

Pay strict attention to the lawyer as he questions. Then turn to the jury, or to the judge if he is sitting without a jury, and answer. Try to speak slowly and distinctly, choosing the correct words carefully. This is not so easy as it sounds for stresses of trial can be great, even for experienced witnesses.



## —Legal Cross Examination—

(I used the wrong word once and a workmen's compensation proceedings were reversed by a superior court. In a case of rapid death from intracranial extra-cerebral bleeding the post-mortem report stated that it was impossible to so clean the brain surfaces of blood as to identify the vessels. I testified that the BRAIN would have to be removed to identify the site and source of bleeding. Reading of the testimony made it elementary that the word should have been BLOOD but the shorthand report and the tape recorder proved that I said BRAIN. It was a disconcerting and salutary experience.)

Try not to look bored or disinterested. Look on the proceedings as a game if need be, but a game so serious that its rules guard life, liberty, and property. Try not to get "smart" and do not get angry. "Those whom the gods would destroy, they first make mad."

If questioned about an extract from a

book or paper, ask to see the writing. Note the author's name, his position, and the date of publication. Then read the passage in full plus the passages before and after the one in question. Take time and refuse to be hurried. If the book, article, or author is unfamiliar, say so. Do not be trapped into claiming awareness of an author or work that is unknown.

Some lawyers whisper; some speak in silky tones; and some roar. Some sit; some stand; some stride about the room; and some gesticulate. Some deliberately adopt mannerisms calculated to distract witnesses. Despite the voice, actions, and manner remember there are only three things he can do. Being forewarned is to be fore-armed. Above all, know this—there is an eleventh commandment which lawyers sometimes fail to obey. It is this: "Beware of cross-examining an expert in his own field or a fool on his own level because they might defeat you."

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*Continued from Page 37*

### CONCLUSION

The importance of having a simple and readily adaptable method for the calculation and administration of parenteral fluids cannot be over-emphasized. There are many methods described; no one in itself universally applicable to all situations. The foregoing, it is hoped, will serve as a useful and flexible guide in managing the many situations where fluid therapy is required.

The author would like to thank Dr. A. Lansing and Miss J. O'Rourke for their assistance in preparing this paper.

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# News and Views

At a Medical Banquet, sponsored by Alpha Kappa Kappa Fraternity at Hotel London on December 17, O.M.A. President Dr. Patrick Bruce-Lockhart presented the case of the O.M.A. in the current government care plan controversy in Ontario. He endorsed the recent Progressive Conservative proposal whereby insurance is available to everyone, with the government assisting but not controlling.

He feels there are two main drawbacks to government administration and planning. Firstly, the patient's responsibility toward his use of the services vanishes causing soaring costs. Controls must be established and this is to the detriment of the patient since the agency restricts the use of the service to what is thought to be the average need of the patient. Medical care is then geared to the needs of the masses, not the individual. Secondly, the doctor-patient relationship, presently a personal contract, becomes a "divided loyalty" when a third party is concerned. Furthermore, the government agency imposes

controls on both doctor and patient and an impersonal "assembly line" results.

Most people can afford to pay premiums and should be offered a choice of plans and agencies with varying types and degrees of insurance. But there are three groups who cannot afford to pay premiums: the indigent, the marginal income group, and the poor insurance risk group (aged or ill). The indigent are the responsibility of the government who already renders partial remuneration. The marginal income group should be government-aided either by an expanded Medical Welfare Plan or through ordinary carriers with the government paying the premiums. Some of the poor risk group is covered by P.S.I. through community-rated premiums. The C.H.I.A. has suggested pooling the people among all insurance companies, thus enabling them to buy insurance at a reasonable rate.

Dr. Bruce-Lockhart stressed that the public must be informed of these issues and that the most efficacious method was by direct discussion with the patient.

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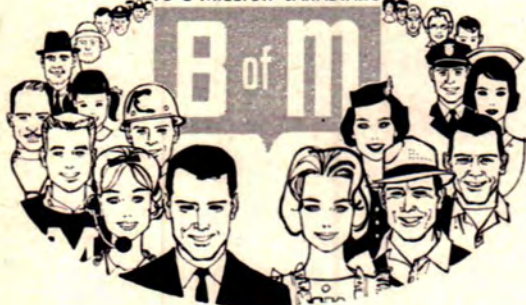
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# The Relationship Between The Pituitary and the Hypothalamus

RICHARD E. WYLIE, '64

## INTRODUCTION

In the last decade research done all over the world has revealed a great deal of information to show that the hypothalamus and higher nervous centers play a major role in the regulation of the secretions of several of the pituitary hormones. These findings are of great importance not only in our understanding of pituitary function, but also because we can now begin to understand how exteroceptive stimuli resulting from changes in an individual's environment influence the nature and quantity of the hormones secreted by the pituitary and thus the endocrine glands under pituitary control.

## HISTORY

It was believed by the Greeks, that, as a result of a chemical reaction in the brain, blood received "animal spirits", and the waste products of this reaction drained into the pituitary gland. From here there were supposed to be ducts which carried this material to the nose where it made up the "pituita" or nasal mucus. This view was held for many hundreds of years, and it was not until after 1890 that the actual functions of the pituitary began to be explained. Marshall, in 1942, was the first to postulate that the pituitary was under the control of higher nervous centres when he drew attention to the fact that the sexual rhythms of many birds and mammals are conditioned by changes in their external environment.

## ANATOMY AND EMBRYOLOGY

Anatomically, the pituitary is divided into two parts, the adenohypophysis (anterior lobe) and the neurohypophysis (posterior lobe). This division is closely related to the embryology of the gland and is important in understanding the functions of the gland and their regulation. The adenohypophysis is derived from Rathke's pouch, an ectodermal pocket arising from the posterior wall of the nasopharynx, which appears in the embryo at four weeks. This pouch elongates, and soon comes in contact with

a sac-like projection of the infundibulum which is the analogue of the neurohypophysis. By the second month, the adenohypophysis has lost its connections with the nasopharynx. This migration of the anterior pituitary is fundamental to the mechanism that has developed for its regulation by the nervous system.

Most investigators are agreed that there are no direct neural connections between the hypothalamus and the adenohypophysis. However, two large nerve tracts, the tubero-hypophysial, and the supraoptico-hypophysial extend from nuclei in the hypothalamus to the posterior lobe of the pituitary. The anatomical pathway by which the central nervous system influences the anterior lobe was difficult to explain until attention was turned to the previous work of Popa and Fielding in 1930, in which a portal vascular system between the hypothalamus and the hypophysis was described. There is now good evidence that these portal vessels form the functional link between the hypothalamus and the anterior pituitary. The first direct evidence that these portal vessels were concerned with anterior pituitary function came in a series of experiments to investigate the effect of pituitary stalk sections. It was found that if a plate was placed between the hypothalamus and the pituitary, normal anterior pituitary function (e.g.



cyclic secretion of the gonadotrophin) was upset. However, without this small plate, function usually returned and in these cases it was found that the portal vessels had regenerated. The importance of these hypothalamico-hypophysial portal vessels was also demonstrated in experiments in which the anterior pituitary was transplanted. If the anterior pituitary was placed at some distance from the hypothalamus, in the subarachnoid space, normal function was lost, but if it was transplanted to the subarachnoid space inferior to the hypothalamus, normal function soon returned. It has also recently been shown that anterior pituitary tissue transplanted under the capsule of the kidney loses normal activity which is recovered when the graft is subsequently replaced beneath the hypothalamus.

The cells in the hypothalamic nuclei are neurons that appear to have developed secretory functions and hence are called "neurosecretory cells". Several investigators have described "neurosecretory material" which is specifically stained and appears to originate in the supraoptic and paraventricular nuclei and migrate down the nerve axons to their endings in the posterior pituitary. This material appears to contain the posterior lobe hormones, although several investigators have stated that the stainable material is probably only a carrier for the hormones.

### **HYPOTHALAMIC CONTROL OF THE POSTERIOR PITUITARY**

The posterior pituitary is thought to be responsible for the function of three hormones, Oxytocin, Vasopressin and Anti-Diuretic Hormone (ADH). Of these it is now considered that Vasopressin and ADH are the same hormone. The posterior pituitary is now considered to be primarily a storage depot for the two hormones and it is thought that the hormones are produced in specific neurosecretory cells of the hypothalamus. The hormones, as previous-

ly stated, then pass down the axons of these cells to the posterior pituitary, from where they are released into the systemic circulation.

The control of the antidiuretic hormone was first clarified about 1938 when it was found that lesions placed in the supra-optico-hypophysial tracts caused a condition similar to clinical diabetes insipidus. It was also later shown that electrical stimulation of these tracts caused an increased release of ADH. The idea that neurohypophysial activity is affected by the composition of the blood, especially by changes in the osmotic pressure was later put forth to explain water diuresis. It was suggested that the ingestion and absorption of water caused a decrease in the osmotic pressure of the blood which in turn inhibited the secretion of antidiuretic hormone. Subsequently when the circulating hormone was removed or inactivated, there was a resultant water diuresis. The site of the osmoreceptor mechanism has not been established. It has been postulated that it is in the territory of the supply of the internal carotid artery, and that it lies in the diencephalon, but not in the neurohypophysis. The most likely site is the supra-optic nuclei since this area is extremely vascular and because of the specialized intracellular vesicles found there.

Oxytocin has a great effect which can be noticed on the lactating breast and on the uterus. It has been established that secretion of oxytocin results from a nervous reflex or by conditioned reflexes. Stimulation of the hypothalamus causes ejection of milk from a lactating breast and lesions in the hypothalamus will depress the reflex secretion of milk. The essential nature of the hypothalamico-hypophysial system for normal parturition has not yet been demonstrated. Animals with hypothalamic lesions are either unable to deliver their young or deliver them only after a prolonged and difficult labor. It has been postulated that in some animals oxytocin secretion is elicited reflexly during coitus



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with the result that the uterus contracts, moving sperm in the uterus towards the cornua and fallopian tubes.

## CONTROL OF THE ANTERIOR PITUITARY

The only known function of the anterior pituitary is the secretion of hormones. To date, seven hormones have been identified as having their origin in the anterior pituitary.

1. Growth Hormone (Somatotrophin)
2. Thyroid Stimulating Hormone (TSH)
3. Adrenocorticotrophic Hormone (ACTH)
4. Follicle Stimulating Hormone (FSH)
5. Luteinizing Hormone (LH)
6. Prolactin (Lactogenic Hormone)
7. Melanocyte Stimulating Hormone (MSH)

In general these hormones are released by feed-back mechanisms. There is much evidence to prove that the central nervous system influences the secretions of the adenohypophysis. However, there is little doubt that the release of these hormones is regulated by the concentration of the hormones, whose secretion has been stimulated by the trophic hormones of the anterior pituitary, present in the blood. Thus, for example, the anterior pituitary secretes TSH which stimulates the thyroid to release thyroxine. Now, the level of thyroxine in turn, if high, depresses the thyroid stimulating activity of the anterior pituitary. The site of this depression, as well as other aspects concerning the control of the anterior pituitary, has been well investigated in the last decade. It may be that the levels of the hormones present in the blood depress the anterior pituitary *per se*, but it is likely that this control also occurs at a higher level, probably in the hypothalamus.

The control of ACTH production has been widely studied and several new theories

as to its control have been put forward. One group of investigators has extracted from the blood of the sella tursica of a hypophysectomized animal, a substance absent from carotid arterial blood, which in other animals will bring forth an adrenocortical response thought to be due to the stimulation of ACTH production. Others have extracted a substance from hypothalamic tissue which has the same effect. Chemical examination of this substance has revealed that it is a polypeptide much resembling the structure of Vasopressin. This substance has been called Corticotrophin Releasing Factor (CRF). In another series of experiments it has been discovered that an animal with the brain removed, so that the hypothalamus is not present, still releases ACTH in response to trauma. Because of this finding it was postulated that a substance is released in the hind brain (Hind Brain factor) which causes release of ACTH.

In the study of thyroid control, it has been found that lesions in the anterior hypothalamus may depress thyroid function by causing a depression of TSH secretion. Further, these lesions reduce, but do not prevent the response of the pituitary to a deficiency of circulating thyroxine, suggesting a feed-back mechanism at two levels. Some authors feel that thyroid hormone suppresses TSH secretion by the anterior pituitary without hypothalamic mediation. A group of Japanese workers has prepared crude extracts from the anterior hypothalamus of the dog which they claim are able to release TSH from the pituitaries of rats, but this has not yet been definitely proven.

Gonadotrophins provide a very good example of central control of the pituitary. In the interplay between the pituitary and the ovaries in the regulation of sexual cycles, the feed-back system is probably of prime importance. However, a great deal of evidence has accumulated to show that other areas in the brain have a major influence through the hypothalamus on the



production of gonadotrophins. The fact that ovulation in some animals, such as the rabbit, occurs only after the stimulus of copulation suggests that the nervous system plays some role in the mechanism of ovulation in the species. Localized stimulation of the hypothalamus has been found to produce ovulation in 3 of 4 rabbits, while electrical stimulation of the pituitary *per se* was ineffective. It has been concluded that in this species, ovulation is induced by the activation of a neurohumoral pathway between the hypothalamus and anterior pituitary. In cattle, injections of oxytocin have a marked effect on estrus and ovulation and because of this it is felt that the humoral mediator between the hypothalamus and the pituitary may be oxytocin or an oxytocin-like substance.

#### SUMMARY

A few examples of hypothalamic and other central control of the pituitary have been cited. It is realized that the feed-back mechanism is very important in the control of internal secretions. Thus the anterior pituitary through its trophic hormones stimulates a target organ which in turn produces its own hormone. The concentration of this hormone subsequently affects the secretion of its own trophic hormone from the pituitary. However, the importance of the central control of the pituitary is becoming more and more evident. The control of the pituitary by the hypothalamus has been demonstrated experimentally by hypothalamic stimulation and ablation. These experiments have shown the marked effect the hypothalamus has on the pituitary, and also the importance of the hypothalamico-hypophysial portal system. Thus the anterior pituitary with direct neural connections can be controlled via this portal system by humoral substances

produced by various "neuro-secretory cells" of the hypothalamus. Other important steps in the elucidation of the interactions between the hypothalamus and the pituitary have been the experiments to find extracts and identify the "releasing Factors" produced by the "neuro-secretory cells." All of these advances have helped a great deal in the understanding not only of the functions of the various endocrine glands of the body, but also of the effect of environment on the central nervous system and thus on these endocrine glands.

The author would like to thank Dr. J. A. F. Stevenson for his help in the preparation of this article.

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# The Hormonal Treatment of Cancer

DONNER DEWDNEY, '63

## INTRODUCTION

In certain patients it is possible to bring about a profound subjective and objective improvement in the most severely disseminated malignancies by modifying the hormonal states of the host. This control may be effected in two ways—either by withdrawing hormonal support from the tumor or by the administration of an "antagonistic" hormone. The two malignancies which respond classically to this treatment are the "hormone-dependent" varieties of breast and prostate carcinoma.

## I. CARCINOMA OF BREAST

The use of hormones in treating cancer of the breast is reserved essentially as a third line of defence once both surgery and radiation have failed to check the advance of the disease. Neither ablation resections nor the administration of steroid hormones is offered to the patient as a curative procedure. None the less, in a great many cases these methods not only reduce pain, but in a significant minority produce a regression in the tumor's growth. The choice as to method lies in the division of mammary cancer into two groups; premenopausal and postmenopausal.

### Premenopausal Carcinoma

As early as 1886, G. T. Beatson<sup>1</sup> reported the beneficial effects of ovariectomy in two cases of breast cancer. Sixty years later Pearson *et al.*<sup>2</sup> report in a review of 77 premenopausal women with metastatic breast cancer that an objective remission occurred in 44% of cases. The same authors report that both primary and secondary lesions appear equally affected by this procedure. The less traumatic procedure of irradiation appears less effective than the actual surgical removal in producing improvement in these cases. Unfortunately, there are no completely satisfactory means of predicting those tumors which will prove to be sensitive to this type of treatment.

If ovariectomy alone fails to effect a remission, or upon exacerbation of the tumor after surgery, one resorts to the use of hormones. Unlike the postmenopausal

tumor which may regress when estrogens are given, the premenopausal growth often exacerbates when this hormone is increased. This may occur with endogenous ovarian function or exogenously when estrogens are given to an undiagnosed breast tumor for other gynecological reasons. Consequently androgen is the recommended hormone for premenopausal breast cancer.<sup>3</sup> It is especially indicated in the metastatic tumor which is showing bone involvement. Androgen is reported as producing relief of pain in as many as 80% of cases. In the same series, a regression of the bone lesion occurred in 25% of the patients reviewed. The average remission produced by androgen lasts approximately seven months in the responding case but may extend for as long as two years. The attending physician must expect the appearance of unfavourable side effects including husky voice, acne, hirsutism, and hypercalcemia.

Patients who respond to ovariectomy on exacerbation may benefit again from attempts to depress adrenal function. Corticosteroids (principally cortisone and prednisone) may be used to induce secondary atrophy of the adrenal cortex by suppressing pituitary function. The more radical approach of adrenalectomy has been recommended by Dao<sup>4</sup> who reports an improvement in 10 out of 25 premenopausal cases reviewed. It must be remembered, however, that the presence of liver metastases is a serious contraindication to this procedure. Nevertheless it is recommended if the breast tumor is inflammatory in type.



Hypophysectomy may offer renewed palliation, but this procedure is fruitless in the presence of liver or cerebral metastases. Pearson<sup>5</sup> reports, in a review of cases in which pituitary ablation was the method of choice, an improvement in approximately 50% of cases. It is interesting to note that in some cases improvement occurred when hypophysectomy followed removal of both the ovaries and the adrenals. This effect has led to the postulation of pituitary hormonal support of breast cancer.

### Postmenopausal Carcinoma

As one might expect, ovariectomy appears to have little value in the management of inoperable postmenopausal breast cancer. Pearson<sup>2</sup> reports that only 2 out of 21 women past the menopause demonstrated improvement in one series reviewed. The same author reports a remission in 16 out of 25 postmenopausal cases if both ovaries and adrenals were removed. Huggins and Dao<sup>4</sup> report that this double operative procedure is most effective in the 40 to 65 age group.

In spite of significant results from surgery the essential hormonal management remains the administration of estrogen and androgen. When estrogen is given alone reports show a subjective relief obtained in 60% of cases, regression of the primary tumor in 50% of cases and regression of soft tissue lesions, including pulmonary metastases, in approximately 40% of cases. Once more, side effects may become a problem and should be noted as including nausea, edema, uterine bleeding and congestive failure. Androgen, although somewhat less effective than estrogen, may be answer in the patient who appears insensitive to an estrogen trial. The American Medical Association<sup>6</sup> reports androgen's beneficial effects in 21% of the postmenopausal cases reviewed. Both estrogen and androgen are more effective after the eighth menopausal year.

Those patients who show exacerbations in spite of continued hormone therapy may be considered as candidates for pituitary ablation. Hypophysectomy appears to have its best results in women within the first decade after cessation of menstruation.

## II. CARCINOMA OF THE PROSTATE

The beneficial effects of orchiectomy in the treatment of prostatic hypertrophy have been known for many years. Until Huggins' initial study in 1940 the further efficacy of castration for prostatic carcinoma was unknown. In his original review of 45 cases, Huggins demonstrated a prolonged inhibition of the neoplastic process in 31 patients. Today the combination of orchiectomy and estrogen therapy is considered the therapeutic ideal in treating non-resectable cancer of the prostate. In a review of 113 cases<sup>8</sup> it is shown that this double approach is successful in producing a 5 year survival rate of 36.3%. If stilbestrol is used alone, this rate is reported to decrease to 18.3%. In prostatic tumors with known metastases, stilbestrol therapy appears to be of little value once castration has been performed.

The side effects of stilbestrol administration include nausea, vomiting, gynecomastia and the accumulation of fat in a feminine distribution. Diethylstilbestrol has been noted to occasionally produce a toxic hepatitis. Stilbestrol, like the estrogen preparations, results in sodium retention and may precipitate congestive heart failure.

Adrenalectomy and hypophysectomy are done occasionally in large centers when patients who first respond to castration show tumor exacerbation. The results of both procedures are nevertheless disappointing.

Androgen control may effect a spectacular response in the patient with advanced disease. The relief of pain is such that bed ridden patients are frequently enabled to walk again. Appetite is improved and a consequent weight gain results. The anemia may often revert to normal levels with-



out benefit of iron therapy. Ackerman<sup>9</sup> reports complete regression of an area of ulceration on the skin in one particular patient. The most striking feature is the frequent finding of regression of soft tissue extensions: lymph nodes become no longer palpable, urinary obstruction is relieved, and shrinking of a swollen prostate occurs. Radiological evidence of regression of bone metastases supports the clinical evidence.

Although the five year survival rate of prostatic carcinoma is grim, Nesbitt<sup>10</sup> has demonstrated that the patient responding to androgen control lives appreciably longer than the untreated patient. Favourable prognostic signs include the reversion of a clinically malignant prostate to a clinically benign state and a drop in acid phosphatase following castration.

## CONCLUSION

Gonadectomy in both sexes is of value in producing a regression of tumors which are shown to be dependent on sex hormones. There is no laboratory test available to predict this dependency. Therefore clinical trial of the procedure outlined appears to be the only solution.

It also becomes obvious that breast and prostate tumors which initially illustrate this dependency, become less so as therapy continues. Whether this is due to take-over of hormone production by the tumor or whether it is due to actual tumor independence from hormones, has not been determined.

It should also be pointed out that once castration and hormones are failing to produce remissions, thoughts of radical surgery should be weighed against the increased risk of death from the operation and the possibility of failure. Corticosteroids which do not present the problems of surgery become an ideal compromise in the debilitated patient where one wishes to suppress the adrenal cortical excretion of hormones. This same adrenal activity appears to increase following gonadectomy

and may in fact support the tumor's growth. The fact remains that at least initially a certain proportion of breast and prostate tumors show a histochemical similarity to their normal tissue origins. This very observation has led to a new development in tumor research and this writer awaits with interest new developments.

I wish to thank Dr. E. R. Plunkett for his assistance in the preparation of this article.

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# The Cortisone Withdrawal Syndrome

LARRY PERSYKO, '64

## INTRODUCTION

Adrenal hormone therapy constitutes a potent pharmacological agent in the armamentarium of every practising physician. It should be his responsibility to possess an adequate knowledge of the pharmacologic actions of these agents as well as the indications and contraindications for their use.

### STEROID PREPARATIONS:

#### (1) Commonly Used Steroid Preparations

1. Cortisone (Cortone)—Merck
2. Hydrocortisone (Solucortef)—Upjohn
3. Prednisone (Meticorten)—Schering
4. Prednisolone (Meticortelone)—Schering
5. Triamcinolone (Aristocort)—Lederle
6. Betamethasone (Celestone)—Schering
7. Dexamethasone (Decadron)—Merck
8. Paramethasone acetate (Haldron)—Lilly

#### (2) Uncommon Steroid Preparations

This group represents only a few of the mixed steroidal preparations now on the market which may be classed as dangerous due to their "hidden" steroid content—i.e. hidden from the patient's knowledge, often from the prescribing doctor's knowledge, but most dangerous of all hidden from any doctor who the patient may see in the future following therapy with these drugs.

1. *Cordex Improved Tablets (Upjohn)*  
Methylprednisolone 0.5 mg., ASA 300 mg. preserved in ascorbic acid
2. *Cordex Forte Improved Tablets (Upjohn)*  
Methylprednisolone 1.5 mg., ASA 300 mg. preserved in ascorbic acid
3. *Aristogesic (Lederle)*  
Triamcinolone 0.5 mg., Salicylamide 325 mg., Aluminum Hydroxide Gel 75 mg., Vitamin C 20 mg.
4. *Metreton (Sbering)*  
Prednisone 2.5 mg., Chlorpheniramine maleate 2 mg., Vitamin C 75 mg.
5. *Decagesic (Merck, Sharp & Dohme)*  
Dexamethasone 0.1 mg., ASA 300 mg., Aluminum hydroxide gel 60 mg.
6. *Colisyl—H (Frosst)*  
Prednisone 0.75 mg., ASA 325 mg., Vita-

min C 25 mg., Methscopolamine nitrate NND 1.25 mg.

7. *Pabalate—HC (Robins)*  
Potassium Salicylate 0.3 gm., Potassium para-aminobenzoate 0.3 gm., Ascorbic Acid 50 mg., Hydrocortisone (alcohol) 2.5 mg.

The danger of these drugs depends not on the amount of steroid present *per se* but on the number of times taken per day. If more than 1 mg. of steroid is taken per day, cessation of the therapy may induce withdrawal symptoms of a varying degree, especially with long-term therapy.

### CASE HISTORY

The following case is presented to illustrate the dangers of cortisone withdrawal resulting from "unknown" cortisone therapy in the past.

The patient, a 50 year old white male was admitted to hospital April 10, 1957, with a complaint of severe abdominal pain.

#### Clinical History

The patient claimed a "usual" state of health until April 5, 1957, when following his supper he complained of severe upper abdominal pain which was relieved by hypo. On the eve of April 10, the pain recurred with vomiting and lasted 4 hours. It again was in the right upper quadrant and radiated to the midline. He was not jaundiced on either occasion.

Past illnesses included rapid onset of permanent blindness in 1939. The patient stated that he had had Simmond's Disease.

#### Physical Examination:

The patient could barely distinguish light and dark and showed nystagmus to the right. His chest was clear. No murmurs were heard. Pressure 175/106. Pulse 80 and regular.



On abdominal examination, the patient complained of slight peri-umbilical tenderness. Murphy's sign was negative and there was no costovertebral tenderness. Bowel sounds were easily heard. No herniae were present.

A preoperative diagnosis of cholecystitis with cholelithiasis was made.

#### LAB FINDINGS:

*Urinalysis—April 10—(random)*

1. Specific Gravity—1.020
2. Pus cells—20 - 25 per h.p.f.
3. RBC—1 - 3 per h.p.f.
4. Sugar-acetone albumin—0

*Urinalysis—April 14—(preoperative)*

Sugar-acetone-albumin—0

*X-Ray—April 11*

Cholecystogram showed a non-concentrating gall bladder containing at least one partially opaque calculus.

#### Course in Hospital:

On April 15, 1957, the patient underwent a cholecystectomy. Wangensteen suction was initiated early on first postoperative morning. The patient at this time was complaining of pain but seemed in satisfactory condition. When seen at noon of the same day he was in shock and died almost immediately, before steroid treatment could be commenced.

#### Post Mortem Examination:

The adrenals were reduced in size and on section showed a very thin pale (less than 1 mm.) yellowish grey cortex which totally lacked normal orange-yellow pigment. On exposure of the sella tursica in the brain, a cystic lesion was seen occupying the sella and enlarging it to thrice its normal size. The cyst compressed the optic nerves and indented the hypothalamus so only a thin rim of cerebral tissue remained over the third ventricle. No pituitary tissue was seen and the optic nerves appeared as flattened cords.

On microscopic examination, the heart revealed congestion. The liver had a hamartoma and focal fatty infiltration. Chronic pyelonephritis was seen in the kidneys. There was loss of zonal architecture and lipid in adrenal cortex but the medulla was normal. The pituitary showed neoplas-

tic cells arranged in anastomosing columns supported by a fine reticular framework with areas of tumor necrosis and the mass was enclosed in a thin fibrous capsule. The tumor was described as a sinusoidal type chromophobe adenoma.

#### Comment:

The patient died of shock along with pulmonary edema along with acute congestion of the viscera due to a cholangitis complicating a recent cholecystectomy. The atrophy of the adrenal glands due to prolonged cortisone therapy was a definite contributing factor. This death could have been avoided had it been known that this patient had taken cortisone previously.

#### DANGERS OF RAPID WITHDRAWAL OF CORTICOSTEROIDS

When steroids are given to patients over prolonged periods and particularly in doses sometimes greatly exceeding the amount required for replacement therapy, several considerations arise.

##### (1) Main Dangers

These are potentially lethal because they are almost impossible to recognize.

(a) *Relative Hypoadrenocorticism*, which involves:

1. atrophy of the adrenal cortex (except zona glomerulosa)
2. decrease in production of endogenous glucocorticoid hormones
3. suppression of the ability of the pituitary to secrete corticotrophin.

Adrenal function may be restored within a few weeks of the acute withdrawal of exogenous steroid, but occasionally relative adrenal insufficiency may persist for from several to many months after the steroids have been stopped. Administration of corticotropin may speed return of adrenal function to normal but it may at the same time inhibit secretion of endogenous corticotropin. Cessation of therapy with corticotropin therefore removes the stimulus to adrenocortical secretion resulting in a temporary state of relative adrenal insufficiency. Although the essential mechanism is different than with adrenal steroids the end result is similar—i.e. hypoadrenalism.



These people with adrenal or pituitary suppression or both cannot tolerate stress and in the presence of stress, fail to respond by an increased output of ACTH and of corticoids. Therefore, patients submitted to such stress who have recently been treated with steroids may collapse and succumb without any satisfactory explanation other than adrenal insufficiency.

(b) *Reactivation of Original Mesenchymal Disease*

During a period of withdrawal of corticoid or corticotropin therapy, there will be a flare-up of the original disease of varying magnitude in most instances. This is due to the continued presence of an antigen-antibody complex, the action of which was previously blocked by corticoids. Small exacerbations subside spontaneously after 3 to 5 days, presumably coincident with the gradual resumption of normal adrenal activity.

(2) **Minor Dangers**

- (a) **Mental Symptoms**—Depression occurs occasionally with abrupt withdrawal of the steroid. The depression may be severe especially if associated with marked asthenia.
- (b) Decrease in urinary nitrogen excretion rate
- (c) Increase in eosinophils
- (d) Decrease in urine steroid excretion

**MANAGEMENT OF THE CORTICOID WITHDRAWAL SYNDROME**

(1) **General Management**

1. *Proper Methods of Termination of Steroid Therapy*

(a) The total dose of corticotropin or of corticoids can be reduced by a small amount each day, or every other day. The corticoid administration is stopped first at bedtime, then at supper time *etc.*, eventually ending up by giving one dose once a day at 9 a.m. The morning dose is then gradually reduced over a 10 day period.

This type of withdrawal allows the pituitary to return to its former nocturnal corticotropin-secreting activity while the

patient is still given a basic maintenance dose of corticoid to cover the relatively deficient period.

(b) More rapid termination of corticoid therapy may be brought about after gradual reduction in dosage by giving ACTH gel or zinc corticotropin every morning starting with 80 units and reducing this dose by 20 units each day. For reasons stated before, this method would appear to be inferior to the above.

Little, if anything, is gained by intermittent stimulation of the adrenals during long-term corticoid therapy since normal adrenal responsiveness can be produced by giving corticotropin for 3 to 5 days when corticoids are stopped, providing the atrophy is not complete.

(2) *Proper Follow-Up of Patients*

(a) All patients on prolonged steroid therapy should have periodic checks to include:

- 1. body weight
- 2. blood pressure
- 3. urine sugar
- 4. appraisal of cardiovascular, digestive and skeletal systems
- 5. inspection for possibility of development of posterior subcapsular cataracts (especially in patients with rheumatoid arthritis or similar states)

(b) Both patient and doctor should be aware of the additional risk of acute stress reactions and supplementary corticoid therapy should be readily available before, during and after the stressful situation.

(2) **Specific Management**

(1) *For Severe Surgical or Medical Stress*

Especially if this occurs within six months after the discontinuance of corticoid and/or corticotropin therapy, the patient must be given 50-100 mg. cortisol or one of its derivatives either I.M. or I.V. to prevent serious adrenal insufficiency and collapse, and the blood pressure followed carefully, and further medication given as indicated.

*Continued on Page 65*



# Embryology of the Reproductive System

DIANA M. WILLIS, '65

## INTRODUCTION

Genetically, the sex of the embryo is determined at the moment of fertilization. The presence of a Y chromosome produces a male gonad (testis) which then hormonally controls the development of a male genital tract. The absence of a Y chromosome results in a female genital tract. However, it is not until the seventh week of intrauterine development that the sex is manifest in genital organs. In the earlier or indifferent stage, the basic primordia of the reproductive system of male and female are indistinguishable. Later, at the 17 mm. stage, differentiation of male and female is manifest in human development.<sup>1</sup>

## INDIFFERENT STAGE OF DEVELOPMENT

Urinary and genital systems are closely related in their embryological development. Certain of the ducts, originating as part of the urinary system of the early (7-10) somite embryo,<sup>2</sup> become part of the genital apparatus.

### 1. Internal genital organs

Internal genital organs consist of gonads (testis or ovary) and a system of genital ducts.

#### a) Gonads

The first primordia of sex glands appear as thickenings (genital ridges) of the celomic epithelium on the medial aspects of the mesonephros. The attachment of genital ridge and mesonephros to the dorsal body wall is a broad ligament called the urogenital mesentery. As the gonad develops, the mesonephros becomes correspondingly smaller and degenerates. The gonad is formed from three parts:

- i) celomic epithelial cells
- ii) underlying mesoderm of the genital ridge
- iii) primordial germ cells which migrate to the genital ridge from yolk sac entoderm.

As development proceeds the surface epithelial cells proliferate and form cords of cells which grow into the underlying mesenchyme. The undifferentiated gonad

consists of two parts, cortex and medulla, the subsequent development of which differs in the two sexes.

#### b) Genital ducts of the indifferent stage

i) Mesonephric (Wolffian) ducts and associated tubules serve for drainage of the mesonephric kidney. However, as the latter degenerates, the ducts become part of the genital system, particularly in the male.

ii) Paramesonephric (Müllerian) ducts appear first in the 10mm. stage, lateral to the cranial end of the mesonephric ducts. Each duct is laid down as a cord which hollows out and extends caudally, eventually uniting in the midline with the duct of the opposite side. The fused caudal portion impinges on the posterior wall of the urogenital sinus, causing a swelling called the Müllerian tubercle. At this point there is proliferation of cells to form the sino-vaginal bulb.

### 2. External Genitalia of the indifferent stage

The development of male and female external genitalia parallel each other in early stages of embryological development.

The cloacal membrane, appearing first in the embryonic disc stage, comes to face anteriorly on the ventral wall of the embryo. It is bounded laterally by the posterior limb buds, caudally by the tail or tail bud, and cranially by the umbilical cord. Mesoderm grows between umbilical cord and cloacal membrane to form a promin-



ent mass of mesoderm, the genital tubercle (destined to become penis or clitoris). Mesodermal cells also proliferate lateral to the cloacal membrane producing genital swellings (future scrotal and labial swellings). The ectodermal area between the genital swellings is the shallow ectodermal cloaca or proctodeum. After division of cloaca into urogenital sinus and rectum by the urorectal septum is completed, the proctodeum is divided into a dorsal (anal) portion and a ventral (urogenital) portion. Anal eminences develop around the anal membrane such that the latter is at the bottom of a 'pit' called the anal canal. The anal membrane divides anal canal and rectum. Anterior to this the urogenital membrane is bounded laterally by genital swellings. These swellings join in the region of the perineal body, and form the labioscrotal swellings.

Simultaneously, the genital tubercle (phallus) elongates, and draws out the urogenital sinus along its lower surface.

## DIFFERENTIATION OF MALE AND FEMALE GENITAL SYSTEMS

As development proceeds past the 17 mm. stage the sex of the embryo becomes manifest in human development. Sex differentiation is controlled by hormones produced by the gonad. This view is supported by the fact that the sex of the individual may be modified, or even reversed, by administration of suitable hormones when the embryo is in the 'neuter' or indifferent condition.

### 1. Internal genital organs

At the 14 mm. stage of development histological differentiation of the gonad begins. As previously stated, the gonads develop from three parts: celomic epithelium, underlying mesoderm, and primordial sex cells.

Surface epithelial cells of the genital ridge proliferate and form cords which grow into the underlying mesenchyme. The gonad can thus be differentiated into

two regions, an outer cortex and a central medulla. In the male development of the medulla is dominant over that of the cortex; whereas, in the female the opposite is true.

### (a) Development of Gonads

#### (i) In Male

The mesenchymal cords of cells of the medulla become differentiated at the seventh week of intrauterine life. These constitute the primary sex cords which in the male give rise to the seminiferous tubules, rete testis, and straight tubules. The seminiferous tubules include primordial germ cells. The cords converge on the hilum of the organ and form the network, rete testis, which becomes linked with genital duct system by way of the mesonephric tubules (straight tubules or efferent ductules). The cords undergo canalization later in the 50 to 90 mm. stage of development. Most of the interstitial cells are derived from the mesenchymal cells of the stroma.

The cortex of the developing testis forms the tunica albuginea, a dense fibrous layer, separating the sex cords from the germinal epithelium.

#### (ii) In female<sup>23</sup>

In contrast to development of the testis it is the cortex which has ascendance in the female.

In the medulla, sex cords form as in the testis, but soon break up into isolated masses. No definite tunica albuginea forms. A rete ovarii forms but is never as well developed as the rete testis.

It is to the cortex that oogonia (sex cells) migrate from the entodermal yolk sac. The small groups of cells resulting from the fragmentation of the sex cords become grouped to form the primordial ovarian follicles, which encapsulate the primordial ova. Underlying connective tissue of the indifferent stage of development forms the ovarian interstitial cells and the cells of the theca interna which surround the follicles.



Some of the primordial follicles become vesicular during late fetal life (probably due to influence of maternal hormones) and then degenerate at birth. Definitive follicles are those which develop after the onset of puberty.

(iii) Positional changes in gonads

(1) Testis

A positional change of the testis<sup>8</sup> occurs concomitant with the histological changes. As the mesonephros regresses, the testis assumes and utilizes its ligaments. The cranial (suspensory) ligament disappears, whereas, the caudal genito-inguinal (gubernaculum testis) ligament passes to the scrotal swelling and anchors the testis.<sup>20</sup> Differential growth of the embryo causes the testis to shift caudally. As a result the peritoneum is drawn out into a blind pouch, the processus vaginalis peritonei.

By the third month of fetal development the testis is lying retroperitoneally in the false pelvis. During the seventh month the testis passes through the inguinal canal lying behind, but invaginating the processus vaginalis. Normally, it reaches the scrotal sac by the end of the eighth month of intrauterine development.

Accompanying the descent of the testis is a corresponding shortening of the gubernaculum. The role of the latter in the mechanism of descent is still controversial.

(2) Ovary

The ovary is anchored to the labial swelling by the genito-inguinal ligament, which later forms the round ligament. Its descent is slight in comparison to that of the testis, and is caused by differential growth of the posterior body wall.

(b) *Differentiation of genital duct system*

In vertebrates the excretory pathways for gametes differ in the two sexes: in male, the mesonephric (Wolffian) ducts persist as the vasa deferentia; in female, the paramesonephric (Müllerian) ducts develop to transmit the ovum.

(i) Male genital ducts

(1) Mesonephric tubules—

In the male embryo the upper end of each mesonephric duct becomes connected to the seminiferous tubules through some of the mesonephric tubules (vasa efferentia) and the rete testis.

(2) Mesonephric (Wolffian) duct—

Immediately below the level of the junction with the vasa efferentia, the mesonephric duct elongates and thickens to form the epididymis. The blind end of the mesonephric duct persists as the appendix epididymis. The remainder of the duct becomes the vas deferens, which opens on each side into the ventrolateral part of the cloaca.

Later that part (common excretory duct) of each mesonephric duct caudal to the origin of the ureter becomes absorbed into the wall of the primitive urogenital sinus,<sup>8</sup> so that mesonephric duct and ureter open independently into the sinus.

Near its junction with the primitive urogenital sinus each vas deferens dilates to form an ampulla from which a diverticulum arises as the 60 mm. stage to form the seminal vesicle. That part of each original mesonephric duct between each seminal vesicle and the urethra becomes the ejaculatory duct.

(3) Paramesonephric (Müllerian) duct in male—

At about the 27 mm. stage of development the paramesonephric ducts in male degenerate and lose their communication with the celomic cavity. The upper extremity of each duct persists as the appendix testis; the lower terminal end may give rise to the prostatic utricle (uterus masculinus); the remainder of the duct completely disappears.

(ii) Female duct system—

(1) Mesonephric tubules and ducts—

In the female embryo the mesonephric duct begins to degenerate at the 30 mm. stage. As in the male, its terminal part contributes to the formation of bladder and urethra. The upper part may form



temporary connections with the rete ovarii and together with the mesonephric tubules, forms the epoophoron, which is retained as a vestige. The remainder degenerates and becomes vestigial.

(2) Paramesonephric (Müllerian) ducts form all of the definitive female ducts. Müllerian ducts form at the 10 mm. stage as invaginations appearing lateral to the gonad along side the mesonephric duct. In the region of the pelvis, these cross anterior to the ureter. Initially, each duct forms as a solid cord of cells which becomes canalized. The Müllerian ducts meet in the midline and pass posterior to the bladder to impinge on the wall of the urogenital sinus. At this point there is cell proliferation producing a solid mass of cells known as the sinovaginal bulb. This later forms the lower one-fifth of the vagina and hymen.

When the urogenital ridges are crowded laterad by the enlarging suprarenal glands and permanent kidneys, the Müllerian ducts are displaced, having two bends which roughly establish three regions, different in future potentialities: a cranial longitudinal portion (uterine tube); a middle, transverse portion (uterine fundus and corpus);<sup>15-26</sup> a caudal, longitudinal portion (uterine cervix) which fuses with its fellow and forms the upper four-fifth of the vagina.

The uterine tubes do not elongate as much as the trunk as a whole, so their ostial ends finally lie opposite the fourth lumbar vertebra. The transverse portion of the Müllerian ducts bulge in a cephalic direction, comprising the definitive fundus and corpus; caudally, the fused portions of the paired ducts form the uterovaginal tube which has thickened walls, and an indentation encircling the tube which marks the site of the vaginal fornices which divides uterus and vagina.

## 2. Differentiation of External Genitalia—

In order to understand the origin of various structures considered in the fol-

lowing discussion, let us review the stages in development of the cloaca.

The cloaca appears early in embryological development as the caudal end of the hind gut. It is continuous cephalad with the hind gut and allantois, and limited caudally by the cloacal membrane. The urorectal septa grows caudally to divide the cloaca into rectum dorsally and urogenital sinus ventrally. The latter is divided into vesicourethral canal and definitive urogenital sinus at the point of junction of the urethra. The vesicourethral canal develops into the definitive bladder and urethra. The definitive urogenital sinus becomes the pars pelvina and pars phallica. The fate of these structures will be considered later.

In the indefinite stage of development, the genital tubercle developed anterior to the urogenital membrane. The development of genital tubercle and that of pars phallica are closely related. The phallus or genital tubercle grows and draws out the urogenital sinus along its lower surface. This extension of the urogenital sinus is the pars phallica which extends as a tube on the lower surface of the phallus.<sup>13</sup> As it extends to near the end of the phallus the cavity of the pars phallica is lost forming a plate of cells. The urogenital membrane breaks down at this stage.

### a) *In male*

In the male embryo the genital swellings become more definite and are called the scrotal swellings. The urethral groove extends forwards as a groove in the pars phallica on the ventral aspects of the phallus, but does not quite reach the tip. On either side, urethral folds bound the primitive urogenital orifice and urethral groove.

At the 45 mm. stage the male genitalia assume their final form by fusion of the urethral folds in the midline, from the posterior edge of the urogenital orifice toward the tip of the phallus, forming a median raphe over the resulting tubular



urethra. The glans penis<sup>12</sup> becomes defined by the development of a circular coronary sulcus around the distal part of the phallus. The urethral groove and folds do not extend beyond the coronary sulcus, and when the folds become completely united a penile urethra is formed. A cord of ectodermal epithelial cells then grows through the glans to reach the distal extremity of the penile urethra and later canalizes to form the terminal (glandular) portion of the urethra.<sup>11-25</sup>

Bulbourethral glands arise from the penile urethra. The corpus cavernosum urethra forms as a dilatation of the posterior extremity of the penile urethra and small glands of Littre develop in the penile urethral wall.

In male the pelvic portion of the urogenital sinus (pars pelvina) becomes the lower part of the prostatic urethra and membranous urethra. A series of solid buds arise from the entodermal part of the primitive urethra and pars pelvina at the 55 mm. stage, and later canalize to form the prostrate gland.

#### b) In female

Male and female development of external genitalia parallel each other to the stage at which the pars phallica forms a plate of cells on the lower surface of the genital tubercle. Development then differs in that the genital tubercle forms the clitoris and fusion of urethral folds and labioscrotal swellings does not occur. These unfused folds form labia minora and labia majora respectively.

As a result, vagina and urethra open separately into the vestibule.<sup>9-19</sup> The vestibule is the opening bounded anteriorly by the clitoris, laterally by labial folds and posteriorly by the perineal body. Analogues of the bulbo-urethral glands are the greater vestibular glands which arise from the lining of the vestibule.<sup>7</sup> Small lesser vestibular glands in the anterior part of the vestibular wall represent the glands of Littre in the male.

### (3) Anomalies of the genital system

#### A. Hermaphroditism

1. True hermaphroditism<sup>14</sup> is the condition in which the gonads of both sexes are present, the external sex characteristics may be male, female, or intermediate.<sup>10</sup> This condition is rare in human, there having been only 75 cases reported as of 1960.<sup>17-21</sup>

2. Pseudohermaphroditism is a condition which is always congenital in origin, the individual possessing gonads of one sex and external genitalia and often the secondary sexual characters are of the opposite sex, or approximate to them. Such cases may be classified as follows:

#### Female pseudohermaphroditism

- adrenogenital<sup>6-16</sup>
- iatrogenic
- associated with multiple anomalies

#### Male pseudohermaphroditism<sup>3</sup>

- testicular feminization syndrome<sup>4-24-27</sup>
- others.

#### B. Abnormal development in male

1. Cryptorchidism — This condition results from a failure of testicular descent, and is seen in 5.7% male births (unilateral and bilateral). At the end of the first year of life only .7% of cases remain undescended.

2. Hypospadias and epispadias<sup>22</sup> — The former is a non-closure or partial closure of the urethral groove; the latter, is a partial or complete absence of the dorsal wall of the urethra. This abnormality is due to a failure in the development of the infra-umbilical mesoderm and, in extensive cases, results in ectopia vesicae, in which the bladder mucosa is exposed on the anterior abdominal wall.

3. Agenesis of penis or testis — this condition is rare although hypoplasia is more common and usually associated with hermaphroditism.



**C. Abnormal development in Female—**

Abnormalities in the female system result from failure of fusion to a greater or lesser degree of the paramesonephric (Müllerian) ducts.

1. Uterine anomalies

(a) Bicornuate uterus results from failure of fusion of the primordia (paramesonephric ducts) in the fundus.

(b) Bipartite uterus is a failure of the partition between the ducts to break down.

(c) Bilateral uteri result from complete failure of the ducts to unite.

2. Agenesis and hypoplasia—This condition may involve ovaries, all or a portion of the ducts, and the clitoris.

3. Hyperplasia of clitoris—This condition is usually seen in association with hermaphroditism.

4. Imperforate hymen—Failure of normal break-through at the Müllerian tubercle to occur.

5. Turner's syndrome has characteristic infantile uterus or infantile genital organs.

**CONCLUSION**

The importance of a knowledge of the embryology of the reproductive system, indeed of all systems of the body, is that it offers a rational explanation for the anatomical disorder found in congenital anomalies and stimulates research into the basic cause of this important aspect of disease.

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# Pattern of Simple Inheritance

THOMAS McGHIE, '64

## INTRODUCTION

It may seem strange to some, that the human body, which has been studied for so many hundreds of years, is still so imperfectly understood. Recently however, many advances have been made to further this understanding. One of the more recent and perhaps more important such advances has been in the field of inheritance.

It is hoped that this very basic description of the mechanisms of heredity will accomplish two goals: firstly, to give the novice a simple understanding of inheritance, and secondly, to convince the reader that there are now clinically important concrete facts in the many excellent books and articles available today.

## I. BASIC MECHANISM OF INHERITANCE

A human being originates with the union of two cells, the ovum and the spermatozoon. What this developing person will be depends greatly upon the hereditary constitution given to him in this primary union.

Before fertilization, both the oocyte and spermatocyte have within their nuclei 46 chromosomes (23 pairs). Along each chromosome, arranged in a linear fashion, are the genes, the hereditary elements themselves. Just as the chromosomes are paired, the genes are also paired, with each pair of genes representing a particular hereditary trait. We know that the hereditary potential of the developing child is received from both parents. He receives 23 chromosomes from his mother and 23 from his father.

Thus we see that the child is theoretically offered 46 chromosomes by each parent and since only a total of 46 may be accepted, it is obvious that the 46 chromosomes in each of the sex cells must be reduced by one-half. In reality this is a complex process, but it can be understood if one simply remembers that as each sex cell undergoes

two divisions, the chromosomes divide only once. As a result the ovum and spermatozoon each have only 23 chromosomes and when these unite, the fertilized ovum will have the normal complement of 46 chromosomes with equal genetic representation from each parent.

## II. PATTERN OF INHERITANCE

As stated, the genes responsible for the expression of a specific trait are paired, one member of the pair being donated by each parent. One gene is situated on each of the corresponding pair of chromosomes. These genes may be identical in which case they are termed homozygous, or may be dissimilar and are termed heterozygous. When speaking about one member of the pair, its mate is referred to as its allele.

Using these terms, the basic types of inheritance may be more clearly discussed.

### A. Dominant Inheritance

If a gene exerts its influence, whether present on one or both members of a pair of chromosomes, it is said to be dominant. Transmission of a disease, by means of a dominant gene, will now be discussed using Huntington's Chorea as an example. In considering this disease, we find that there are six possibilities:

- 1) One parent has the dominant gene for Huntington's Chorea on only one chromosome (heterozygous) and the other parent does not harbor the gene.

- 2) One parent has the abnormal gene on both chromosomes (homozygous dominant) and the other parent is normal (homozygous recessive).



## —Simple Inheritance—

- 3) Both parents are heterozygous.
- 4) Both parents are homozygous dominant.
- 5) One parent is homozygous dominant and the other is heterozygous.
- 6) Both parents are normal (homozygous recessive).

By bearing these possibilities in mind and by going back to the reduction phase in the oocyte and spermatocyte, one can predict the probability of occurrence of Huntington's Chorea in offspring of the above parents.

As an example let us first consider case number one, where one parent is normal and the other has only one abnormal disease-bearing gene (heterozygous). In the reduction phase, the sex cell of the diseased parent will have its chromosomes reduced by one-half. Thus, there is only a fifty percent chance that the abnormal gene will be retained and passed on to the developing child. If this gene is passed on, the offspring will develop Huntington's Chorea, for the gene is dominant. If however, the abnormal gene is discarded in the reduction phase, the child will be spared. Therefore in case one, if the parents have eight children they should statistically have four diseased children. In reality however, the children need not be affected in equal proportions, for just as one flips a coin, the equal appearance of heads to tails need not occur, and the departure from equality may be great indeed. It is also important to realize that if the offspring of an affected parent escapes the disease they may in turn marry a normal person and have only normal offspring.

By applying these basic principles to cases 2, 3, 4, 5 and 6 we may show that the probability of producing offspring with Huntington's Chorea is 100%, 75%, 100%, 100% and 0%, respectively

Because Huntington's Chorea is not a common disease, it is unlikely for one parent to be homozygous dominant or for

both parents to be heterozygous. (It is uncommon for two people with Huntington's Chorea to marry).

### B. Recessive Inheritance

A recessive gene will express itself only if it is present on both members of the chromosome pair. One abnormal gene produces no clinical effect since the normal allele is dominant.

We often see a disease or trait which is hereditary spring up in the offspring of normal parents. This is understandable if we realize that each parent may have a heterozygous, recessive gene for the expression of this trait. One gene will give no effect in the parent, but if one such gene from each parent is given to the offspring in the reduction phase, the child will be affected. Listed below are the possible occurrences of recessive genes in the parents and the probabilities of the offspring showing the characteristics carried by the genes.

- 1) Both parents homozygous recessive (100%).
- 2) One parent homozygous recessive, one heterozygous (50%).
- 3) Both parents heterozygous (25%).
- 4) One parent homozygous recessive, one normal homozygous dominant (0%).
- 5) One parent heterozygous recessive, one normal homozygous dominant (0%).
- 6) Both parents normal homozygous dominant (0%).

The possible presence of unseen recessive genes is a major reason why marriage of relatives is undesirable.

### C. Sex Linked Inheritance.

When investigating the 23 pairs of chromosomes present in the nucleus of a human cell, it was found that one particular pair was different than the others. These bear a special relation to sex and are appropriately termed sex chromosomes. The remaining 22 pairs are called autosomes. The sex chromosomes of the female are equal in size and are named "X" chromosomes. In the male, however, the



sex chromosomes are unequal in size, there being one "X" chromosome identical to those of the female and one "Y" chromosome which is one of the smallest of human chromosomes.

These sex chromosomes, in addition to determining the sex of the offspring, carry genes which affect all types of body structures and functions. Abnormal genes can be carried on these chromosomes, just as previously described for the autosomal chromosomes. To date, only the "X" chromosome has been found to carry abnormal genes.

With these facts in mind, let us consider the transmission of a sex-linked disease such as Haemophilia. In the male since there is only one "X" chromosome the problem is simple: If this chromosome bears the abnormal gene for haemophilia, the man is stricken with the disease. In the female however, since haemophilia is carried as a recessive gene (most sex-linked traits are) both "X" chromosomes must bear the abnormal gene. For these reasons, a female who has only one abnormal gene will not exhibit haemophilia but there is a 50% probability that her male offspring will have the disease. In order for female offspring to develop haemophilia both of her "X" chromosomes must be abnormal. Obviously, in this case, the father must be haemophiliac and the mother must have at least one abnormal chromosome.

#### D. Mutations

Genes occasionally change their character giving rise to new genes. This is extremely rare, occurring about once in one hundred thousand times. Once formed, this new gene is stable and can be transmitted to the offspring. The cause of the mutation in most cases is unknown. In certain cases it may be due to exposure to high energy radiation, ultra violet radiation, high temperatures and chemicals such as mustard gas.

Several genes may be altered at one time due to loss, duplication, inversion or adhesion of a part of one chromosome to another. The damage is so great in these cases that the bearer seldom survives.

An abnormal gene may similarly change into a normal gene (reverse mutation) although such cases are extremely rare.

#### CONCLUSION

These are the basic principles of inheritance. Applying this knowledge, a doctor can predict with a certain degree of probability when diseases such as Haemophilia or Huntington's Chorea will occur or he may give counsel to help prevent these diseases.

It should be stated however that inherited diseases due to single, fully expressed genes are rare. At the same time inheritance probably plays some part in many common diseases. Here siblings or relatives are predisposed to certain disease by an overall genetic makeup. These people are more prone to develop this disease in a given environment.

New techniques will eventually uncover many of the unknowns in this field. In the meantime it is clinically beneficial for the physician to become accustomed with present knowledge in genetics.

Suggestions and assistance from Dr. H. C. Soltan, Assistant Professor of Human Genetics, are gratefully acknowledged.

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# Obituary:

## Igor Nicolas Asheshov

DR. R. G. E. MURRAY\*

The former students and colleagues of I. N. Asheshov will be very sorry to hear of his death in London, England, in September 1961 at the age of 70. He was an indefatigable research worker (of a most inventive turn of mind when new apparatus was required), a great expert in his field of interest (the bacteriophages), and capable of the most lucid and fascinating exposition, which made him a memorable teacher. With all this he was a gay and courteous gentleman of a handsome and engaging aspect. It is probable that few of his colleagues, and almost none of the young and impressionable, would forget Asheshov in formal dress and sporting a gold-rimmed monocle.

He was born in Russia on August 13, 1891 in Nijni-Novgorod, the son of a distinguished journalist. He was a student of medicine in the Saratov Imperial University and when the Revolution came round he was serving his "internship" in the Imperial Army. He had, by all report, been interested in scientific matters as a student but it was during his army service that he became attached to the Central Bacteriological Laboratory of the Armies of South Russia in 1918. When the British Military Mission to South Russia arrived on the scene in 1919, to aid in work on the devastating epidemic of typhus that was then raging throughout the country, Asheshov was attached to them to continue in experimental work on typhus. I wish I could remember all the tales he told of those days; but I do distinctly remember his tale of one of the early and ineffective approaches to immunization against typhus by utilizing the antigenic similarity of certain strains of *Proteus*. Being in the midst of a raging epidemic they were willing to take almost any short-cut to positive information and Asheshov himself was one of a very few volunteers who were supposedly immunized and then challenged by

direct infection. He said that the resulting typhus deprived him of twelve days of his life, for he had no memory of them at all. When the British Mission retired from Russia in 1920 he went with them to be in charge of the Bacteriological Laboratory in Salonika. Despite his attainments and abilities, a suitable berth for a stateless person was no easy matter in those days. But fortune was kind to him in many ways and he lived on the shores of the Adriatic, enjoyed its beauties, and was director of the State Bacteriological Laboratory at Ragusa in Yugoslavia from 1921 to 1928. Here, well isolated from the scientific communities of the world, and virtually alone, he started work on bacteriophage. And, indeed, he must have started practically immediately after d'Herelle's initial report on the phenomenon, (I do not remember him saying that he knew before this of Twort's earlier (1917) observation) because his first paper in the *Comptes Rendus de la Societe de Biologie* was "*Sur les particularités des souches de bacteriophage*" in 1922. And the author has saved a Petri dish dated in May of that year which shows the Asheshov understood at that time the possibilities of phage typing or, at least, was doing experiments towards that end. Before he left Yugoslavia he had published 14 papers, mostly in French, on the characteristics of various bacteriophages, on their reproduction, on their antigenicity and immunological changes with inactivation, on the obtaining of pure strains of bacteriophage in quantity, and on filtration with collodion membranes. He would wish it to be remembered that it was the Rockefeller Foundation that kept him in touch with the world and encouraged him by sending to him the main current journals.

\*Professor and Head of the Department of Bacteriology and Immunology.



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It was likely the work on purification of the viruses and the patterns of host resistance that led to his invitation by the Indian Medical Service to take over d'Herelle's work on cholera bacteriophage. He took charge in 1928 and organized the bacteriophage inquiry which culminated in 1933 with a series of reports by his group of workers on general techniques for working with phage, on the classification of Cholera phage and on the effects of its administration to cases. These were all very considerable contributions. This was, perhaps, the first convincing investigation of bacteriophage in a disease process and indeed remains as a clear example of the pitfalls involved. It led to his appointment as a research officer in the Medical Research Council, working at the National Institute for Medical Research, Hampstead, England. Soon he was working at the London School of Hygiene and Tropical Medicine with Professor W. W. C. Topley, formidable critic of experiments and himself a remarkable experimentalist in the field of epidemiology. This collaboration produced the paper on the effect of bacteriophage and typhoid infection in mice and further understanding of the problems of applying bacteriophage to clinical conditions.

In 1937 he came to Canada as Associate Professor of Bacteriology in the Faculty of Medicine, University of Western Ontario. He entered a new phase in his life because he was now faced with teaching successive classes of second year medical students the elements of bacteriology, immunology and virology. He had the gift of lucid explanation and graphic description, but teaching did not come to him easily and he had to work very hard in those early years on the preparation of his lectures and his laboratory classes. The measure of his success was in the affectionate enthusiasm of his students for his endearing foibles and the amount of useful information they managed to carry away with them for life's work in the practice of medicine. So many of his old students have asked for news of him that he must have made a mark

on them. Not many of us will forget the affectionate response from his classes to the inevitable, Russian accented "good afternoon", which was the preface to his lecture. Certainly none of his students or colleagues will forget the magnificent, elaborate and imaginative doodles that covered the white note sheets in front of him at the oral examinations or at meetings of committees or councils. I am glad to report that few of these have been preserved and are much treasured by their owners.

It is rather sad to see that between 1937 and 1945 the flow of papers that marked the earlier years was interrupted and very little appeared to show what was in his mind. He had to be heavily concerned with the clinical bacteriology function of the department associated with Victoria Hospital and this in earlier years took a lot of his time. After 1942 when he became head of the newly separated and independent department of bacteriology and immunology there was a new turn in his work and he was able to get the assistance he needed for research work on antibiotics. At first this was involved in the search for substances active in the inhibition of tubercle bacilli as well as the development of some methods of detecting and isolating active substances, so necessary in those earlier days or research on antibiotics. Asheshov's interest in bacteriophage led him to try, with all the technical skills that he had at his command, to find antibiotics active against bacterial viruses with the hope that they might be of practical medical interest. Indeed he was able to report at the end of 1947 the detection of more than one substance that seemed to inhibit the activity of several bacteriophages. This significant and useful endeavour was running well in his department at the University of Western Ontario and had the devoted help of his assistants the late Miss Freda Strelitz and Miss Elizabeth Hall (later Mrs. Asheshov). In 1948 The National Foundation for Infantile Paralysis set up in the laboratories of the New York Botanical Gardens a special project on the



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inhibition of bacterial viruses and Asheshov was given charge of this work. Despite the successes of the project and the finding of many active substances with diverse mechanisms of action and diverse properties, the support of the research project lasted for only five years. In 1953 he transferred his work to the Lister Institute for Preventive Medicine in London, England, where his project was supported by the Medical Research Council. The active and productive work continued right up to his retirement in 1958, and indeed there were trials of the most interesting of his substances in the virus laboratories of the Medical Research Council.

It seems unlucky that the tremendous energy and ability that Asheshov and his colleagues put into this work did not happen to turn up a substance of practical medical interest. Practical application was very much in his mind always. His research sense told him that it should be possible to find therapeutic substances useful in virus diseases and I can only say how excited and interested he was at the early reports of interferon which he heard about shortly before his death.

He was prepared for retirement and looked forward to an active life collating some of his later work, as well as adorning

the garden of his newly acquired home in Ickenham. But little more than a month after his official retirement he was stricken by the first of a number of cerebral accidents which left him partially paralysed, but fortunately able to talk and enjoy the life around him in his home. His characteristic courage and cheerfulness stood him in good stead and made it easier for his friends and those dear to him to contribute to his enjoyment of life and activity.

He had many things to be proud of: sound research work with good basic training for many young people; and this despite almost extreme isolation and the prosecution of intricate research problems under considerable difficulties. Many students were inspired by him towards new and useful understanding of problems in medicine and in the therapy of infectious disease. He had a knowledge second to none of the biology of the bacterial viruses and a wealth of experience stretching from the very earliest discoveries. He was fully appreciative of all the exciting developments of the work on bacteriophage since 1945 and he was never heard to have a rigid attitude that ignored the newest discoveries in this field. This bespeaks a man of high ability. He retains the loving respect of all who knew him well.

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## Book Reviews

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**Textbook of Endocrinology:** Robert H. Williams, M.D., editor, Third Edition, 1204 pages, W. B. Saunders Company, Philadelphia. 1962.

In the Preface to the Third Edition the editor states, "Since thousands of papers on endocrinology and metabolism are published annually, the incorporation into one book of the most pertinent information in a clear, concise and authoritative manner is most important." To achieve this goal, twenty-one pre-eminent scholars from the

fields of endocrinology, biochemistry, physiology, pharmacology, dermatology, pediatrics, obstetrics and gynecology, anatomy and internal medicine have contributed to this excellent textbook, which has been almost completely rewritten since the last edition.

The first chapter deals with the general principles of the physiology of the endocrines. Each endocrine organ is then exhaustively treated in a separate chapter. Approximately one half of the book deals



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with subjects of an integrative nature and includes chapters on Clinical Neuroendocrinology, Hormones and Cancer, and Genetics and Endocrinology. The final chapters deal with laboratory tests in endocrinology, and diagnosis and treatment of the endocrinopathies with special attention to hormone preparations.

Since each topic is dealt with from biochemical and clinical points of view, the book is of value to anyone with a particular interest in endocrinology. The bibliographies, though not exhaustive, contain all the important references with special attention to recent papers. The index contains many cross-references and is very complete and detailed.

R. B.

**Synopsis of Genitourinary Disease** by A. I. Dodson and J. E. Hill, The C. V. Mosby Co., St. Louis, 1962. 384 pp., price \$7.75.

This pocket-sized volume's avowed purposes are to present the essential facts connected with urology to the medical student and to be used as a reference for the practicing physician. In the later the authors succeed well, but the argument for the former is rather doubtful.

The opening chapters are good; symptoms and signs of urogenital disease, instruments needed in general practice for urological work, an anatomical review of the area and also congenital anomalies are covered succinctly but well. The remaining chapters are arranged largely according to the etiology of disease entities, for example, "calculous disease" and "injuries". The student would gain better acquaintance

with the general features of specific entities from the sections on urology in the general surgery texts commonly used. For the general practitioner who has the opportunity to modify suggestions in the light of his own experience the book would prove a valuable aid. D.B.

**Fundamental Skills in Surgery:** Thomas F. Nealon Jr., W. B. Saunders Co., Phil., 1962.

This text is written by a surgeon who over the years of his training noted many "useful little tricks" and procedures which were learned by experience or by word of mouth. He has endeavored to present many of these techniques in a formal manner by means of this book. In an effort to compile a complete text, many accessory facts and topics have been added yet the limited size of the text has only enabled a brief coverage of some topics.

The book is well written and the different topics are well presented. It is hard to say who would most benefit from its context. A medical student with limited practical experience would have a better lecture coverage of many topics and little need for many of the practical data. Possibly in the same way that the Merck Manual appears on every floor for the interns benefit this text might be useful in regards to some of the surgical procedures. The intern might be saved the embarrassment of having to ask how to do some of the minor procedures which have never been explained or formally taught. The text is small enough to enable one to read it just to cover the many little useful tricks, and the illustrations such as those on suture tying are excellently documented and a good aid to self-instruction.

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*Continued From Page 52*

(2) *For Minor Surgical Procedures, Minor Injuries and Minor Infections:*

Little, if any, increase in hormone dosage may be necessary. However, such

patients should be carefully watched for evidence of shock, circulatory collapse, or other signs of adrenal insufficiency. If such indications supervene, I.V. corticosteroids should be given, followed by oral therapy



when sufficient improvement occurs.

#### Contraindications to the use of Corticosteroids

1. Acute Psychoses
2. Active peptic ulcers
3. Hypertension
4. Congestive failure
5. Systemic Infectious Processes
  - (a) Miliary tuberculosis
  - (b) Fungus infections
  - (c) Pyogenic abscesses

#### CONCLUSION

Because of the dangers mentioned above and others perhaps not yet recorded, sudden cessation of treatment with corticosteroids is strongly contraindicated and the dosage should be gradually reduced over a period of weeks or months.

Patients on steroids now or in the past, when seeking medical advice for any

reason should have been warned to inform their doctor about such treatments. *It is also a valuable precaution for these patients to carry a card with appropriate details of their past and present treatment with steroids in the same way as diabetics are advised to do in regards to their treatment with insulin.*

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# Defects of Communication: The Aphasia

R. MORRISON HURLEY, '65

## INTRODUCTION

"Some people say that the heart is the organ with which we think, and that it feels pain and anxiety. But it is not so . . . Men ought to know that from the brain and brain alone, arise our pleasures, joys, laughter and jests, as well as our sorrows, pains, griefs, and tears. Through it, in particular, we think, see, hear and distinguish the ugly from the beautiful, the bad from the good, the pleasant from the unpleasant . . . to consciousness the brain is the messenger. Wherefore I assert that the brain is the interpreter of consciousness." —Hippocrates.

So it is with speech. To the speaker the brain becomes "the messenger," and for the listener the brain serves as the "interpreter." The message is a sequence of words.

These sequences, however, can become disorganized and distorted. Aphasia which exemplifies such a disorder may be defined as a difficulty in the ideational elaboration of speech as distinguished from defective verbal articulation.

## HISTORY

In 1861 there was considerable argument over whether the cerebral hemispheres functioned equipotentially or whether there was a discrete functional localization present. This basic disagreement still exists, but it is in a modified form. Neither do the hemispheres act equipotentially nor do they act as discrete local units. This would negate the modulating influences of lower centers and association areas.

Paul Broca, an anthropologist and surgeon, believed in the principle of cortical localization, chiefly based on the embryological and anatomical work of Gall, Gratiolet and himself. On the basis of two cases of hemiplegia and aphemia with demonstrable cortical lesions at autopsy, he contended that the center for articulate speech was the posterior part of the third frontal gyrus.

Broca was the first to accredit a specific cortical lesion to aphasic manifestations. Since his time numerous workers such as Wernicke, Jackson, Marie and Head elaborated on the aphasias, at first anatomically, then physiologically and finally psychologically. From such work has evolved the present knowledge of speech centers and the resultant disturbances arising from lesions in or near these areas. From these various studies have come the following conclusions. The closer the lesion is to Broca's area (the posterior part of the third frontal convolution) and the

precentral face area, the more the motor components of speech are involved. The nearer the lesion is to the vicinity of the junction of the parietal, temporal, and occipital lobes, the more reading and writing are affected, and the more the posterior superior temporal region is involved, the greater the difficulty in the comprehension of the spoken word.

## APHASIA AND HANDEDNESS

Any discussion of aphasia must be accompanied by its relationship to handedness and cerebral dominance.

Penfield and Roberts in their investigation of speech defects showed these relationships between aphasia and dominance. In right handed people less than 1% have some representation of speech in the right hemisphere. Less than 10% of the left handed have some, and probably all, speech representation in the right hemisphere. Upon observation of 527 patients there was no significant difference in the frequency of aphasia after operation on the right hemisphere whether left or right-handed. Thus it seems clear that the left hemisphere is usually dominant for speech regardless of handedness. The reason why the right hemisphere is sometimes dominant is unclear but it is not solely related to handedness. Because recovery of speech occurs following damage to part of the left hemisphere, it does not indicate that the right hemisphere



necessarily takes over the function. It seems that if other areas on the left are capable of functioning during speech, they will. If the left hemisphere is completely removed, the right hemisphere takes over the role. This, naturally, occurs much more rapidly if the person is young.

## CLASSIFICATION OF APHASIAS

### A. Psychophysiological Aspect of Speech and Its Disorder in Aphasia

#### I. *Receptive Aspect*

(i) The cortical centers for hearing are situated in the transverse temporal gyrus of both hemispheres. Destruction of one of these areas causes little hearing impairment, but destruction of both causes total cortical deafness.

(ii) A patient though not deaf may fail to recognize the nature of any sound he hears. Because of the inability to differentiate sounds he cannot understand speech. This is known as auditory agnosia.

(iii) There are patients with normal hearing who cannot understand the spoken word, repeat spoken words, or take dictation. However, they can speak spontaneously, read aloud and write normally. Such patients hear the words as if they were in a foreign language. Often, in mild cases simple commands may be understood but not whole sentences.

(iv) There also exists a condition in which there is a difficulty in understanding words as names for objects, conditions or qualities, even though the meaning of the whole sentence is comparatively well understood. This is known as nominal aphasia.

#### II. *Expressive Aspect*

(i) As thought passes into words it has to assume the form of sentences which possess syntactic structure. This determines the order and grammatical framework for the words employed. Disorganization in this phase leads to a disorder of syntax and grammar, choice of wrong words, errors in the phonetic structure of words, and even to the use of non-existent words.

(ii) In expression there may be a specific disability in the use of words to name objects. This is also known as amnesic or nominal aphasia.

(iii) Organized thoughts with the words chosen and grammatically related must be expressed in speech and writing. Mild defects manifest themselves as disorders of the detailed structure of the word itself, or the telegram style disorder of sentence structure, that is, the omission of auxiliary and relational words.

### B. Varieties of Aphasia

To discuss the varieties of aphasia an attempt must be made to give a classification which is relatively free from handicaps. A pure anatomical classification is handicapped since pure forms of aphasia are rare. Psychological classifications introduce too much of a personal factor and tend to disregard cerebral function. To overcome these difficulties an empirical classification is necessary.

#### I. *Pure word deafness*

This is a form of aphasia in which the patient has lost the ability to understand spoken language, but can speak, write and read spontaneously. The lesion responsible is situated generally in the middle part of the temporal convolution of the left hemisphere adjacent to the auditory cortex in Heschl's convolution.

#### II. *Central aphasia*

This form is characterized by both receptive and expressive disturbances. There is a defective appreciation of the meanings of words both spoken and written and of the meanings conveyed by their grammatical layout in the sentence. Expressively there are errors in syntax, and grammar, and the use of wrong words or non-existent words. The lesion responsible involves the posterior part of the superior temporal gyrus on the left side.

#### III. *Nominal aphasia*

This is characterized by a difficulty in using words as names of objects, conditions or qualities. The lesion responsible for nominal aphasia lies in the angular



gyrus of the left hemisphere. It is thus localized between the areas for central and visual aphasia which explains complications of nominal aphasia by either of these two types.

#### IV. *Expressive aphasia* (Broca's aphasia)

In severe cases of this disorder the patient is unable to utter or write a word. By gesturing he may signify that he is capable of proportional thought. In less severe cases there appears to be a disruption of the physiological processes by which ideas are formulated as well as the manner in which sentences are constructed, words chosen and articulated. The lesion responsible lies most often in the posterior two-thirds of the frontal gyrus, that is, the pars triangularis and operculum (Broca's area).

#### V. *Pure motor aphasia*

This constitutes a loss of the following: voluntary speech, the repetition of words heard, spontaneous writing and writing to dictation, copying written characters and the comprehension of spoken and written speech. All that can be said for the site of the lesion is that it may be anywhere in the frontal speech area especially in the neighborhood of the lower precentral gyrus.

#### VI. *Visual aphasia*

Pure word-blindness is characterized by an inability to comprehend the significance of the visual symbols of speech but the ability to write and speak normally is retained. The probable lesion may be found in the pathways from both occipital visual cortices to the left angular gyrus and its surroundings.

#### VII. *Visual asymbolia*

This is a form of aphasia in which difficulty in reading (see VI) is associated with difficulty in writing. Lesions producing this defect are found in the angular gyrus and the adjacent part of the supra-marginal gyrus.

These are the main aphasic types. There are others, however, which are seen more rarely and usually in conjunction with one of the preceding types. Pure agraphia,

acalculia, and amusia fit this category. These varieties in practice are not as straightforward as the classification might suggest. Only rarely do pure aphasias occur; more readily speech disturbances manifest themselves as a mosaic.

### TESTS OF APHASIA

There are certain preliminary considerations which must be borne in mind. The examiner must first endeavor to determine the general mental state of the patient. Mental confusion and deteriorated intellect will both affect the responses to speech tests. The examiners must next make sure that the patient's vision is intact and that his hearing is sound.

Since fatigability and variability are typical of patients suffering from cortical lesions, the test time should be shortened to 15 or 20 minutes. The patient should be made to feel at ease and the test applied in such a way as to be more a natural act than a problem to solve.

#### A. *Spontaneous Speech*

If the patient can speak at all, note the fluency, grammatical coherence, and word structure. If there are errors, does the patient leave out small words or does he completely change the sentence structure to end in complete jargon? Can the patient sing words better than speaking them? Can he speak one language better than another?

#### B. *Repetition*

On repeating a series of words, phrases and short sentences, can the patient repeat words which cannot be uttered spontaneously?

#### C. *Naming*

Can the patient name objects correctly, e.g. watch, ring, ear, comb, etc., or can he describe its uses without actually naming the object. It is necessary to make sure that the patient understands the nature of the object. This problem is accentuated in foreign patients.

#### D. *Understanding spoken language*

In addition to understanding the ex-



planations of the above tests the patient should be given a series of verbal commands increasing in complexity, such as "stick out your tongue", "raise your left hand", "touch your right ear with your left hand". If the patient passes these tests, more complicated questions should be asked.

#### E. Reading

Reading ability is tested by having the patient read a simple passage and comply to a series of written commands similar to those used in D.

#### F. Writing

The patient is first asked to write his name and address and then write a short story about himself or his employment. He is then asked to write a series of dictated words and to copy a printed paragraph.

The rarer aphasia such as amusia can be detected by asking the patient to recognize a tune and to sing or whistle a tune. Language intelligence tests are of great value in detecting the slighter degrees of disturbances.

### **PATHOLOGY**

Aphasia may be transient, that is, as occurs in migraine and part of an epileptic attack. Transitory attacks may also occur as a result of atheroma or syphilitic endarteritis of the cerebral arteries. These are especially prominent on awakening when the left internal carotid is involved.

Lasting aphasia of rapid onset is due primarily to vascular lesions: cerebral embolism, arterial obstruction due to atheroma, endarteritis, polyarteritis or temporal arteritis. Cortical venous thrombophlebitis is rarely a cause.

Aphasia of gradual onset is most frequently due to a space-occupying lesion, i.e. intra-cranial neoplasm, cerebral abscess or more rarely a subdural hematoma.

Aphasia developing over the course of years may be due to arteriosclerotic cerebral softening, presenile dementia or more rarely to general paresis or diffuse sclerosis.

In addition, aphasias due to cortical lesions may be the cause of nondevelopment of speech, whereas in adults they cause a loss of speech function. Developmental slowness generally and sensory deafness should be ruled out as etiological factors.

Some children of normal intellectual and physiological development may not speak for psychological reasons. An early illness may be used as a means of gaining attention and having the child's needs satisfied so that speech is not necessary to gain these wants. Children may use mutism to gain attention because of their feelings of unwantedness due to the presence of a new baby in the family. The schizophrenic child does not acquire speech because, in his autistic world, speech is unnecessary.

### **PROGNOSIS**

Prognosis, of necessity, depends on the severity of the lesion. In adults, the important aspect is the reversibility of the pathological condition.

An inflammatory lesion which tends to recover spontaneously or in response to treatment can be followed by considerable recovery from the aphasia. Aphasia due to physical trauma to the head usually improves as the cerebral edema subsides, however, residual defect generally remains to some extent. Prognosis is good after the removal of an extra-cerebral tumor which has compressed but not infiltrated the brain substance. Even if an intra-cerebral tumor can be successfully removed the speech disturbance is not improved.

In lesions of vascular origin the prognosis is better if the lesion is hemorrhagic rather than thrombotic or embolic. This occurs since cerebral infarction necessitates permanent neuronal damage.

In children in whom speech has developed a fractional loss usually occurs, not a complete absence as occurs in children who have never talked or in whom speech function is not fully developed. In time the child will usually begin to talk just

(Continued on Page 89)



# Recent Advances in Neurosurgery

MICHAEL O'DWYER, '63

## INTRODUCTION

Great strides have been made in neurosurgery in recent years, particularly in the treatment of Parkinson's disease and ruptured intracranial aneurysms—disorders in which the physician could hitherto offer little.

This paper is a brief review of the recent developments in these fields, and also in the treatment of trauma and epilepsy. Stress is placed on the use of hypothermia and stereotaxy.

As an article of this nature could not hope to be technical, this paper is designed to be more a general survey of the subject, rather than a detailed report.

## DEFINITION

Neurosurgery may be defined, tersely, as the surgical treatment of disorders of the nervous system. By definition, all components of the nervous system are included; however most of the emphasis in this article is placed on the central nervous system.

## HISTORY

The surgical invasion of the skull has been the practice of man since the tenth millenium B.C. Skulls found in excavations show evidences of holes made by scraping away the bone. It is of interest to note that some of these patients, or victims, lived after the procedures, as indicated by the formation of new bone around these defects.

The production of holes in the skull was recommended in early times for headaches, eye troubles and epilepsy,—not very far away from modern indications!

Trephination, or the boring of holes through the skull was introduced by Fabricius of Aquapendente and the procedure was well known at the time of Hippocrates.

The step into the modern era of neurosurgery depended upon a knowledge of neuroanatomy and neurophysiology. The studies of men such as Galen, Vesalius, Vicq d'Azyr and Soemmering gave knowledge of the gross anatomy, and Blum,

Nissl and Golgi brought enlightenment in microanatomy. Neurophysiology was pioneered by such men as Broca, Fritsch and Hitzig.

Antiseptic technique, as first proposed by Lister made surgeons less afraid to enter the skull. Studies in localisation and function allayed even more the unwillingness to cut into the mysterious seat of life.

Among the first operations on the brain was that done by Macewan (1879) in which he removed a meningioma from the left frontal fossa,—with full recovery of the patient.

The birth of neurosurgery in North America came in 1919 with the skill of Harvey Cushing, and it was Cushing who introduced electrosurgery to the world in 1928.

Since that time, researchers, too numerous to mention, have developed and refined techniques to ever increase the efficacy and safety of neurosurgery.

## GENERAL ADVANCES

### 1. Hypothermia

By definition, hypothermia is the state in which the temperature of a homo-thermic animal is reduced to a subnormal level. It was introduced by Smith and Fay in 1939 and first used in neurosurgery by Fay in 1945.

The purposes of hypothermia are four in number:

1. reduction of metabolic activity.



2. decrease in brain size due to decreased cerebral blood flow.
3. decrease in cellular excitability
4. decrease in the time required for the development of collateral circulation to areas which might otherwise become infarcted. Hypothermia may be used in practice in two ways—the cooling of the entire body, or cooling of a localized area.

#### A. Total Body Hypothermia

This method of hypothermia may be effected by many methods but usually by either ice packs or cooling blankets, or both. The temperature may be measured by an esophageal or a rectal thermometer, or thermocouple.

Advantages:

1. Very little anesthetic agent is required because anesthesia occurs spontaneously when the temperature drops to 30°C (86°F).
2. It decreases the stress effect of trauma on the pituitary and adrenal cortex.
3. At 30°C the metabolic activity of the brain is reduced by 50%.
4. The size of the brain is decreased due to lessened cerebral blood flow and the danger of foraminal herniation is reduced. Also in this regard an easier access is gained to structures at the base of the brain.

Hazards:

1. Ventricular fibrillation is liable to occur at temperatures below 30°C.
2. If shivering occurs then cerebral oxygen consumption may be increased and the purpose of hypothermia defeated.

Indications:

1. Adjunctive to neurosurgery.
2. Therapeutic—to decrease temperature in cases of brain damage due to trauma, strokes or cardiac arrest.

#### B. Local (regional) Hypothermia

This method of tissue cooling involves only a localized area of the central nervous system and may be effected by vascular

perfusion or ventricular and subarachnoid irrigation. Temperatures may be reduced below 20°C.

Advantages:

1. Permits rapid hypothermia of an area in emergency cases.
2. Eliminates the undesirable effects of total body hypothermia.
3. It is rapidly reversible.

If profound hypothermia is desired, it can be achieved by employing body surface hypothermia to reduce the core temperature to 30°C and then by means of regional technique the area of the brain concerned may be taken down to 20°C or lower. This method allows the use of low temperatures at the surgical site without the morbidity associated with temperatures below 30°C in the rest of the body.

The use of hypothermia has brought hitherto impossible procedures within the realm of practicability.

#### II. Hypertonic Solutions

The introduction of such hypertonic solutions as urea or mannitol into the general circulation procedures remarkable reduction in brain size.

Indications:

1. Reduces the size of the brain and permits exploration of previously inaccessible areas within the skull with trauma to the brain.
2. Controls post-operative and post-traumatic edema of the brain.
3. Buys time by reducing intracranial pressure if the patient must be moved prior to surgery.

#### III. Stereotactic Procedures

These techniques are based on the premise that a probe or needle can be introduced into a small target area in the depths of the brain, using coordinates established by careful anatomical measurements. The apparatus is firmly attached to the head and the point of the probe can be moved in any of 3 planes of space by micrometer screw attachments.



In practice an oil or air ventriculogram is done so that the probe can be moved in relationship to central landmarks such as the anterior and posterior commissures at the foramen of Monro and the suprapineal region.

**Advantages:**

1. There is minimum damage to the brain because the trial and error location of areas is eliminated.
2. Large exposures of brain need not be done.
3. Results using stereotactic techniques can be duplicated with amazing accuracy from case to case.

The procedure is at present almost entirely restricted to the treatment of abnormal movement disorders such as Parkinson's disease, athetosis, dystonia and intention tremor.

## ADVANCES IN SPECIFIC FIELDS

### I. Trauma

The treatment of cranio-cerebral injury and its complications have changed little in the past few years and may be seen outlined in any text of surgery.

Physicians are more aware of the "interval" syndrome and of the special care available to these cases in neurosurgical units. Of special interest has been the use of surface body cooling to 30°C to control brain swelling and hyperthermia in cases of severe cerebral contusion and laceration. However, although more patients are surviving, many are left severely handicapped by paralysis and dementia. On the other hand the results in children may be striking.

### II. Epilepsy

Epilepsy is a disease characterized by seizure activity of any one or a combination of several types of symptoms, among which are:

1. Paroxysmally recurring loss or impairment of consciousness.
2. Involuntary excess of muscular movements.

3. Psychic or sensory disturbances.
4. Perturbation of the automatic nervous system.

Status epilepticus is a term used to describe the condition in which fit follows fit without intervening restoration of consciousness.

#### A. Classification:

1. Idiopathic makes its appearance before adult life is reached.
2. Symptomatic due to pathology in the brain, such as cortical scarring, new growth, and arterio-venous malformations.

#### B. Etiology:

The etiology of epilepsy is poorly understood, making the treatment, whether medical or surgical, rather more symptomatic (palliative) than curative.

#### C. Treatment:

In the past, the surgical treatment for epilepsy has been excision of an epileptogenic cortical scar, (as determined by seizure activity with an electroencephalogram) or a new growth thought responsible. In certain cases of temporal lobe epilepsy, a temporal lobectomy has been done.

It is the characteristic of symptomatic epilepsy to be rather refractory to medical treatment, but Ommaya and Baldwin have indicated that regional hypothermia has been very effective in stopping status epilepticus and that following this procedure the seizures were more easily controlled by medication. If not stopped completely, they were at least reduced in number and intensity.

### III. Parkinsonism

Parkinson's disease (paralysis agitans) is a disease characterized by involuntary tremor at rest, muscular weakness and rigidity, a shuffling gait and a leaning forward of the trunk when walking, (festination). The facies are devoid of expression, although not paralyzed. It is a slowly progressive disease of the degenerative period of life. The etiology of the



condition is unknown but it is seen to follow some cases of injury, infection or therapy with some drugs.

#### A. Pathology

There are degenerative changes in the cells and fiber tracts of the corpus striatum and substantia nigra.

#### B. Treatment

Medical treatment has been the standby up to the recent past, but with developments in neurosurgery, a great future may be ahead in the surgical palliation of Parkinsonian symptoms.

The essence of surgical treatment lies in the production of lesions in the lateroventral thalamic nuclei and the mesial globus pallidus. Lesions have been made in a multitude of ways:

1. heat thermolesions at 55°C
2. cold probe of Cooper at -5°C
3. vascular occlusion
4. alcohol
5. leukotomy
6. radio isotopes
7. electrocoagulation

The method of production of the lesion seems to matter little as long as it is placed accurately.

The success story of surgery for Parkinsonism depended upon the development of stereotactic equipment and procedures. By this method lesions can be very accurately placed and the problem of injury to adjacent structures, for example, the internal capsule, has been minimized.

The general consensus seems to be that lesions made in the medial segment of the globus pallidus alleviate rigidity and those in the lateroventral thalamic nuclei have more effect on tremor. In work done by Meyers, it was found that a lesion in the substantia nigra always resulted in an abolition of tremor and reduction of rigidity. In some cases reported by Spiegel and Wycis, lenticular ansiotomy reduced and sometimes eliminated tremors.

#### IV. Aneurysms

An aneurysm may be defined as a sac

formed by the dilatation of the walls of an artery or vein and filled with blood.

Aneurysms may be of two types—saccular (berry) and fusiform. They may occur anywhere in the blood vessels supplying the brain itself. They occur chiefly in the arteries at the circle of Willis.

The potential danger of an aneurysm is that it may rupture, producing a catastrophic hemorrhage into the subarachnoid space or the parenchyma of the brain itself. Occasionally it may become so large as to cause pressure symptoms by involvement of the neighbouring structures, for example, the optic chiasma, trigeminal nerve, etc.

#### A. Diagnosis

The diagnosis of aneurysms is seldom made prior to rupture and is verified by cerebral angiography.

#### B. Treatment

In the past the treatment for intracranial aneurysms consisted of watching and waiting, although sporadic attempts were made to deal with them surgically.

Modern surgical treatment is directed towards obliteration of the sac by clip or ligature. It has been made possible because of access to the aneurysm and has been made simpler by the development of such surgical adjuncts as hypothermia, infusions of hypertonic solutions to decrease the size of the brain (urea), and the development of new surgical instruments.

In general, the means of dealing with an aneurysm surgically may be classified:

1. Ligation of the involved artery or the blood supply to the area. In such cases the carotid artery or the vertebral (or basal) artery may be tied off on the affected side (Hunterian ligature).
2. Occlusion of the neck or a saccular aneurysm by ligatures or metal slips.
3. Induction of thrombosis in the aneurysmal sac, by injecting a mammalian hair into it. For such purposes a unique "hair" gun has been designed.



- Wrapping of the aneurysm with some substance to prevent enlargement and recurrent hemorrhage. Materials employed in this technique are hammered muscle, surgical gauze filigree or a fast-setting plastic. The advantages of the wrapping technique is that it now enables surgeons to treat aneurysms of the trifurcation of the middle cerebral artery without clamping off all the branches.

## CONCLUSION

The scope of neurosurgery is ever-broadening. New techniques and instruments are finding their way into the increasingly skilful hands of more and more neurosurgeons. I think that it is safe to say that before too far in the future surgical procedures will be carried out that would strike fear into the hearts of present-day men; and neurosurgeons of the next era will look back on today, as those of this era view the first attempts to Fabricius.

## SUMMARY

A brief presentation is given to the history of neurosurgery and some of the more recent general and specific advances in the field.

Special consideration is given to surgical intervention in cases of trauma, epilepsy, Parkinsonism, and cerebral aneurysms, with emphasis on the integration of new techniques in their management.

I would like to thank Dr. C. G. Drake for his invaluable assistance in the preparation of this article.

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# The Management of Coma

RICHARD CLARK, '64

The comatose patient can be placed into three categories. First, there is the patient who is beyond medical help and has deteriorated to an unresponsive state. Second, there is the patient who requires only good nursing care and will return to a completely normal life. The patient discussed here is one who can be cured by either medical or surgical means. If therapeutics are not instituted, he may regress into a hopeless condition.

Coma is defined as an abnormal state of depressed responsiveness with absence of adaptive response to tactile, thermal, proprioceptive, visual, auditory, olfactory or verbal stimuli.<sup>3</sup> Magoun<sup>4</sup> has shown that the anatomic physiological basis of wakefulness is the intact synaptic relationship between the reticular formation of the brain stem and some of its cortical subcortical connections.<sup>4</sup> Chemical or physical disturbances of the anatomic-physiological relationship may result in coma.

Coma is not an independent disease entity but is a symptomatic expression of disease.

## DIFFERENTIAL DIAGNOSIS<sup>2</sup>

The diseases which cause coma can be divided into three classes.

- I. *Diseases which cause no focal or lateralizing neurologic signs or alteration of the cellular content of the cerebral spinal fluid.*
  - A. Intoxications (alcohol, barbiturates, opiates, etc.)
  - B. Metabolic disturbances (diabetic acidosis, uremia, Addisonian crisis, hepatic coma, hypoglycemia, and hypoxia.)
  - C. Severe systematic infections (pneumonia, typhoid fever, malaria, Waterhouse-Friderichsen syndrome).
  - D. Circulatory collapse (shock) from any cause, and cardiac decompensation in the aged.
  - E. Epilepsy

- F. Hypertensive encephalopathy and eclampsia

- G. Hyperthermia or hypothermia.

- II. *Diseases which cause meningeal irritation, with either blood or an excess of white cells in the cerebral spinal fluid, usually without focal or lateralizing signs.*

- A. Subarachnoid hemorrhage from ruptured aneurysm, and occasionally trauma

- B. Acute bacterial meningitis

- C. Virus encephalitis

- D. Neurosyphilis

- III. *Diseases which cause focal or lateralizing neurologic signs, with or without changes in the cerebral spinal fluid.*

- A. Brain hemorrhage

- B. Brain softening due to thrombosis or embolism

- C. Brain abscess

- D. Epidural and subdural hemorrhage and brain contusion

- E. Brain tumor

- F. Miscellaneous, i.e., thrombophlebitis, some forms of virus encephalomyelitis

## TREATMENT

There is no symptomatic treatment for coma; the treatment must depend solely on the cause. It is essential in dealing with the comatose patient to institute certain therapeutic measures regardless of the cause of the coma.

### I. Respiratory System

It is obvious that respiration must be maintained. Therefore, the following should be checked:

- A. Air passage for obstruction

- B. Paradoxical movement of the chest wall

- C. Depth, strength, and rhythm of breathing.



In order to maintain the air passage, an elective tracheostomy may be indicated. Mucosal secretions and vomitus should be removed from the mouth and pharynx to prevent aspiration. The patient should be placed in a semi-prone position to facilitate postural drainage.

The chest wall should be fixed by sand bags or a suture in order to prevent paradoxical breathing.

If indicated, artificial respiration may be carried out by one of the various methods.

## II. Circulatory System

The circulatory system must be considered for hemorrhage, external and internal, and shock. Both external and internal hemorrhage must be stopped and shock treatment must be instituted.

## III. Skeletal System

X-rays of the skeleton should be taken, especially of the head, neck, and back as more damage can be caused by shearing the spinal cord at the site of a fractured vertebrae.

IV. At regular intervals, the pulse, respiration, blood pressure and temperature should be recorded.

## V. Temperature Regulation

Often the temperature regulating mechanism is disturbed in coma. In cases of hyperthermia, blankets should be removed from the patient and alcohol sponges and ice packs used. Acetylsalicylic acid given by a nasogastric tube is useful in combating fever.

## VI. Urinary System

The bladder should not be allowed to become distended. To prevent this a catheter should be inserted into the bladder. Urine excretions should be kept above 800 to 1000 ml. per day.

## VII. Bowels

The bowels must be evacuated at regular intervals. If the normal physiological method is not functioning, enemas may be tried but the manual method may be required.

## VIII. Nutrition

If possible, a nasogastric tube is passed into the stomach. The proper carbohydrates, fats, proteins, vitamins, minerals, and water may be given through the tube. An acute therapy may be given intravenously.

## IX. Blood Chemistry

At regular intervals the acid-base balance and electrolytes should be studied. Any deviation from the normal should be corrected, especially the potassium blood levels.

## X. Skin

To encourage good circulation to the skin and to prevent decubitus ulcers the skin should be massaged frequently and the patient rotated on a Stryker frame.

## XI. Infection

In the care of the comatose patient, one should attempt to prevent bronchopneumonia, furuncles, phlebotrombosis, and other such complications.

A temperature chart will be of value to indicate infection. Harrison<sup>2</sup> suggests the use of prophylactic antibiotics.

## XII. Convulsion

During coma, convulsion should be controlled by the accepted medical management. Phenobarbital is useful for this purpose. If the patient is restless, restraints may be necessary to prevent self-inflicted trauma.

## Definitive Treatment of Coma

In order to relieve the coma, it is necessary to treat the cause. Therefore, a diagnosis is necessary.

## Diagnosis

### I. History

Because the comatose patient cannot communicate, the history must be obtained from others. The person who brought the patient to the hospital should be questioned thoroughly before he leaves. Relatives should be located, even if police assistance is required, and questioned also. From them, a past history of diabetes mellitus, epilepsy, or even a portacaval anastomosis would give direction to an investigation.



## II. Physical Examination

### A. General

- (i) The temperature is noted—hyperpyrexia is characteristic in heat stroke.
- (ii) The pulse may be regular or varied. In head injuries, it is very often varied.
- (iii) The blood pressure may be either hypotensive or hypertensive; both levels can lead to coma.

### B. Skin

The skin should be examined for

- (i) Color
- (ii) Signs of trauma
- (iii) Hypodermic injection sights as in drug addiction, diabetes
- (iv) Rash and petechiae

### C. Head

- (i) Scalp—the scalp should be inspected for any laceration, bruises, or boggy areas indicating trauma.
- (ii) Facial muscles—any unilateral or bilateral paralysis should be noted.
- (iii) Eyes—the examination of the eyes should include
  - size of pupils
  - reaction to light
  - ocular palsyUsing an ophthalmoscope, the fundi should be inspected for
  - papilledema
  - vascular sclerosis
  - hemorrhage, etc.

- (iv) Ears—watching the patient's response to a loud noise may be used to test his hearing. Both the ears and nose should be inspected for possible signs of inflammation or cerebral spinal fluid leakage.

- (v) Mouth—the mouth should be examined for remnant of ingested pills, poisons and any burns. Particular attention should be directed to the odor of the breath as it might give assistance in alcohol poisoning, uremia or acidosis.

### D. Neck

If the neck resists passive flexion, meningeal irritation might be suspected; if the neck resists passive movements in all directions, neck injury might be indicated or it may be part of a general rigidity.

### E. Chest

- (i) The lungs should have a routine examination for rales, rhonchi or signs of massive consolidation.
- (ii) The heart should be auscultated for any possible murmurs.

### F. Abdomen

The abdomen should be examined for signs of peritoneal irritation from hemorrhage or ruptured viscus.

### G. Extremities

Flaccid extremities may signify paralysis; spastic extremities may signify decerebration. The symmetry of the flaccidity or spasticity should be noted. The characteristics of the tendon reflexes should be observed and any pathological reflexes should also be elicited if possible (e.g. Babinski Sign).

## III. Laboratory Tests

### A. Gastric Lavage

If poisoning is suspected, a gastric lavage should be carried out with the content kept for further analysis.

### B. Urinalysis

The urine should be examined for

- (i) Sugar
- (ii) Acetone
- (iii) Albumin
- (iv) Bromides and barbiturates may be tested for by special techniques.

### C. Blood

A sample of blood should be taken and examined for

- (i) White blood cell count
- (ii) Glucose
- (iii) Non-protein nitrogen
- (iv) Carbon dioxide content
- (v) Sodium
- (vi) Potassium
- (vii) Chloride



#### D. Lumbar Puncture

The cerebral spinal fluid should be examined for

- (i) Pressure
- (ii) Protein
- (iii) Glucose
- (iv) Chloride
- (v) Cells
- (vi) Wasserman reaction
- (vii) Blood
- (viii) Infective agents—i.e. bacteria

#### E. Radiology

The following x-rays of the skull should be taken

- (i) Flat plate
- (ii) Air studies
- (iii) Angiograms

#### Specific Treatments

The treatable forms of coma usually encountered are:

- (a) Drug intoxication
- (b) Toxemia due to systemic infection
- (c) Meningitis
- (d) Epidural and subdural hemorrhage
- (e) Diabetes acidosis
- (f) Hypoglycemia

##### (a) Drug Intoxication

In drug intoxication, the skin is often cyanotic and respiration is shallow and slow. The treatment is the maintenance of respiration, thus permitting the body to metabolize the drug.

##### (b) Toxemia due to systemic infection

The diagnosis is usually obvious with a high temperature. Treatment includes treating the infection and controlling the temperature.

##### (c) Meningitis

With meningitis, the neck resists flexing and the patient has a fever. The cerebral spinal fluid shows an increase in protein and pus cells, a decrease in glucose and chloride, and usually the infective agent can be demonstrated. The administration of an antibiotic which affects the organism is used as the treatment.

##### (d) Epidural and subdural hemorrhage

A history of trauma to the head is usually available with epidural and subdural hemorrhage. Respiration, blood pressure, and pulse are variable. The cerebral spinal fluid is increased in pressure and may contain some blood. The patient's condition is usually deteriorating. On x-ray, the pineal body is displaced. Treatment includes removal of the blood clot by a neurosurgeon or general surgeon and prevention of any further bleeding.

##### (e) Diabetic acidosis

Diabetic acidosis can be diagnosed by the acetone and glucose in the urine and elevated levels in the blood. There are general signs of dehydration. The characteristic Kussmaul breathing can be observed. Hydrate the patient and bring his blood glucose level under control with insulin.

##### (f) Hypoglycemia

Acute hypoglycemia is usually due to an overdosage of insulin. At the onset, convulsions may be present, the deep reflexes exaggerated, and a Babinski sign shown. The blood glucose level is low. Intravenous glucose in water is used in treating the patient.

#### SUMMARY

Coma is a medical emergency. The speed and accuracy with which the diagnosis is made and the treatment instituted can make the difference between life and death.

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# Genetics of Mongolism

FRANCES HARLEY, '65

## INTRODUCTION

Mongolism was first described by Langdon Down in 1886. Although the possibility of a concomitant chromosomal abnormality was suggested in the 1930's it was not until 1959 when Lejeune studied the chromosomes of nine mongoloid children that this theory was substantiated. In order to understand the mechanisms which could produce such chrom-abnormalities a brief review of cell division is given below.

## GENETIC PRINCIPLES

The process of cell division includes the division of both the nuclear material and the cytoplasm. Nuclear divisions are of two types. Mitosis results in the production of two daughter cells with the same number of chromosomes and the same amount of genetic material as the parent cell. Meiosis, which occurs only during the formation of gametes, results in each of the daughter cells containing half the number of chromosomes or half the genetic material in order that the zygote, formed by the union of the two gametes, contains the same number of chromosomes as that of the cells of the parents.

Mitosis occurs in four stages. During the first stage, prophase, chromatin material assembles into visible strands, each strand consisting of two identical strands, held together at a centromere. One chromatid is the result of reduplication of the other. In the cytoplasm a spindle structure is forming from fibers which radiate outwards from the centrioles at opposite ends of the cell.

As the nuclear membrane disintegrates the chromosomes line up on the equatorial plane of the cell between the opposed halves of the spindle. This is the stage of metaphase. Next, in anaphase, the centromere, or body holding the chromatids together, splits longitudinally freeing the two chromatids. These move to opposite ends of the cell. At the ends of anaphase each pole of the cell has a complete set of chromosomes. The cytoplasm finally divides in the telophase. Each chromatid is

now a chromosome which at a subsequent division would appear at prophase as two joined chromatids.

Meiosis consists of two divisions of the nucleus. The first division is referred to as the reduction division while the second is essentially a mitotic division.

Chromosomes exist in pairs, identical in appearance and carrying identical genetic factors. In prophase of meiosis the chromosomes of each pair lie in apposition at the equatorial plate. At this stage each chromosome is composed of two chromatids joined at the centromere. The human cell has 46 chromosomes so that 23 pairs of double stranded structures are seen at this phase. These pairs then merge and exchange genetic material. After this exchange, which blends genetic material from both parents from which that cell was derived, the chromosomes of each pair are drawn apart and the cytoplasm of the cell divides. In the second mitotic division, the centromere divides and each half migrates with one of the chromatids into each newly forming cell. The chromatid now with its own centromere has become a chromosome. Not surprisingly, errors in these divisions can occur, which will affect the chromosomal content of future cells.

Abnormal numbers of chromosomes can arise as a result of non-disjunction of a pair of chromosomes. By this is meant that two members of the chromosome pair fail to separate at anaphase. For example, if two members of a pair fail to orient themselves at metaphase and just lie singly in the



cytoplasm, they may each go to the same pole on cell division. The chromosomes may line up correctly but fail to separate. One member of the pair might fail to line up in the equatorial plane and become lost from the cell when it divides. Non-disjunction at some stage after formation of the zygote may produce two or more stem lines of cells with different chromosome complements. An individual of such constitution is known as a mosaic. For example, non-disjunction of one pair of chromosomes in one of the cells at the second cleavage would result in four cells, two having the normal chromosome complement of 46, one having 45 and one having 47 chromosomes. If such a non-disjunction took place at a much later cleavage of the zygote, the proportion of abnormal cells might be so small as to pass unnoticed.

Sometimes one chromosome can be attached or translocated onto another and, at division, move with that chromosome rather than as an individual entity. This can lead to errors in chromosome number in the new cells.

Chromosome number, size and shape are most usually studied by arresting the dividing cells of a tissue culture at metaphase, using Colchicine to inhibit spindle formation. These cells are treated with a hypotonic solution to swell their cytoplasm and separate the chromosomes still further. They are then squashed, strained and examined with a light microscope. It was such methods developed by Ford, Tjio and others that led to the conclusion that the normal human chromosome number is 46, and not 48 as had previously been thought. The chromosomes are identified by their relative length and by the centromere position. The longest human chromosome measure about 7  $\mu$ , five times longer than the shortest chromosomes. The centromere varies in position: median, submedian, (or metacentric), and nearly terminal or acrocentric.

A karyotype is a systematized array of chromosomes of a single cell prepared either by drawing or by photography. By

the Denver Convention, chromosome pairs are divided into seven groups. For example, group A consists of chromosome pairs, 1, 2 and 3. Chromosome pairs 13, 14 and 15 make group D, the long acrocentrics. Group G is composed of the small acrocentrics, pairs 21 and 22.

## MONGOLISM

Mongolism is a condition in which abnormalities of development of many tissues produce a clinical picture which is usually apparent at a glance. In 1959, Lejeune and his co-workers in Paris found that mongoloid children have an extra small acrocentric chromosome, identical with chromosome 21. Since then, it has been recognized that this extra chromosome may be distributed in different ways. The extra chromosome invariably results in mongolism, but its distribution and method of transport at cell division has considerable genetic implications.

The trisomic mongol, sometimes referred to as "normal" mongol is by far the most common type, accounting for about 95% of mongoloids. The karyotype shows 5 chromosomes instead of 4 in the 21, 22 group. The extra chromosome is considered to be an extra chromosome 21, derived by non-disjunction at mitotic division of the maternal gamete, the ovum.

Mongolism, although having an over-all incidence of 1:600 births, is much influenced by maternal age. At age 25 the chance of a mother having a trisomic "non-disjunction" mongol is about 1:2500. At the age of 35 the risk has increased to perhaps 1:150. At 40 years of age the risk is much higher—1:40. The aging gonad seems more subject to non-disjunction. The chance of a mother who has had one trisomic mongol having another mongol child is difficult to assess, for maternal age may not be the only factor influencing the risk of non-disjunction. A hereditary tendency to non-disjunction at meiosis is becoming suspect.



Chromosome translocation has also been associated with mongolism. Such translocations occur between one of the 21 chromosomes and the chromosomes in group D (13 to 15) or even with other chromosomes within group G (21-22). It has been found that the parents of some mongols, although phenotypically normal, have abnormal karyotypes. In them, all the genetic material is present, but one of the chromosomes is stuck or translocated onto another. It might be one 21 chromosome translocated to a chromosome 13. At meiosis in such an individual, four possible types of gamete could be produced:

- (1) normal gamete with a 13 chromosome and a chromosome 21 separate from one another.
- (2) a carrier gamete, having the 13/21 translocation.
- (3) a gamete having the translocation 13/21 plus the other member of the 21 pair,
- (4) a gamete with no chromosome 21 at all.

The first two gametes on fertilization would produce phenotypically normal individuals, although the second would be a carrier of the translocation like its parent. A child from the third gamete would be a mongol, while the fourth appears to be non-viable. It can be seen that one out of every 3 children (one out of every 4 conceptions) would be a mongol. These are the rather uncommon but genetically important translocation mongols. The risk is still greater if in the parents, both chromosomes 21 are reciprocally translocated. Two possible gametes can be formed. One would contain the genetic material of two 21 chromosomes, the other would have none. When such gametes are fertilized the zygote would either have three 21 chromosomes or only one. Since the latter appears to be non-viable, each living child of such a parent would be a mongol.

Mongol mosaics have been described. By error of division involving chromosome 21

after formation of the zygote, an individual can exist in whom more than one stem line of cells exist. Some, perhaps half, the cells are trisomic for chromosome 21, while others are normal. Such cases show less clear cut features of mongolism, a state midway between mongolism and normality. More than one tissue may have to be cultured for karyotype to clarify this situation.

## CONCLUSION

Karyotype studies of the mongoloid were the first such studies to produce a definite link between an autosomal chromosomal abnormality and a clinically recognized syndrome. Much has been learned since 1959. The classification of mongols by their karyotypes is of interest not only to the research worker but also to general practitioner. The chromosome pattern will not influence the management of the individual case, but it will aid the physician in advising the parent as to the possibility of having another mongol child or perhaps mongol grandchildren. In fact, genetic counselling on this question cannot intelligently be attempted without first studying the child's and parents' karyotype.

The advice and criticism of Dr. G. H. Valentine is gratefully acknowledged.

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# Osler and Medical Education

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## INTRODUCTION

The following is an address by Dr. Pierre Jobin, delivered at the Annual Osler Banquet, University of Western Ontario, on March 8, 1963. As editor, I feel that his credo should belong to the entire student body and the following complete text represents the warmth and sincerity of a distinguished scholar, teacher and prominent Canadian.

—The Editor

I come directly from the heart of Quebec, land of French culture and of . . . separatism. I am not at all alarmed at being here among you because I am definitely not a separatist. Furthermore, I am very proud of being your Osler Lecturer although I have serious doubts about having earned such a flattering introduction which is prejudiced no doubt through the kindness of your professor of Anatomy, my good friend Alan Skinner, and other colleagues, namely Prof. Murray Barr who was recently focussed in the public eye when he won the Kennedy award for his scientific research.

Like you, I am a Canadian; the only difference is that I was born, brought up and educated in another part of this vast country, the French area of our dear Canada. We are all medical people, indeed, but we express our knowledge in a different language, that in which our mother taught us to pray. Both groups to-day are the indispensable instrument of understanding and unity in Canada. For twenty years I have met and talked with people in Canadian universities and, believe me, human contacts have always been amazingly easy, even though we have, once in a while, some difficulty in understanding one another's language as all of us are not bilingual. Nevertheless, we have a common denominator, a common ground on which we can strive to win the battle of unity, by preserving our original culture and by pooling our assets and achievements for the benefit of Canadian civilization. Let each of us develop to the maximum his individual characteristics, social, cultural and religious — "Notre

langue, notre foi et nos traditions." So much the better for our beautiful country.

When I first went to McGill I was invited to pay a visit to the special medical library entirely devoted to the personal library of Sir William Osler, the "Osleriana"—I was not a little surprised to see a collection of 7964 volumes and publications of all kinds, although I already knew that Osler was one of our greatest names in medicine, and particularly that he was one of the rare initiators of to-day's scientific standards of medicine. I was shown by the librarian, Prof. Francis, some incunabulae of incalculable value and I was deeply impressed by one of them "De Corporis Humani Fabrica", commonly called "Fabrica", by Vesalius, with the following inscription signed by Osler: "I am glad to be able to send this beautiful copy of the first edition to the library of my old school, in which anatomy has always been studied in the Vesalian Spirit—with accuracy and thoroughness".

Of course we know that, in the English "Who's Who", Osler assigns "bibliography" as his recreation. A hobby? Maybe, but his historical and bibliographical knowledge constituted an essential part of his rich equipment as an inspiring teacher and student of medicine. His favorite method was to integrate history into scientific lectures rather than dispensing systematic lectures on the history of medicine.

Moreover, he was a book-lover, a true bibliophile. He would buy both the original and the last editions rather than only the latter. Therefore, I was not surprised



to learn that, apart from his gift of several thousand volumes to McGill, he also donated two collections of books to the Johns Hopkins Hospital: one on modern cardiology, vascular and blood disease, tuberculosis, etc., the other on English literature. He personally has to his credit more than 1000 publications dealing mainly with medicine (pathology, internal medicine and medical education); but he was also a literary writer (144 papers) and he edited 20 volumes. He was incredibly prolific: he himself published ten times more papers than his colleague, the famous surgeon Halstead. The reason for this is due to his position in the Hospital and his devotion to teaching; he never missed an opportunity to address people because his main ambition, his ideal was "EDUCATION". Not only was he not afraid of human contacts but he sought them; being a highly cultivated man and having a strong personality, he enjoyed meeting people. Nothing was more delightful to him than an intimate and open heart conversation, not only with medical and nursing students, but also with his colleagues or anyone who showed an interest in any field of human activity. John Bruce wrote about him; "To his contacts with the young, he brought the tolerance of a great teacher and the personal influence of a good man".

As it is with great personalities, he had the attractive charm of savoir and humility; he truly believed that a sincere human contact always enriches one.

Osler was the perfect modern type of what we call a learned person; he knew almost everything in the medicine of his time, modern successor of Pic de la Mirandole. In three countries he was known and beloved and he was considered to be the peak of what was the best in a wonderful profession. He made no outstanding discoveries but, among the impressive amount of his publications, there is a book that may be considered as the vade mecum of teachers' duty to this generation: "Principles and Practice of Medicine"; it is full of wisdom, fine culture and of charm of style.

It is obvious that he was the best type of clinician that the 19th century produced; he combined the broadest humanism with the greatest science of his days. According to Maude Abbott, "he approached the study of disease in true spirit of scientific inquiry". He was inspired by experimental, physiological and pathological methods of new physicochemical discoveries. Nevertheless he never let the scientific approach overcome his acute sense of clinical observation. On the contrary, he always started the examination of a patient by listening carefully to the history; the physical examination tried to eliminate certain secondary possibilities and to enlighten what the questionnaire had pointed out. Scientific investigation and laboratory procedures then illustrated the findings of the clinical examination. His great merit is to have brought to clinical medicine the help of the scientific laboratory.

Being a natural teacher and educator, he shares with Halstead the credit of organizing the professional staff of the hospital, of affiliating the hospital with the University and of initiating those reforms which are at the threshold of a new philosophy in American medicine. During his sixteen years at Johns Hopkins, he organized, for the first time on this continent, facilities and opportunities for the young resident-physicians and surgeons engaged in post-graduate clinical training and research. Osler is the true initiator of the "residency" as we know it to-day. Of course we are all familiar with the Abraham Flexner Report published in 1910, (after a two year survey in the United States and Canada which was subsidized by the Carnegie Foundation at the instigation of the American Medical Association). The Flexner Report was the turning-point of modern medicine. Fifty years later, it can be said that almost all medical schools in the United States and Canada are first class institutions and that their graduates receive top-rate scientific medical education. They may not be perfect in every aspect, but the lessons taught by Osler and formulated by



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Flexner play an eminent role in to-day's medicine. Yes, Osler was a great teacher for all our generation.

Speaking of teaching, I now wish to underline a few points of interest relating to the history of medical education. Four hundred years before Christ, antiquity's greatest physician, Hippocrates, and his associates, freed themselves of superstition and illogical theorizing and earned great repute as advisors and scholars. They may well be regarded as the fathers of modern medicine for their intellectual curiosity, their open-mindedness and their sound reasoning based essentially on accurate and thorough observation. Their philosophy of medicine encompassed the whole field of health, not only curative but also preventive medicine; they taught people to preserve health through hygiene, exercise, rest, diet and emotional control.

In the Island of Cos, in the Aegean Sea, tourists are still shown the first organized hospital where Hippocrates taught bedside medicine in departments of dietetics, mechanical therapy and hydrotherapy, as well as in wards for treatment of diseases—the first teaching hospital in the world:

But this wonderful philosophy (to-day we would call it comprehensive medicine) faded and vanished with the centuries. In the middle ages, empirical medicine was taught by very dignified professors with inflexible authority, recalling only what was left from the wonderful Hippocratic descriptions, dogmatic, encyclopedic enumeration of facts and fancy. The only exception to this state of rigidity was in Salerno, where surgery and hygiene were important activities. Salerno also became famous by admitting the first women to the study of medicine.

Some 2000 years after Hippocrates, the Renaissance marks the return of an open state of mind and of bedside teaching. Vesalius, in his "Fabrica," proved that accurate observation and objective reasoning were the basis of modern medicine. He came at an exciting time when every human activity—arts, science, literature—

was in evolution: Leonardo da Vinci with his scientific study of anatomy and his Mona Lisa, la Joconde; Copernicus and his revolutionary work on the celestial sphere; Christopher Columbus and his discovery of America; Gutenberg and his discovery of printing. It was, indeed, a true revolution with a new philosophy of life, *humanism* based on a return to ancient culture, Latin and Greek.

At this time of the Renaissance, anatomy was taught on the public square; "il n'y avait pas que des curieux en mal d'émotions fortes; au contraire, on y voyait beaucoup d'hommes de science". Vesalian dissections were carefully supervised by physicians and scientists such as Fallopius, Ingrassia, Colombo, Paracelsus, Cochleus, Sylvius, etc., and the Mayor of Padua, the painter, the Titian, the editor of "Fabrica", Jean Oporinus, the religious reformer, Luther. All this scene is shown on one of the best wood engravings of the XVIth Century.

Medicine was taught and learned under an apprenticeship system. In the early days of Canada, at the time of the French Colony, medicine was practised by graduates from abroad, France, of course. The first of importance was Michel Sarrazin, (1659-1735) member of the French Academy of Sciences (he was a fairly good naturalist and published many good papers on Canadian flora); he also was a member of the Academy of Medicine and his training was ear-marked by the Vesalian method of accurate observation. He took with him young Canadians and for three to four years they followed their master in his daily practice in the homes, military headquarters, Indian huts and in the Hôtel-Dieu Hospital in Quebec City (1639). After a certain period of training and when their preceptor saw fit to do so, they were allowed to practise freely. This preceptorship or apprenticeship method prevailed also during the time of the English colony when the Governor of Lower Canada appointed Examining Commissioners to control the licensing of medicine.



This was, of course, an improvement, as candidates had to pass examinations before a board of qualified physicians. As an example, Pierre de Sales Laterrière had studied medicine in France but had no diploma. After practising three years he failed his examinations twice. He then decided to cross the border and after completing his medical education (3 years) he successfully passed his exams in Boston at the Harvard Medical School in 1789. He then returned to Canada with a diploma of "Medicinae Doctor"; finally he got his licence from the Commission, after many difficulties, and started to practise medicine quite independently but legally at last.

Schools of medicine were gradually organized in the last century and those responsible tried to build up a satisfactory curriculum, inspired by the Edinburgh and Paris traditions of bedside teaching. The McGill medical school was founded in 1828, Toronto and Montreal in 1843, Laval in 1853, Queens in 1854 and Western in 1881, etc. Laval was originally organized by bilingual persons such as Prof. Sewell, Jackson, Morrin, Ahern, Blanchet, Frémont and Larue, etc., because the English representation at that time was a third of the population. They placed great emphasis on the teaching of anatomy as in the Vesalian method that was still up-to-date, as the whole philosophy of medicine was based on anatomy. Then along came physiologists and pathologists who, with the influence of Laënnec and Pasteur, Virchow, Hunter and Harvey brought about a rapid evolution in the teaching methods and learning of medicine.

Osler studied under this new system at McGill University. When, in 1889, he was called to Johns Hopkins where he found a favorable environment and a group of open-minded confrères, he took this unique opportunity to launch his great reform that influenced the XXth Century. He organized the professional staff of the hospital because he sincerely believed that the hospital was the *sine qua non* condition of teaching facilities. He integrated basic and scientific matters into the clinical field

for the undergraduate as well as for the graduate. He was a great teacher and he had a deep conviction that teaching is profitable, inasmuch as it brings out a taste for learning.

As the study of medicine encompasses all the facets of the human being, he thought that it was necessary to cope, not only with the cure, but also with the prevention of disease and with environmental hygiene on a physical as well as on a psychological basis. He promoted the idea that medicine was the profession for the preservation of health. "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (W.H.O.).

Nowadays, I can see two main factors which have a deep influence on the practice of medicine. On the one hand, *research* of all kinds has produced such a stockpiling of new knowledge that it has become impossible for a physician to master the whole field of medicine. This very science has led us to *specialization* and has made compulsory an option in and a narrowing of the vast field of practice; even the general practitioner has, for the sake of better service, limited himself to a specific activity.

On the other hand, *education* has developed at all levels and in all classes of society; people know more about almost everything, including disease and promotion of health. Medical services and facilities have increased and expanded to such a point that medicine, which has always been the privilege of the rich, is now available to most of the population through insurance and security measures.

These two factors, research and education, have tremendously increased the demand for more and better medical services. Therefore, it has become more difficult to practise medicine to-day than thirty years ago, because of the quality of service and care; there are more tools, more responsibilities and more power.

Nevertheless, our profession is still highly attractive for energetic and talented young people; but its practice requires



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great devotion and integrity. "The physician needs a clear head and a kind heart" (Osler). The "clear head" gives to understand that "the very first step towards success in any occupation is to become interested in it . . . and that the master word in medicine is work".

Yes, you must work hard and well: work hard, work now; don't waste the least opportunity to learn something; be alert and satisfied but with the best. Be the driver of your own car for, if you follow the others, you will get nowhere. You must arrange a way of living that will allow you to fulfill the numerous requirements of a student's life. May I suggest that you read and re-read Osler's philosophy in Verney's book, "The Student Life", in which you will find answers to your questions. And please don't forget that after the hardships of a week you must find a moment in which to relax—sports, arts, hobbies of all kinds—before undertaking another one. So much for the first part of work: "work hard". But may I now add "work well". The medical student's mental attitude should be one of humility before the enormous amount of knowledge to be acquired. Have a great reverence for your books, study them carefully so that they will become familiar to you and this will always be helpful, particularly later on when you practise. You will return to your books as to a friend. Do you recall the anecdote about the professor of anatomy, who started his first lecture by showing his students a pile of books dealing with anatomy and saying: "I don't know much of it but I know where to find it".

Humility also towards your own skills. You are all, indeed, talented and privileged, but don't forget that you must be trained and that you have a long journey ahead. H TEXNH MAXPA O ΔE BIOS BPAXUS—art is long and life is short—. Trained and educated so as to understand and care for human beings not only physically but morally. The aims of medicine are high and they require men of quality.

Humility, at last, towards your teachers; they have experienced medicine and they know your needs. An average medical student to-day across Canada and the United States has a need for a method of learning. Most of our young people don't know how to correctly read a book, to profitably attend a lecture and perform laboratory or clinical work. Ask your professors to help you: they know your requirements and they are dedicated to the very important task of education.

Yes indeed, humility towards your professors and teachers; they have knowledge and experience and you may rest assured that whenever you seek their advice you please them, "car ce qu'un professeur peut faire de mieux, en plus de donner une méthode de travail, c'est une référence, un conseil, ou une idée générale".

The trend in medical education to-day rests on *human responsibilities* as well as the mastery of scientific knowledge. Perennial *human responsibility!* In all times man has been interested in and preoccupied with his state of health; the least disturbance in his soma has an immediate bearing on his psyche; you realize that "nihil novi sub sole" and that psychosomatic medicine has always existed. *Human responsibility* of the present! because various media of advertizing and publicity (newspapers, radio, television) have favoured a better and broader education, reflecting its influence even on medicine.

Therefore we realize that the demand for medical services is increasing rapidly; unfortunately many are unable to understand much of it and they need to be *educated*. Who is going to do this education? Are you going to let the layman deal with your affairs and settle the question? I am sure you will not accept this. Therefore it is your personal responsibility to educate your patient and the population at large. Accept this duty and face it with courage.

You will *teach your patients* how to behave in illness and how to cooperate with you; you will *teach* them to deal with problems of housing, clothing and food; you will



*teach* them physical and mental hygiene, and finally you will *teach* them to grow old in ease and comfort; in short, you will *teach* them a philosophy of life, both material and spiritual. Therefore, you yourselves will be educators; but what main qualities must one acquire to become a good educator? The first one is a thorough knowledge of his subject, the second is to impart the love of this subject. "Enseigner c'est faire aimer la matière".

You must accept the philosophy that you belong to your profession and that medicine is your *master*, a lovable master indeed, but a true master in all the meaning of the word. But since public education has increased to a point where everyone has an eye on medicine and on physicians, you must admit that medicine does not belong exclusively to the medical profession and must be shared with the public. If you doubt that we are living in an era of social security and that we are surrounded by a community-minded population, *consider* the extraordinary number of voluntary agencies which have an interest in and deal with the welfare of people: the blind, the needy, indigents; the aged and convalescents; victims of arthritis, rheumatism, heart, cancer, tuberculosis and mental disorders; the handicapped and retarded, etc. Health and security are in the air but they are no longer the physician's prerogative alone.

This situation emphasizes your responsibility to educate the public. It does not mean that you should teach on the public square, as your forefathers did, e.g. Vesalius; indeed, not! You must be of your time and use modern facilities to contact audiences through service clubs, newspapers, radio and television. These are your modern public squares. You must not lose an opportunity to educate people on question of health so that they may understand your rôle and position in life.

I must admit that we have lost a few feathers and that the public doesn't necessarily accept our advice; "Nous devons nous employer à redorer notre blason".

A most profitable education can be given through the daily practice of medicine. Listen carefully! The personal contact with a patient is the best way to improve his understanding of health and to ensure his collaboration.

You are personally responsible for this specific education of the public and consequently for the recovery of the physician's reputation. And I do not delude myself in thinking that this is all we have to consider. What is the true purpose of life? What is one's position on earth? Here is my answer and I give it to you from the bottom of my heart. I wish to talk very frankly to you, even though conversation between the old and the young is not always easy.

Being a *Christian*, I have certain responsibilities towards society. Being a *physician*, I consider that medicine was not given to me for my own sake, but for the benefit of others; like a mirror reflecting light, I received the talent of medicine to reflect on others the benefit of health. Medicine does not belong to me. As a matter of fact people living in society have felt the need of health and have asked some of their members to specialize in medical care so as to render them a service; thus medicine comes from a need of society and must return to society in services. I would apply the same concept to all the liberal professions. It is the need for justice that has developed the legal profession; the need of exchange that of trade and commerce; the need of production has developed industry. Therefore I am right when I say that my profession does not belong to me; it was lent to me to help others live in society.

From a *natural* point of view, I cannot refrain from helping people when I practice medicine and when I fulfill the requirements of my professional duties. From a *spiritual* point of view, I am only an intermediary between God and man; God uses me to better others. In other words, God has need of men, "Dieu a besoin des hommes".



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Thus you must never hesitate when your professional duty commands and you must never keep silent when you have something to say, for, in this capacity, your profession is commanding you.

This is my position; this is, as I see it, the true purpose of life. Do not fear! "la dragée n'est pas trop haute pour vous"; you are young, and richly endowed by nature. Be grateful but never forget that

your natural talents will be actualized but with willpower; "Where there's a will, there's a way".

With students such as you, willing to face their responsibilities and with such devoted teachers as yours, dedicated to your education, I rest assured that our wonderful profession is in strong and able hands.

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(Continued from Page 70)

like an infant learning to speak. It seems that during the process of recovery the speech functions are developed in the subordinate hemisphere. It is also much easier for a child to make this adjustment than an adult.

## SUMMARY

Speech disturbances have been studied for over one hundred years. Aphasia is shrouded in complexity and controversy. A working classification is given and specific tests to determine the quality of aphasic disturbance is outlined. Treatment is not discussed because of its complexity and voluminosity.

The author is greatly indebted to Dr. G. Hinton for his criticism and ready assistance in preparing this article.

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## Book Reviews

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**Synopsis of Obstetrics:** Charles E. McLennan, Sixth Edition, C. V. Mosby Company, St. Louis, 1962, \$6.75.

This book, as its title suggests, is not intended as either a reference text or a detailed study of obstetrics. For review purposes this is an excellent supplement to notes. Each chapter is written concisely and illustrated with adequate diagrams.

The introductory chapters cover the basic anatomy and physiology of fertilization, implantation, placental formation and function. After outlining maternal physiology and fetal development, the author begins the body of the book. Prenatal care, complications of pregnancy, the course of normal and abnormal labor and the puerperium are described briefly, but accurately. The final chapter contains a description of obstetrical surgery which is rapidly becoming outdated.

In summary, this book is a good aid if used as a synopsis. J.C.

**Current Diagnosis and Treatment:** by H. Brainerd *et al*, Lange Medical Publications Los Altos, California, 1963, Price \$9.50.

This book is the latest of a series by Lange Publications that are widely used and well-liked by many students. It deals primarily with internal medical disorders but also includes commonly encountered disturbances found in other specialties, for example, Eye, Obstetrics and Gynaecology.

It is a handy reference for the essentials of diagnosis, clinical and laboratory findings and "standard" treatments of the wide range of common medical disturbances. The chapters on "Skin and Appendages", "Heart and Great Vessels", "Peripheral Vessels" and "Poisons" are particularly interesting and well-developed from a practical viewpoint.

As the authors state, "it is not intended to be used as a textbook of medicine" and it certainly does not serve this aim. However, the excellent tabular and graphic material and large clear type in double columns is well suited to the needs of the student. D.B.

**A Textbook of Histology:** Bloom and Fawcett, 720 pages, W. B. Saunders Company, Philadelphia, 1962, \$14. Available in Canada through McAinsh and Co. of Toronto and Vancouver.

The aim of this book is to provide students of biology, and especially medical students, with a text on histology and histophysiology. It also acquaints students with the revolutionary changes taking place in biology and medicine as a result of the fusion of microscopic and submicroscopic histology, physiology, biochemistry, biophysics, and molecular biology.

The book consists of thirty-three chapters. The first chapter deals generally with the cell and principles of microscopic analysis; the next eight chapters discuss the various types of tissues; the remaining thirty-four chapters deal in succession with the organs, glands, and system of the body. The subject material is presented in a clear, easily readable fashion.

The book contains many electron micrographs, photomicrographs and excellent colored illustrations. These illustrate more than adequately the subject material concerned. Special topics of academic interest are presented in finer print along with illustrations. There are abundant references at the conclusion of each chapter.

In summary, this book is well illustrated and is logically written in a concise manner. It is recommended for any student of histology. D.W.



# Editorial

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The Journal staff regrets the departure from London of Dr. A. M. Lansing, formerly Assistant Professor of Surgery and Physiology. He has taken a position in the Department of Surgery at the University of Louisville. During his two years on the staff at Western, Dr. Lansing excelled in research and surgery but was best known to students as an outstandingly lucid and inspiring teacher. His interest in the students was exemplified in that he served as Faculty Advisor to the Journal, which capacity he filled admirably. We are sure the student body joins us in thanking him for his help and wishing him great success in Louisville.

We are pleased to announce that Dr. G. H. Valentine, Associate Professor of Pediatrics, has accepted our invitation to become the new Faculty Advisor. Dr. Valentine is well known to everyone in the clinical years as an enthusiastic and erudite pediatrician and teacher and the Journal staff is eagerly anticipating this further association with him.

We wish to take this opportunity to thank all the Faculty of Medicine staff who have helped students with their difficulties writing articles for the Journal. That they take time during their busy lives to advise and criticize with respect to style and content of the articles is much appreciated.

Article-writing develops the art of self-expression, encourages clear and precise thought and is a good way to learn. The experience is most enjoyable and the rewards great. Students in all years are encouraged to take part in this most valuable extra-curricular activity.



# Medical Impressions from Tanganyika and Pakistan

MICHAEL GRACE, '64

I have been fortunate to spend the last several summers in distant areas of the world. In 1962, I was a member of an Operation Crossroads Africa group in Tanganyika and this year I attended the World University Service of Canada Seminar in Pakistan. In this report I shall give some of my impressions of medical conditions and problems in these countries and I shall outline briefly the purposes of the organizations I represented.

## TANGANYIKA

Operation Crossroads Africa is a private organization founded in the United States with the purpose of increasing the understanding between young North Americans and the people of the new nations of Africa. During the summer about two hundred American and thirty Canadian students are sent to Africa to work in nearly twenty different countries. Manual work projects, such as building a school, are carried out by groups of ten or twelve. These students, who come from a variety of racial and religious backgrounds, are required to pay some of the summer expenses and receive no pay.

I was a member of an experimental team of medical students and nurses which was scattered amongst mission hospitals in Tanganyika. I spent five weeks at a Lutheran Mission Hospital in a rural area of Southern Tanganyika and worked there with a nurse who was originally from India.

Tanganyika is a fellow member of the Commonwealth and has been a republic since 1962. It is a land of poverty where the average annual income is only about fifty dollars per person. Yet it is a very pleasant country which provides beautiful scenery, comfortable climate, and remarkably smooth race relations.

The level of medical care in this country is still low and there is only one doctor for every fifteen thousand people. Government hospitals have been set up in the larger towns and cities but most rural areas depend on mission hospitals which provide half the medical care of the whole country. Treatment is free in government hospitals whereas many of the missions must charge to keep running. Government hospitals also have relatively good facilities but suffer from a lack of trained personnel. I visited the new and modern five-hundred bed Princess Margaret Hospital in Dar es Salaam, the capital of Tanganyika. Here there were five well equipped operating rooms but only two general surgeons. There was also a shortage of nurses and laboratory technicians. Apparently, there were only twenty-five graduate Tanganyikan doctors by 1962, out of a total population of ten million.

Ilembula Mission Hospital, where I was, had one hundred and fifty beds but never seemed to contain less than two hundred and twenty-five patients. Further overcrowding was caused by the presence of many relatives who slept in the wards as well. Most mission hospitals do not have facilities for preparing meals and so must allow the relatives to bring food for the patients. As a result, it is often difficult to tell who is a relative and who is a patient.

The hospital itself was seventy miles from the nearest telephone and most supplies were brought in from Iringa, one hundred and fifty miles to the North. Facilities at the hospital were not extensive. The laboratory was small and had very little equipment. In the operating room, a small gas stove served as the autoclave. The hospital did have running water pumped from a shallow muddy well



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by a gasoline engine. A generator had also been installed in the preceding year and electricity was available for several hours in the evening and during the night for emergency surgery.

The staff of the hospital included one doctor, two European nurses, and about thirty Africans. The German doctor was a man of nearly sixty who had spent twenty-seven years in Africa. During his twelve-hour day he would do a great variety of work, covering all fields of medicine and dentistry. He was trained as a surgeon and performed many operations ranging from cataracts to gastrectomies. Open drop ether anesthetics were given by his wife. The European nurses, German and Swedish, were also extremely busy and very dedicated to their work.

The Africans on the staff worked hard but had little formal training. One medical assistant had a grade ten education and three years of practical training and was a very valuable member of the staff. The other Africans had little more than a grade four education. The local village people were helping to construct a new building at the hospital so that about ten girls a year could receive some training in nursing.

The number of Africans treated at the Mission Hospital in a full year was impressive. At Ilembula there were four thousand in-patients and ten thousand out-patients in 1961. Although the hospital did not have much money for equipment, every effort was made to have adequate supplies of drugs which were shipped in from the Coast. Hospital charges to each patient were about two shillings (28 cents) per day but many could not afford this and some paid with sheep or chickens.

The local people were poor and superstitious but they were making use of the hospital and village school facilities in rapidly increasing numbers. However, scarred bodies still bore testimony to the

activities of tribal medicine men. The diet of the rural people consisted almost entirely of maize and they received little in the way of fresh fruit or vegetables. Protein deficiency was also common.

The most prevalent disease of the area was malaria. Deaths from this disease occurred almost entirely amongst the very young but most patients showed some degree of anemia and splenomegaly. Chloroquine proved quite effective in treatment but reinfection usually occurred promptly when patients left the hospital. No major attempt at malaria control has been made yet in Tanganyika.

Tuberculosis is also a very common disease and in the month of July 1962, twenty-seven new cases were admitted to the hospital. These were often advanced cases with tuberculous meningitis, arthritis, and osteomyelitis occurring relatively frequently. Isolation was almost impossible and many patients left hospital before receiving an adequate course of drug therapy. Thus, tuberculosis continues to spread relentlessly. There were about thirty chronic cases of leprosy living near the hospital and these people would come in once or twice a week to receive D.D.S. (diamino diphenyl sulphone). Infectious cases were sent to one of the two leprosaria in Tanganyika.

Because of the low level of sanitation, gastrointestinal diseases were common, as I found out on a number of occasions. Infections with tapeworm, hookworm and amebae were found among many patients. The actual incidence of typhoid fever was unknown because of the absence of proper facilities for a laboratory diagnosis, but certainly some cases were seen. Bacteriological and pathological specimens were sent five hundred miles to Dar es Salaam, and the result was usually not available for three weeks. Many specimens did not survive the rough 'bus trip to the coast and a number disappeared entirely. This was just one of the many frustrations for a doctor in rural Tanganyika.



Schistosomiasis was spreading rapidly with the development of irrigation in the area. This disease is becoming one of the most serious health problems in Africa. Trachoma was also found here but was not very frequent. Smallpox still occurred occasionally and most of the rural people had not been vaccinated. I saw little malignancy while at the hospital. During five weeks there was one carcinoma of the stomach, one of the cervix, and two primary carcinomas of the liver.

The infant mortality rates in Tanganyika are very high and estimates place the figure at fifty per cent. Whooping cough and measles were seen frequently in children and encephalitis was a common complication. Tuberculosis was also very common in children. Most women did not go to the hospital for deliveries unless complications occurred. At Ilembula the doctor did a number of Cesarean sections because of the contracted pelvis which often resulted from a combination of poor diet and heavy work. Of course there were no incubators at the hospital, but the smallest baby to survive was one of two pounds fourteen ounces.

In a country like Tanganyika more emphasis should be placed on preventive medicine. Too often mission hospitals concentrate only on the curative side without developing a well balanced program. Yet, it is amazing how much good may be accomplished by a few dedicated people with a minimum of equipment. For an energetic doctor, service in a rural hospital in Africa provides a great deal of experience and satisfaction.

## PAKISTAN

During the summer of 1963 I spent six weeks in Pakistan on a seminar sponsored by World University Service of Canada. This organization holds summer seminars in a different country every year with the hope that Canadian students will improve

their knowledge of the people and problems of another nation and will leave behind some understanding of Canada. I was one of thirty-seven students and five professors representing twenty-five Universities of Canada and a wide variety of fields of study. The lectures and discussions on the seminar were not on medical topics but I did have some opportunities to learn about medical problems in the country.

Pakistan is a new nation, only sixteen years old, and like Tanganyika is a republic inside the Commonwealth. By Canadian standards, Pakistan is small in area, but it includes rich agricultural land, barren deserts, snow-capped mountains, and tropical jungles. It is a land of paradoxes where the products of modern industry may be hauled by donkey or camel cart.

Four-fifths of the Pakistani people live in rural areas and yet most of the medical facilities are still concentrated in the larger towns and cities. As a result, the health standards of most of the country remain low. The Government has been attacking this problem and has opened hundreds of rural health centres in the last few years. Because Pakistan is a Muslim country there are relatively few hospitals run by Christian groups.

One of the main problems of the country has been the shortage of trained medical personnel. At the time of the partition of India in 1947 many of the doctors in Pakistan were Hindu and left the country and there was only one medical college. Now there are nine medical colleges producing more than six hundred graduates per year, but there is still only one doctor for every ten thousand people in the country. The medical course is five years long and there are fewer requirements for a prospective medical student than in Canada. The emphasis in Pakistan seems to lie on the practical side of medicine rather than on the basic sciences.



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Medical students are reluctant to work in the rural areas where conditions are often poor and the pay low. As a result there is an excess of doctors in the cities while most rural areas have no medical help. Now the Government is paying higher salaries in an attempt to attract doctors to the areas where they are needed.

Because of the feeling in an Islamic society that women should not work outside the home, particularly if married, there are few women in the medical profession. Recently a modern medical college for women was started in Lahore and some women are entered in the other medical colleges. The shortage of women is particularly evident in the nursing profession. Very few nurses are seen in Pakistan hospitals and there is still only one trained nurse for every forty thousand people in the country.

The health conditions of the country would be improved greatly by better sanitation. A Westerner finds it difficult to become accustomed to the dirt, and the flies, and the warm, often contaminated drinking water. Yet these conditions are all that most of the people have ever known. For this reason the education programs sponsored by the Government are slow in taking effect and they are further hindered by the illiteracy, the lack of medical personnel, and the relatively poor development of mass communications.

The major health problems of malnutrition and communicable diseases are similar to those of other developing countries. Wheat and rice shortages are common in Pakistan but malnutrition is more often the result of ignorance than of food shortage. Malaria still causes many thousands of deaths and much illness in Pakistan, and an eradication program has been started with the help of the World Health Organization. Tuberculosis is widespread and yet there are very few tuberculosis hospitals. Smallpox is still common, particularly in East Pakistan. A vaccination pro-

gram started in one city in 1956 cut the death rate from five thousand to zero in five years, but many people throughout the country still have not been vaccinated. Dysentery is common and cholera and leprosy are found in some areas. The conquest of these diseases and others depends on an integrated program of improved sanitation, more education and better medical facilities.

A result of the improving health conditions and the Muslim belief in large families is a rapidly exploding population. Pakistan now has one hundred million people and the increase next year will be about 2.8 million. Although the Pakistan national income is increasing substantially, the per capita income and standard of living are increasing slowly because of the population growth. One Pakistan official described the situation by quoting from "Through the Looking Glass" by Lewis Carroll, "You see it takes all the running we can do to keep in the same place."

For this reason family planning is essential in Pakistan and the Government has started hundreds of family planning clinics in recent years. Signs to promote family planning are put up in the big cities like Karachi and Lahore and posters are put up in rural areas. These often show a wealthy small family and a poor large family. Unfortunately many rural Pakistanis do not notice the economic status of the families on the signs, but instead show sympathy for the members of the small family because there are not more children. The Muslim people of Pakistan are proud of their big families and for some farmers children are an economic necessity. To be successful, family planning, like other social reform, must proceed hand in hand with a higher standard of living and more education.

Many health problems were created in Pakistan by the large influx of more than six million refugees from India after partition. Today thousands more are flocking



to the cities to look for work in industry and are housed in small crowded dwellings with no water supply, sewage, or electricity. The Government has done some valuable work in resettlement but the problem is large. Korangi Colony is one settlement area just outside Karachi where hundreds of thousands of refugees who formerly lived in filthy huts are now accommodated in small clean dwellings.

One other problem which cannot be changed but which demands adjustment is the heat. For Canadians the summer warmth of Pakistan is almost unbelievable. Daytime temperatures on the inner plains of West Pakistan often reach 120 degrees with a night range of 85 to 90

degrees. For those not used to such a climate it is difficult to maintain salt balance, and any exertion becomes a major effort. Pakistanis dislike the heat also and as a result summer work is often not done. For them there is no escape to a summer cottage or an air-conditioned room and even water is scarce.

The medical problems in Pakistan remain serious but the progress in recent years has been impressive. The most urgent need is for some method to slow the rapid population growth. This problem is found in most of the developing countries of the world and must be solved if the people of these countries are to escape from poverty.

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## Genetic Studies in Duchenne Muscular Dystrophy

KATHLEEN ARMITAGE, '66

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Muscular dystrophy is a progressive hereditary degenerative disease of skeletal muscle. Three major clinical types of this disease are recognized and each type has a specific mechanism of inheritance. The *facioscapulohumeral* or adult type is inherited as an autosomal dominant trait, the *limb-girdle* type is autosomal recessive and the *pseudohypertrophic* or *Duchenne* type is inherited by a sex-linked recessive mechanism. Only the latter type was selected for investigation in this study.

A typical case of Duchenne muscular dystrophy is that of a boy who was probably late in starting to walk and at the age of three years has difficulty in running and climbing stairs. He has a peculiar "waddling" gait and an equally characteristic manner of rising to his feet from the prone position. By the age of about seven this boy will likely be unable to walk and will be confined to a wheelchair. Progressive atrophy continues with involvement of the muscles in the shoul-

der and upper arm region. There is no pain and the patient is usually quite alert mentally. Eventually contractures, progressive muscle wasting and scoliosis lead to confinement in bed. Wasting of the intercostal and other muscles reduces the ability to withstand respiratory infections and death usually occurs in the late 'teens. Variations from the typical case include late onset and slow progression. This is exemplified by one atypical patient studied who was 60 years of age.

The purpose of the study was two-fold. The first phase would assemble detailed and complete family histories of the patients with Duchenne muscular dystrophy in Southwestern Ontario. These histories were to be assembled by standard genetical procedure including personal interview with relatives and checking clinical histories and hospital records. The second phase of the study would include

*Continued on Page 109*



# Medicine in Australia

JAMES D. CURTIS, '64

Australia is comparable to Canada in that there is a small population in a large country but the medical problems are interestingly different. Some knowledge of the geography, climate and population of Australia may be helpful in understanding this difference. Of the 10½ million people inhabiting Australia, the main concentration is found in cities on the eastern coastal strip. The remaining four-fifths of the country is, for the most part, sparsely settled. This comprises the vast, dry and hot "Outback" where the land varies from absolute desert to semi-arid sheep and cattle raising territory. Of further note is that the northern one-third lies north of the tropic of Capricorn.

## NATIONAL HEALTH SCHEME

Perhaps of greatest interest to Canadians at the present time is the Australian National Health Scheme described by Dr. Patrick Bruce-Lockhart as the best in the world. The scheme, instituted 1950-53, is based on voluntary health insurance operated by non-profit-making insurance organizations which are subsidized by the government. To be accepted by the state for registration, the benefits and regulations of the companies must conform to a predetermined pattern. To remain solvent, administration costs must be minimized. The benefits and services provided are the Pensioner Medical Service, the Hospital Benefits Scheme, Pharmaceutical Benefits, and the Medical Benefits Scheme.

### 1. Pensioner Medical Service

General medical care and drugs are provided free to recipients of a disability, widow's, or ex-serviceman's pension (and their dependents) who qualify under a special means test. This scheme allows only general practitioner care but the pensioner (or his dependents) has complete freedom of choice of doctor. Practitioners are reimbursed for about 60% of the current private fees, on a fee-for-service basis,

by the government on presentation of a voucher. Exclusion of a third party preserves the doctor-patient relationship.

This plan has provided pensioners with complete medical care coverage since this group is entitled to free treatment in public hospitals. In addition, the pensioner can own his own home, earn a small income, and receive his pension.

### 2. Hospital Benefits Scheme

One hundred and fourteen non-profit health insurance organizations subsidized by the government operate the scheme. Every hospital patient has \$1.00 per day paid by the government and an additional 50 cents per day is paid for insured patients. The scheme further encourages voluntary insurance by paying an additional \$1.40 per day if the person is insured for a Fund benefit of \$2.00 or over.

For a premium of 6—30c per week for single persons and 12—60c per week for families, contributors receive \$5.25 to \$9.60 per day. The average daily cost of a bed is about \$13.30, but public ward beds cost only about \$6.75 per day. Thus, patients can meet all hospital charges provided they pay a suitable premium (family payment of 36c per week). The vast majority are insured for the higher benefit ranges. Seventy-three per cent of the population is enrolled in a hospital insurance organization.

The Commonwealth government also pays \$4.30 for each hospital day in the case of pensioners who are treated in public hospitals.

'Special Accounts' has been instituted to enable the voluntary insurance organizations to cover those with chronic disease or pre-existing ailments. Contributors to the special account, including everyone over 65 years, pay no more than the ordinary premium. The organization pays a standard benefit of \$4.30 per day for these



people. If an insurance Fund's special account loses money over the year the government meets the deficit. Furthermore, nursing and convalescent homes, where care is long term, are given \$2.40 per day per patient.

On the whole there seems to be little to complain about in this thoughtfully devised scheme.

### 3. Pharmaceutical Benefits

Most drugs are free of cost but a 60c dispensing fee is charged on each prescription to everyone except pensioners and their dependents. To curb expenses, a few of the more expensive drugs, including the more important antibiotics, are provided only for the treatment of specified diseases. There are also some limitations on the quantity of any one drug prescribed. A 33% margin of profit on the wholesale prices is allowed the pharmacists. The total cost to the government in 1961-62 was \$84,000,000, admittedly high.

### 4. Medical Benefits Scheme

Eighty-three non-profit, voluntary health insurance organizations supported by government subsidy run the scheme. Recipients and suppliers of medical services are completely free agents and the government neither possesses nor exercises any controlling or coercive powers. The organization must pay as a benefit to its contributors an amount not less than the Commonwealth subsidy.

The premium varies as the scale of benefit desired but the average contribution is 15-25c weekly for single persons and 30-50c weekly for families. The patient pays the fee and, on sending in his claim, receives a partial rebate. The average rebate is about 60% but for the commonest services, that is, those of a general practitioner, about 80% is rebated. In order to preserve the proper doctor-patient relationship, at least 10% must be paid by the patient. Of the 64% average rebate the insurance companies pay 37% and the Commonwealth government 27%.

The doctor is free to charge whatever he likes according to the value of his services and the patient's ability to pay. There is, however, a usual professional fee. The amount of the benefit varies with the type of professional service or procedure but for any particular procedure the rebate is the same, regardless of the fee the doctor charges or whether the doctor is a general practitioner or specialist. Thus, although the scheme attempts to restore "the position, prestige, and fullest usefulness of the general practitioner",<sup>4</sup> weakness lies in the fact that there is no restriction of payment for specialized work to specialists. There is, in fact, a good deal of specialized work done by non-specialists. In the remote areas, however, a general practitioner may be obliged to carry out specialist procedures. The specialist is protected by discouraging direct specialist consultation: the rebate is larger if the consultation is referred by a general practitioner.

Thus, the scheme allows the physician great freedom and provides incentive. He can charge whatever he likes and treat whoever he wants. The harder he works, the greater the material gain. Exploitation of the system is prevented by professional conscience and by the fact that it is in the interests of both the doctor and the people to protect the basic principles and economic integrity.

In 1961, 72% of the population was covered for medical benefits. Of the remaining 27%, pensioners and ex-servicemen constitute 14%.

### HOSPITAL SYSTEM

There is an approximately equal number of public and private hospitals in Australia. The public hospitals are financed by the state government. They accommodate mostly public ward patients who receive all professional medical care absolutely free. About half of all hospital accommodation in Australia is of the public ward type. Except in Queensland



where public ward accommodation is free, general hospital accommodation is not provided by the government. Admission is free if there is real hardship. Admission to public wards in all states except Queensland and Tasmania is dependent on a liberal means test. As well as public and private beds intermediate beds are provided. These are partly subsidized by the state but much less so than public beds and the patient pays the full amount of the doctor's fee.

Most of the private hospitals are smaller and are owned and operated by religious orders. All beds are private and most doctors can admit and treat in these although general practitioners are beginning to find themselves excluded from larger hospitals. In general, these hospitals are more efficient and operate more economically than the public hospitals.

The scattered population in most of Australia has necessitated the establishment of many small hospitals usually administered by local practitioners, one of whom may receive a salary as part-time superintendent. In the eastern states, many of the small hospitals are attached to larger base hospitals which are virtually state hospitals. The medical superintendent and several of the senior staff may be salaried.

In state-subsidized hospitals, including teaching hospitals, in suburban community hospitals, an honorary system has been developed whereby the most experienced and best trained doctors treat public ward patients free of charge. Public hospitals are staffed by interns, residents, and salaried full-time specialists, as well as the honorary physicians. In smaller centres, senior general practitioners may be on the honorary staff. In Queensland, however, both large metropolitan public hospitals and base hospitals in the larger rural towns have salaried medical staff but much of the clinical work is done by a visiting consultant staff. These hospitals are closed and local general practitioners have only limited access.

## MEDICAL EDUCATION

Of the seven medical schools in Australia, I am qualified to say something about only one, the University of Sydney, but this may be considered fairly representative. Entry into medical school is made immediately after high school upon attainment of satisfactory grades. The medical course is six years. The subjects in first year are comparable to those of Western's first year pre-medicine, although English is not compulsory. The next five years are comparable to our four year course in subject material. Good students are encouraged to indulge in a year's research after either third or fourth year and obtain a Bachelor of Science (Medical). Probably due to the large number of patients available for teaching, there are fewer lectures and more clinics, tutorials, case workups and presentations.

With respect to fees, the total cost for the six years is only about \$2200, most of which is paid for by Commonwealth Scholarships held by most students. These students are also eligible for a sizable living allowance, payable subject to a means test. This commendable situation alleviates most of the financial distress experienced by medical students.

The university professors are heads of the corresponding services in the teaching hospitals. Each is assisted by four to eight paid staff and a host of honorary physicians. The honorary physicians are responsible for most of the teaching. These prominent specialists teach students on their own (assigned or referred) patients in the public teaching hospitals. The teaching and the treating of public patients is said to be repaid them by the honor and reputation they acquire by being an honorary physician to the hospital. In my experience, the quality of teaching and the enthusiasm is high. One thing of particular note is that interns and residents aid in teaching by conducting ward rounds and tutorials after hours. This proved an excellent way for both student and teacher to enhance his knowledge.



At Sydney, there are four general teaching hospitals having 400, 450, 640 and 800 staff patients. Two more general teaching hospitals will be available soon. As well, there is a children's hospital of about 500 beds, and two obstetrics hospitals. Some obstetrics is also taught at the general hospitals. Most hospitals have large out-patient sections. These are all public hospitals and any patient may be used for teaching.

Upon graduation, a year of rotating internship must be spent before practicing. As everywhere, there is a definite shortage of general practitioners. Graduates intending to specialize in the past have always done their post-graduate work and membership or fellowship in Britain. Recently, however, there has been a greater tendency to do fellowship work in Australia. Relatively few graduates go to America for fellowship work although the American literature is widely read.

Research is of a high standard and voluminous for such a small population. Of the many notables in this field, Sir MacFarlane Burnet and Sir John Eccles head the list. Australian medical journals are widely read and highly thought of in other countries.

#### ROYAL FLYING DOCTOR SERVICE

In my mind, the most fascinating aspect of medicine in Australia is the Royal Flying Doctor Service. I was extremely fortunate to spend a week with Dr. A. G. Walker, the Flying Doctor at Broken Hill, New South Wales. Firstly, a further word is in order about the Outback, the area served by the Flying Doctor. This is a roughly defined area comprising the dry, sparsely settled area of Australia. In the better grazing areas are found the great Australian sheep flocks. The land at best being poor due to lack of rainfall, each sheep may require 1-15 acres to survive. Accordingly the sheep stations (ranches) are huge, varying in size from 40,000

acres to 10,000 square miles in the more arid parts. Thus the population is very sparse. Each homestead is separated by 10-15 or more miles and may be hundreds of miles from supplies and medical aid.

The history of the foundation of the Royal Flying Doctor Service is well known to all Australians. In 1912, Reverend John Flynn was appointed the first superintendent of the Australian Inland Mission. Struck with the extreme isolation, tremendous difficulties in communication, the frightening problems in illness, accidents and childbirth and the many heroic treks, often in vain, for medical aid, he soon became convinced that a combination of the airplane and radio communication was the answer. Suitable airplanes became available in the early 1920's and in 1927 Alfred Traeger devised a suitable radio. In May, 1928 the first Flying Doctor base was established at Cloncurry in northern Queensland. Soon more were developed and there are now fourteen bases from which the air-borne doctors serve the inhabitants of two-thirds of Australia.

Now, most of the 600 homesteads in the 150,000 square miles served by the Flying Doctor at Broken Hill have airstrips near the homestead where the Flying Doctor can land, and radio transceiver sets with which the settlers can communicate with the Flying Doctor or with other settlers. The radio is of inestimable value as a medium of social intercourse over vast distances and they provide great security and comfort to these hardy, courageous and independent souls who form the core of the Australian national character.

Each year over 650,000 miles are flown, 10,000 calls are taken, many thousands of patients seen, and over 1200 flown to hospital by the Flying Doctors in Australia. The annual cost of operation is over \$650,000, which is raised through voluntary contributions from patients, funds from events organized by local people, public donations and legacies, and Federal



and State grants and subsidies. An active telegram service (260,000 telegrams in 1961) provides additional income.

In order to illustrate the work of the Flying Doctor Service, I shall attempt to describe a typical two-day clinic visit which I made with the Flying Doctor. These routine monthly or bimonthly visits are made to isolated communities. Some of these have small Bush Nursing Service hospitals or stations operated by nursing sisters. With a ready means of communication one can admit, treat, and discharge patients, making a final check on them on the next routine visit. Other of the communities have no local medical service of any kind.

After embarking at 7:00 A.M. we headed north over the vast expanse of red soil broken by the occasional tree-lined, dry creek bed and the very occasional homestead with its several buildings. The aircraft are either owned by the Royal Flying Doctor Service itself and flown by its pilots or operated under charter by commercial pilots. The airplane at Broken Hill is a three-engine Drovler but Cessnas, Piper Cubs, etc., are used also. The craft has six seats and a stretcher, and, of course, a two-way radio.

Each day at 8:00 A.M. and 4:00 P.M., wherever he may be, the Flying Doctor gives medical advice by radio to anyone who calls in. Thus, at 8:00 A.M. while airborne about eight people called with complaints such as bronchitis, an infant feeding problem, an infected hand, etc. Drugs are prescribed according to their number in a standard Royal Flying Doctor Service home medicine chest kept at each homestead. The difficulty of diagnosing and treating an illness without seeing the patient should be appreciated; however, the callers become expert in presenting the details of the ailment or injury for which they seek help.

At about 9:00 A.M. we set down at a homestead airstrip, a path cleared of scrub and surrounded by red flatness. A fam-

ily, which had driven from the homestead, a distance of about four miles, met us at the airstrip. Dr. Walker examined a man with a large carbuncle on his neck and prescribed further treatment. We had tea and cake and were off again.

The next stop was Wanaaring, a small hamlet in the middle of nowhere, 220 miles from Broken Hill. We were met by a member of the police force, the backbone of the Outback, who transported us in his Land Rover to the bush nursing station in the town. This is a three-bed hospital manned by one nursing sister. Here, Dr. Walker gave several immunizations, gave antenatal advice, examined patients with healing wounds and treated a menstrual disorder. Patients came from a radius of 50-60 miles or more over poorly defined and sometimes non-existent roads, through the sparsely vegetated expanse of the Outback. In Wanaaring, I had the opportunity to see the appalling conditions under which the aboriginals live.

After lunch, we headed for Hungerford in Queensland, just across the border. About twenty patients were seen in the community hall for the same type of thing as at Wanaaring.

The next stop was Tibooburra. This was the destination of an old aboriginal, blind from trachoma, who was being returned to his home from Broken Hill where he had been treated for a cerebral vascular accident. At Tibooburra, there is a fifteen-bed bush nursing hospital with three nursing sisters. They are to be highly commended for their dedication, courage, skill and responsibility. Dr. Walker saw several cases before dark.

After dinner at the Hospital, I spent a thrilling evening with Dr. Walker and the district policeman shooting kangaroos. The famous Australian kangaroo is plentiful and is a pest—he eats the sparse, and therefore valuable, grass and destroys fences. The animal is spotted with and attracted by a searchlight on a Land Rover. They are easy game for a .243 caliber



rifle with telescopic sights. The Flying Doctor's dog enjoys the meat. Others shoot "roos" for the skin and others for the tail which is used to make kangaroo tail soup.

In the morning, fifteen more patients were seen. After dinner we left Tiboo-burra and reached Broken Hill, 120 miles away, about 5:00 P.M., passing over some of the famous salt lakes on the return.

Most of the time is spent making such routine flights to small isolated communities and the Flying Doctor is virtually a flying general practitioner. However, at any time, he may be called upon to make a dramatic emergency flight to a gravely ill or injured patient at a homestead. These patients are either treated there or they may be transferred to the base hospital at Broken Hill. Unfortunately for the Flying Doctor, he is not allowed to treat these patients at the base hospital because of the uncertain nature of his employment. Thus, in this respect he has become somewhat of a flying ambulance man.

Obstetrical cases are electively taken to the Broken Hill hospital by road within a safe time of the expected date of delivery but, needless to say, some are delivered by bush nursing sisters or the Flying Doctor in emergency situations.

Part of Australia is tropical and therefore the Flying Doctors must deal with diseases unfamiliar to us, e.g. malaria, trachoma, hookworm, yaws, leprosy, ulcerating granulomas, and bacillary dysentery.

During off hours when the radio base is not operating, a patient may reach the Flying Doctor in an emergency by blowing a whistle into the microphone. This trips a switch, a bell rings, and the Flying Doctor is notified.

In 1951, the first School of the Air was established at Alice Springs utilizing the Royal Flying Doctor Service two-way radio communication network. Several more have been established since. Teaching is done from a modern class-room studio in Broken Hill by four teachers, three of whom are part-time. The School operates for 2½ hours each week day. Every effort is made to simulate the education other children receive. Each student is enrolled in a state correspondence school which provides further educational opportunities. At Broken Hill there are 173 students from 90 station homesteads scattered over about 150,000 square miles.

Thus, the Royal Flying Doctor Service has solved the medical problems of the Outback and thereby greatly increased security. It has also enabled the people to live more conventional lives by enabling inter-communication and education to be carried on.

## CONCLUSION

Australia is a large and promising country and Australians are justly proud of it. The geography and the nature of Australians themselves account, in the most part, for the interesting features of the medical spectrum.

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# The Medical Management of Uncomplicated Peptic Ulcer

D. JAMES HENDERSON, '64

The management of the peptic ulcer patient should be directed toward three objectives:

- (1) relief of acute symptoms — pain and distress
- (2) healing of the mucosal lesion
- (3) prevention of recurrences and complications

The following account will deal with the *medical* management of *uncomplicated* peptic ulcer. It is proposed to present first a reasonable plan of treatment for a patient suffering an acute attack of ulcer pain then to discuss briefly the rationale of this plan of therapy, and finally to outline briefly the factors influencing prognosis of such a patient. Reference will be made to controlled study evaluation of certain specific aspects of ulcer treatment.

Approximately five to ten percent of all persons eventually develop a duodenal or gastric ulcer.<sup>8</sup> It is likely that problems of medical and surgical management will continue to vex the medical profession until the etiology of peptic ulcer can be more precisely pinpointed, nevertheless there would seem to be little to substantiate a philosophy of therapeutic nihilism which holds that peptic ulcer pursues an independent course uninfluenced by environmental changes or known treatment. Prompt and effective management of peptic ulcer is important.

## A PLAN OF THERAPY

Medical management is effective in relieving pain promptly and in healing the ulcer within three weeks to three months

in a large proportion of peptic ulcer patients. However peptic ulcer is a potentially chronic relapsing disease. While many ulcers heal completely without relapse, many continue to plague the afflicted victim for many years. Furthermore, the well-known complications of hemorrhage, perforation, penetration, and obstruction may develop at any time.

Accordingly, treatment has two phases: first, the active period of treatment for about ten weeks; second, the interim management during the asymptomatic period.

There is no one satisfactory regimen—the accompanying plan is a working method of treatment based on a consensus of authorities which may be adapted to suit the needs of the individual patient.

## DISCUSSION OF THE RATIONALE OF THERAPY

### A—Philosophy and Approach

A peptic ulcer occurs when localized areas of the gastro-intestinal mucosa fail to withstand the digestive action of hydrochloric acid and pepsin present in the gastric juice. Hypersecretion seems to be the major factor in *duodenal* ulcer; decreased mucosal resistance may predominate in *gastric* ulcer. But while tissue vulnerability is an important variable influencing individual susceptibility, the presence of hydrochloric acid is mandatory to the development of all benign peptic ulcers, whether esophageal, gastric, duodenal iatrogenic, or whatever.

There appear to be four outstanding trends in therapy in addition to the time-



## A PLAN OF THERAPY FOR UNCOMPLICATED PEPTIC ULCER

ACTIVE TREATMENT  
(about 10 weeks)

## FOLLOW-UP CARE

Philosophy and Approach	prompt and effective institution of a planned program of therapy designed to relieve the patient's distress and promote healing of the ulcer	education concerning the nature of the disease, the tendency to recurrences, the possibility of complications, and the factors likely to predispose to exacerbation
Physical and Psychological Well-Being	in cases resistant to therapy, bedrest with bathroom privileges for about ten to fourteen days may be indicated. sedation of choice—phenobarbitone is satisfactory avoidance of business contacts and professional responsibilities	eight hours sleep or more every night encouragement to retire by 10:00 P.M. and to obtain an additional one half day rest in bed each week during seasons of usual exacerbation friendly yet objective discussion of emotional problems and sources of anxiety
Diet	<i>acute distress:</i> 8 ounces of milk or cream every hour on the hour with antacids every hour on the half hour <i>moderate distress:</i> two-hourly small bland feedings <i>mild distress:</i> full diet with 8 ounces of milk or cream at 10:30 A.M., 3:00 P.M., and before retiring (avoid spicy and greasy foods, and chemical irritants)	<i>stress regularity of eating</i> three regular meals a day with a glass of milk midmorning, midafternoon, and at bedtime avoidance of foods known to cause difficulty: spices, greasy foods, and chemical irritants such as mustard and vinegar
Antacids	<i>acute distress:</i> adequate antacid therapy, preferably as oral liquid suspension, administered every hour on the half hour <i>moderate or mild distress:</i> hourly administration of antacid of choice <i>during sleep:</i> antacid administered one hour before discomfort usually experienced	discontinue antacid therapy except in hypersecretor patients, patients experiencing frequent exacerbation, and patients with a history of chronic ulcer
Parasympatholytics	increase dose to obtain xerostomia or difficulty in micturition, then slightly reduce administer before meals and at bedtime as adjuncts to antacid therapy	
Habits	Irritant substances, such as nicotine, are carried to the stomach in the saliva. Smoking should be avoided if possible, otherwise restricted to 2 pipes or 10 cigarettes a day after meals and with antacids. Alcohol and caffeine should be eliminated or restricted.	
Drugs	Aspirin, chloral hydrate, phenylbutazone, steroids, and other ulcerogenic drugs should be prescribed only when strongly indicated and with hourly antacid medication.	



honored standard regimen:<sup>8</sup> (1) the rejection of all forms of treatment based upon the philosophy that peptic ulcer pursues a course independent of treatment; (2) therapeutic liberalism, emphasizing the lack of objective evidence for the value of diet and antacids; (3) the psychiatric concept of etiology, attributing successful medical therapy to subtle psychogenic influences of the physician; (4) the organic concept stressing healing substances, protective tissue factors, hormones, and a variety of tissue extracts. Accordingly, it is not surprising that some confusion and uncertainty exist with regard to the management of peptic ulcer.

A proper medical regimen, however, continues to emphasize protection of the gastro-intestinal mucosa from the digestive action of acid-pepsin gastric juice. Unfortunately, satisfactory methods for directly increasing tissue resistance without altering gastric secretion have not been established. Therapy is therefore directed towards reducing the digestive action of the stomach contents, and controlling certain empirically determined variables which have been thought to bring about exacerbation and remission in the disease process.

#### **B—Physical and Psychological Well-Being**

The common denominator to many of the rather vaguely defined psychogenic factors which have been implicated in the pathogenesis of peptic ulcer is conscious or subconscious anxiety. A detailed psychiatric evaluation of every ulcer patient is neither feasible nor desirable, yet an attempt can and should be made to give the patient some insight into this aspect of his disease. A friendly yet objective discussion of any sources of anxiety in the patient's emotional life should not be omitted.

During the acute phase, mental and physical rest are two important aspects of management. Avoidance of business and professional contacts, including telephone calls, should be advised. Regarding bed-

rest, ten to fourteen days usually suffices; in chronic cases, four to six weeks may be advisable.

During remission, the patient should be advised to indulge in at least eight hours sleep a night, to stay in bed an additional half day a week during the seasons when he is prone to relapse, to enjoy leisurely meals uninterrupted by phone calls, and to avoid heavy exercise. A winter holiday in a warm climate should be encouraged.

These points should be brought before the patient in a frank, firm, and thorough fashion. The casual and thoughtless advice to "take it easy and get lots of rest" is to be avoided. However, drastic alteration in living habit and changes of employment are very rarely indicated.

#### **C—Diet**

Controlled studies tend to de-emphasize the role of diet in the management of ulcer. Certainly there is little good evidence that a bland diet *per se* is curative; in fact, it may well be that the only rationale for diet therapy lies in the tendency of food in the stomach to neutralize gastric acidity. Generally, modifications of diet during active treatment aim to maintain good nutrition and to avoid foods directly irritating to the ulcer.

The dietary regimen will, of course, vary with the patient's symptoms. The patient with moderate to severe distress will likely tolerate best two-hourly small bland feedings of such foods as custards, junkets, porridge, bread and butter, peanut butter, honey, fruit juices, bananas, fish, and puree of spinach. Persistent pain may call for the more restrictive regime of hourly feedings of milk and cream. Patients with mild distress do quite well on full diet with eight ounces of milk or cream mid-morning, mid-afternoon, and before retiring. Greasy and spicy foods and those known to aggravate pain should, of course, be avoided. In the asymptomatic period, it is regularity of eating rather than the diet itself which is most important.



## Uncomplicated Peptic Ulcer

It is interesting to refer to studies which have attempted to substantiate the role of diet in therapy. Rider and Moeller<sup>14</sup> studied a group of 116 patients who had previously responded inadequately to ulcer regimen. The patients were given adequate antacid therapy and assigned in a random fashion to a highly restrictive dietary regimen, or to one closely paralleling the regular hospital diet. The clinical results of their study were evaluated as excellent, good, fair, or poor; a patient was considered to have had an 'excellent' response if his symptoms were completely controlled within two or three days with no recurrences during the remainder of treatment. A 'good' response consisted of the relief of symptoms within two weeks and occasional recurrences during the duration of treatment. It was found by these investigators that the more restrictive regimen produced the greater number of 'excellent' results, while the non-restrictive regimen produced, for the most part, 'good' results. The more restrictive regimen, however, was associated with a five times higher incidence of side effects (chiefly constipation) and a higher patient drop-out rate. Statistical analysis indicated that there was no significant difference between the two forms of treatment. The authors conclude that a bland diet is probably indicated during an acute exacerbation of peptic ulcer, but plays little role in the prevention of recurrences or in the long-term management of ulcer patients.

### D—Antacids

The traditional method of administering antacids three or four times a day is practically useless since they are swept out of the stomach well within an hour.<sup>6</sup> Since emptying usually occurs within forty-five minutes, hourly administration of antacid is essential for effective neutralization. Ideally, the gastric content should be maintained at pH 4.0 to 5.0 or higher: at this pH, acid and peptic activity are practically nil. (Actually peptic ulcer has been shown to heal with less complete control). There are several hundred commercially avail-

able antacids. The multiplicity of preparations suggests that no one product is definitely superior to another, and in fact there is probably little to choose among many of them.

Oral liquid or powder forms (such as Amphojel, Gelusil, and Maalox) are generally more effective than tablets for the relief of acute ulcer pain. A number of commercial antacids incorporate various combinations of aluminum and magnesium hydroxide gels, magnesium oxide, calcium carbonate, magnesium carbonate, magnesium trisilicate, and dihydroxyaluminum aminoacetate. The addition of non-fat milk solids has been claimed to increase the duration of action of the preparation,<sup>3</sup> however this claim has been difficult to substantiate.

The principle advantage of the *tablet* form of antacid medication is its convenience. Commonly encountered examples include Gelusil, Maalox, Nulacin, Prodexin, Tums, and many others. Two tablets every hour of a good antacid preparation will usually maintain the gastric contents at a pH of 4 to 7, occasionally as high as 9. Rather well-controlled studies have been made of certain antacid tablets, and their efficacy well substantiated.<sup>6</sup>

Systemic antacids, such as sodium bicarbonate, should probably be avoided because of their tendency to produce alkalosis on continued administration.

An attempt to reduce the free acid in the stomach without producing excessive alkalinity within that organ has resulted in the manufacture of preparations which buffer at a lower pH than do the ordinary non-systemic antacids, since they reduce the *free* acid only. The total acid may actually increase. Examples include Prodexin, Riopan, and many others.

Continuous antacid administration through an intragastric tube is occasionally indicated for patients with gastric hypersecretion and severe pain not responding to ordinary measures. The drip



may be maintained for the twelve hour night period, or it may be administered continuously for several days. Milk and cream, alkali, and food supplements may all be given by this route. A satisfactory regimen for a patient suffering from a severe relapse in 3 liters of milk in twenty-four hours by continuous intragastric drip and antacid suspension at the bedside to be taken if and when pain occurs. Drugs, other than sedatives, are unnecessary, and a light diet may be taken in addition (with the tube in situ) if the patient so desires. This is perhaps the quickest way of controlling ulcer pain.<sup>9</sup>

Patients on any antacid regimen who suffer from nocturnal pain should be awakened by alarm clock one hour prior to the usual onset of pain, and should receive medication at that time. Antacid therapy should continue for from three weeks to three months after the patient is felt to be clinically well, even though the symptoms have abated earlier.<sup>8</sup>

#### E — Parasympatholytics

The purpose of anticholinergic therapy is threefold: to retard gastric emptying and thus to enable more prolonged neutralization of the stomach contents; to reduce gastric motility and ease pain due to spasm; and to inhibit the vagal stimulation of acid secretion. Conclusive evidence of inhibition of secretion by anticholinergic medication is not abundant. These agents should *not* be used as sole therapy—they do *not* produce a true "medical vagotomy".

The ideal gastric antisecretory compound depresses acid and pepsin secretion for long periods after oral ingestion without the development of tolerance, and without causing troublesome side-effects. Such a drug remains to be synthesized. Tincture or powdered extract of belladonna in average doses does not inhibit acid secretion significantly. Atropine sulphate, 0.5 mgm orally three or four times a day is partially inhibitory; the same dose intramuscularly is more effective. Synthetic

atropine substitutes (amprotopine, homatropine, adiphenine) are generally less effective than atropine; methantheline bromide ("Banthine") and diphemanil methylsulphate are slightly superior to atropine.<sup>2</sup> Anticholinergic drugs are more effective when given intramuscularly than orally.

There is some clinical evidence to support the use of anticholinergic, antisecretory drugs as *adjuncts* to the management of peptic ulcer. Darbid (isopropamide iodide), Piptal (N-ethyl-piperidyl-benzilate methobromide), Nacton (poldine methyl methosulphate), and many others have received favorable reports.<sup>5,6</sup> An anticholinergic drug chosen for this purpose should not inhibit protective alkaline gastric secretions nor produce other undesirable side effects in therapeutic doses. A good antisecretory agent may reduce the total amount of gastric hydrochloric acid by up to 60 percent.<sup>6</sup>

It has been customary to increase the dose of the anticholinergic drug until some side effects are noted (usually xerostomia or difficulty in micturition), then to decrease the dose slightly to give a satisfactory therapeutic level. Some of the newer preparations, however, have been claimed to be effective antisecretory drugs at doses well below that required to produce these side effects.

The use of anticholinergics at bedtime (as basal conditions are approached) seems most reasonable. Their administration before meals may also cause a decrease in acid output extending through the digestive phase of gastric secretion.

The most common side effects of anticholinergic medication include xerostomia (dry mouth), blurred vision, urinary retention, constipation, headache, and impotence. These drugs are contraindicated in the presence of cardiospasm, pyloric obstruction, incipient glaucoma, and prostatic hypertrophy.



## —Uncomplicated Peptic Ulcer—

### F—Alcohol, Tobacco, and Caffeine

It is altogether likely that nicotine, alcohol, and perhaps caffeine have a more or less direct adverse effect upon peptic ulcer.

One need only observe the stubborn refusal of the human animal to relinquish these psychological and physiological crutches (even when faced with overwhelming evidence of their harmfulness) to appreciate how truly dependent upon them certain of us have become. The physician must weigh in his own mind the harmfulness of these agents (so far as peptic ulcer is concerned) against the harmfulness of the psychological unrest induced by their withdrawal. Nevertheless, probably no patient should be referred for surgery of uncomplicated peptic ulcer who still smokes or drinks, or who consumes inordinate amounts of caffeine on an empty stomach.

### G—Other Factors in Therapy

The multiplicity of ulcer medications based upon a wide variety of concepts (some quite ill-founded) defy listing, let alone discussion.

Gastric freezing and gastric hypothermia are currently receiving much attention—their effect is to diminish for variable periods of time the gastric output of hydrochloric acid and pepsin. These approaches are highly experimental.

A number of agents are claimed to increase the resistance of the gastro-intestinal mucosa to acid-pepsin gastric juices. Among these, carbamide, stilboestrol, and certain steroids have been given some study. This approach may prove fruitful in future years.

Radiation has been shown to cause inhibition of gastric secretion for up to 18 months. The usual hazards of radiation must be considered. However, this method has been claimed to have some place in the treatment of psychotic patients, patients with hemophiliac disorders, and patients who are felt to be poor surgical

risks and who respond poorly to a comprehensive plan of medical management.

### FACTORS BEARING ON PROGNOSIS

Certain criteria may be used to evaluate the prognosis in a case of peptic ulcer.

The length of ulcer history is a most important factor: the prognosis worsens considerably from the third year onward. For a group of patients suffering from chronic gastric ulcer, the number of failures on a comprehensive plan of medical management in hospital increased by fifty percent if the history of ulcer exceeded two years in duration.<sup>7</sup>

A second important variable is ulcer size. In a certain study,<sup>7</sup> chronic gastric ulcers are graded radiologically as large, medium, and small, according to diameters of one inch, one-half inch, and one-quarter inch, respectively. The approximate failure rates on medical management were: for small ulcers, 50%; for medium ulcers, 60%; and for large ulcers, 80%. It is of interest that ulcer size showed little correlation with duration of history.

Sex and age are of some importance. A study of chronic ulcer cases on comprehensive medical management showed that about one-third of male patients responded well to treatment, as compared to about one-half of the women. Furthermore, the greater the patient's age, the worse the prognosis,<sup>7</sup> even discounting the tendency of older patients to have longer histories.

Interestingly enough, the presence or absence of a family history of peptic ulcer was not of significance in this particular study.

In summary, it is the large ulcer of greater than two years duration in a male patient over forty-five years of age which appears to offer the poorest prognosis on medical management.

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specific genetic studies on a small number of families selected for their appropriateness for such studies. These studies would involve measuring the activity of serum creatine phosphokinase in certain female relatives of the patients. This would be done in an effort to confirm the recent findings that heterozygous carriers of the gene can be frequently identified by this means. Another study of appropriate families would involve the measurement of genetic linkage between the locus for Duchenne muscular dystrophy, the loci for red green colorblindness and the Xg<sup>a</sup> blood group. All three loci are known to lie on the X chromosome and there is some evidence that the latter two lie on the short arm of this chromosome. The "map position" of the muscular dystrophy locus with respect to Xg<sup>a</sup> has not been established although preliminary reports suggest that these two loci are not closely linked.

During the summer of 1963 only the first phase of this study was completed—that is, the assembling of detailed family histories.

Forty families with known Duchenne muscular dystrophy patients were interviewed in the 9 counties comprising Southwestern Ontario. The total number of cases of the disease was 66. Thirty-three of these patients are alive at the present time. Twenty-four or 60% of the 40 families had only one case of the disease. Of the families where more than one case of the disease had occurred, 10 consisted of affected brothers only. The remainder of the patients with a positive family history had affected relatives who were maternal uncles, great uncles and cousins on the maternal side. This distribution of affected relatives is, of course, in agreement with a sex-linked recessive pattern of inheritance.

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# The Biochemical Basis of Genetics

DONALD T. WIGLE, '66

The present century has witnessed the tremendous development of two independent and important branches in biology: genetics and biochemistry. The geneticists, following the laws of heredity in large samples of a selected population, concluded that hereditary characters are controlled by genes which are localized in the chromosomes. On the other hand, the biochemists discovered the importance of the enzymes or biocatalysts in the continuous changes which take place in living cells or organisms.

Genes are specific, since every one of them ultimately controls the appearance of a distinct morphological character; but enzymes also are specific, since they only attack one given substance (substrate) or substances which are closely related to this substrate. In recent years it has become obvious to the geneticists and biochemists that they are facing the same fundamental problem: the control of specific protein synthesis. Beadle's "one gene-one enzyme" theory (1946) states that the synthesis of every enzyme is ultimately controlled by one given gene. The specificity of the gene is expressed in the production of a specific protein, the enzyme, which itself controls a specific chemical reaction. If a gene is absent from the chromosomes, the cell will never be able to synthesize the corresponding enzyme.

The "one gene-one enzyme" theory of Beadle's is fundamentally correct but is probably too restricted. Ingram (1956) has shown that a mutation of a single chromosomal gene can lead to a chemical change in a non-enzymatic protein, hemoglobin. People suffering from sickle-cell anemia have hemoglobin with one single

amino acid replaced by another. It may then be said that each specific protein is synthesized under the control of a given chromosomal gene.

The synthesis of proteins is not a nuclear but a cytoplasmic event: this suggests that there must be some intermediary between the chromosomal gene and the specific protein synthesized in the cytoplasm. Except for one isolated case in bacteria, all the evidence at present clearly shows that the control exerted by the chromosomes on the synthesis of specific proteins is an indirect one. The genes must release into the cytoplasm substances which carry the amount of "information" which is required for the synthesis of specific proteins.

Gene replication occurs with fantastic accuracy. This may be demonstrated by introducing a single bacterium into a tube of nutrient medium. Within several hours the tube will contain more than a billion bacteria, each with a set of genes which apart from very rare exceptions is identical to those of the original parent. Similar accuracy is present in the genetic replication of all organisms. How can such accuracy be possible? It is now known that the chromosomes bearing the genes of organisms as different as man, fish, plants, bacteria and viruses, contain deoxyribonucleic acid, or DNA, for short.

The discovery of DNA was made by the Swiss biochemist Friedrich Miescher. In 1869 he isolated a material which he called nuclein from the nuclei of pus cells. He also extracted nuclein from salmon sperm which are very favourable cells for investigation since almost half of their make-up is DNA. When it became clear



that nuclein was an acid another worker suggested that it be called nucleic acid. The work of Miescher and other chemists, notably Levene, showed that DNA is constructed from phosphate, a sugar called deoxyribose, and four nitrogenous bases. The four bases consist of two purines (adenine and guanine) and two pyrimidines (thymine and cytosine).

Base — sugar > Phosphate  
Base — sugar > Phosphate  
Base — sugar > Phosphate  
Base — sugar > Phosphate

The regular sequence of sugar and phosphate provides the backbone of the DNA molecule. For convenience, each group of a base, sugar and phosphate is called a nucleotide. DNA is therefore a polynucleotide or a type of polymer. The electron microscope shows DNA to be a long, rather stiff molecule.

Two biochemists, E. Chargoff of Columbia University and G. R. Wyatt of the Canadian Department of Agriculture, performed many very careful analyses of the relative amounts of the four bases which occurred in DNA isolated from different organisms. It had been assumed that the bases were usually present in equal amounts. Chargoff and Wyatt found that this was not the case but the proportions differed widely from one organism to another especially in different species. However, DNA from such widely different organisms as the pig, salmon, turtle, yeast, or viruses always contained equal amounts of guanine and cytosine and equal amounts of adenine and thymine. Thus all types of DNA contain equal amounts of purines and pyrimidines. These results suggested that the purines and pyrimidines occur in pairs, but the full significance of this fact was not appreciated at the time.

The first X-ray diffraction pictures of DNA were taken by W. T. Astbury and F. O. Bell at University College, London, in 1938. More extensive work was carried out later by M. H. F. Wilkins, Rosalind

Franklin and collaborators at King's College, London. By analysing these diffraction patterns information was obtained about the position of the regularly repeating units which occur in the molecular structure, and so about the position of individual atoms in the molecule. The X-ray diffraction pictures of DNA showed that the bases, which are flat molecules, were arranged perpendicular to the length of the chain. These flat bases were 3.4 Angstroms apart (1 Angstrom =  $10^{-10}$  metres) and a regularity existed in the molecular structure which repeated every 34 Angstroms along its length, that is every 10 bases. The most probable explanation for this was that the chain formed a helix which completed one turn every 34 Angstroms. The measured density of DNA suggested that either two or three such polynucleotide chains made up the DNA molecule.

This then was the knowledge of DNA structure at the beginning of 1953. There was some difficulty in fitting the purines and pyrimidines, which are of different size and shape, into a perfectly regular helical structure. A brilliant theory (hypothesis) was put forth by J. D. Watson and F. H. C. Crick at the Cavendish Laboratory in Cambridge. They said that the structure consisted of two DNA chains in which the sugar-phosphate backbones of these chains are wound in the form of a double helix around a common axis. The two chains are linked together by pairs of bases; the base pairs are held together by hydrogen bonds. By building accurate molecular models of their structure Watson and Crick were able to show that not any purine-pyrimidine pair could link together the two chains. Only two such pairs turned out to be possible; these were adenine with thymine and guanine with cytosine. The adenine-thymine and guanine-cytosine base pairs could, however, follow each other in any sequence along the DNA double chain.

The Watson-Crick model satisfied the main requirements for a DNA structure.



The structure and its dimensions all fitted in with the X-ray diffraction data. It incorporated the differently shaped purines and pyrimidines into a regular structure. Moreover, it explained the puzzling chemical data which had shown that in DNA from different origins, the amount of adenine equalled that of thymine and the amount of guanine equalled that of cytosine. The general impression of the structure is one of a spiral staircase in which the pairs of flat bases are the stairs and the sugar-phosphate backbones are the balustrades on either side.

The model was established by further X-ray diffraction patterns; Wilkins and his group at King's College utilized refined techniques and obtained much more detail on DNA. They showed that some modifications to the Watson-Crick model had to be made (such as decreasing the proposed diameter of the double helix) but it could be considered correct in all its essentials.

The Watson-Crick model is especially valuable in explaining the process of gene replication. Due to the specific base pairing between adenine-thymine and guanine-cytosine the DNA molecule is, in effect, a pair of templates each of which is the complement of the other. If the bases occur in any arbitrary sequence along one chain the sequence along the other is automatically determined. This suggests the scheme for DNA replication. Because of the way the two strands are wound together they can separate only by untwisting. Even in small organisms such as viruses the two strands are intertwined more than ten thousand times. A formidable amount of untwisting is therefore necessary before the two strands separate. Watson and Crick proposed a scheme in order to reduce this difficulty. The two strands do not at first separate completely. They begin to untwist at one end and the two new chains of DNA are synthesized along them as they separate. There is only a short section of the DNA chain that is single at any one time. In the cell at any one time there is a supply of the

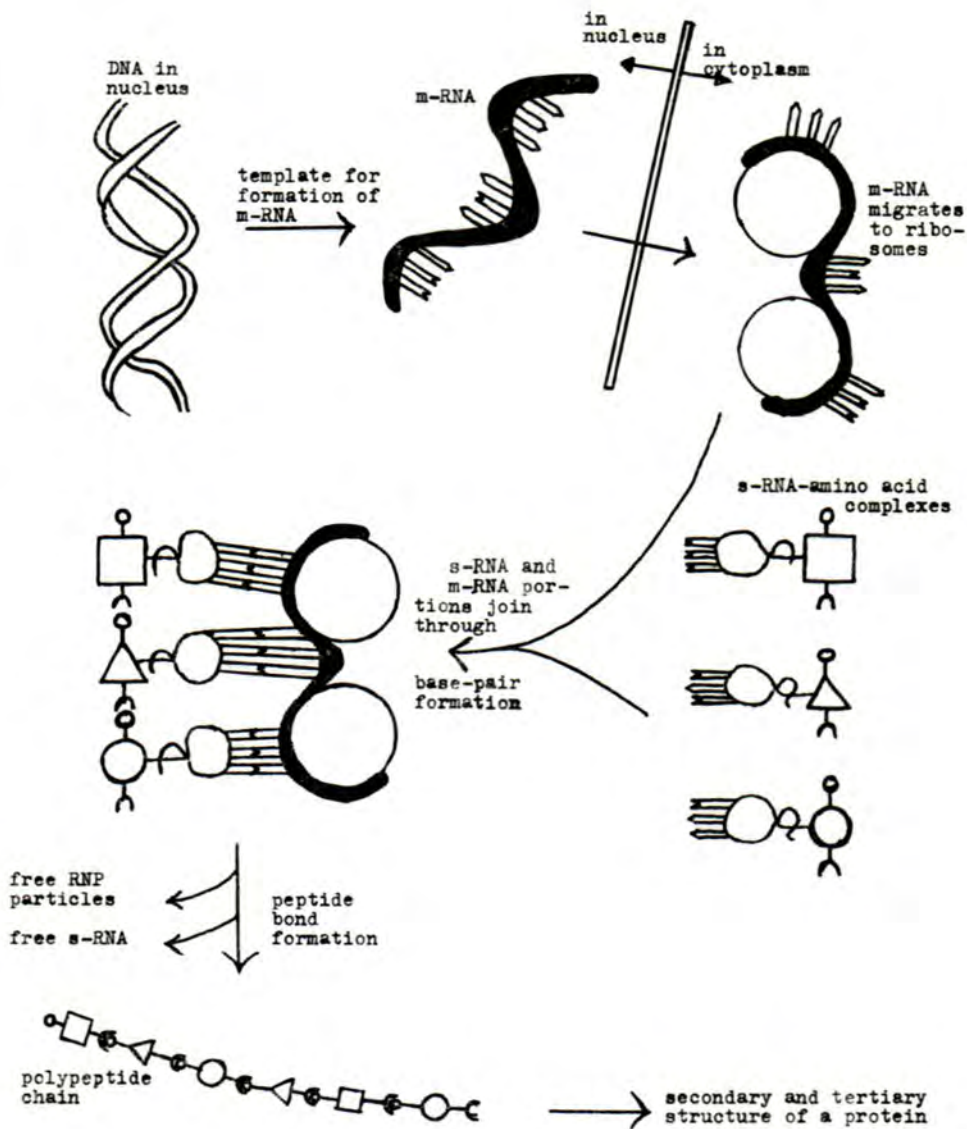
building blocks necessary to form DNA, possibly already synthesized into the four possible types of nucleotides. The base of one of these nucleotides will attach itself by hydrogen bonds to one of the bases on a single DNA chain. Soon another attaches by hydrogen bonds to the adjoining base on the chain. If these nucleotides are correctly paired to the chain they will be properly orientated for the sugar-phosphate bond to form between them. The only bases which will remain fixed are therefore those which pair correctly with the bases on the single chain. Thus a complete complementary chain of nucleotides is ultimately assembled and forms with the template chain a new molecule of double-stranded DNA which is identical to the original. A similar synthesis simultaneously occurs along the other single chain of the original molecule of DNA.

M. Meselson and F. W. Stahl at the California Institute of Technology have conducted experiments using nitrogen-15 tagged DNA to confirm this scheme of gene replication. Their work and that of others seems to confirm this scheme.

Kornberg has done in vitro experiments on the enzymatic synthesis of DNA. His conclusions were that, in order for synthesis of DNA to occur, all four nucleoside triphosphates, an enzyme called DNA-polymerase, and a DNA primer must be present. The DNA may be double or single stranded; the DNA is necessary as a template for the hydrogen-bonding. Without all four nucleoside triphosphates, synthesis stops for lack of a hydrogen-bonding mate for each base in the template. The DNA that is synthesized in such a system is complementary to the DNA used as a primer. These results are in excellent accordance with the Watson-Crick scheme.

The genes control the chemical processes that give each cell its specificity; this is because DNA contains information which directly or indirectly controls formation of enzymes. As the sugar-phosphate backbone is perfectly regular, the only variable







characteristic of the DNA structure is the sequence in which the base-pairs follow each other along the molecule.

Ribonucleic acid or RNA is chemically similar to DNA except that the sugar in RNA is ribose (DNA has deoxyribose) and RNA employs uracil instead of thymine. DNA is always found in the nucleus of the cell, RNA both in the nucleus and the cytoplasm outside the nucleus. Much less is known about the structure of RNA. There are indications that natural RNA consists of two chains but it gives poor X-ray diffraction pictures suggesting an irregular structure. RNA is found mainly in combination with protein in the ribosomes of the cell. These particles are believed to contain the templates on which specific proteins are modeled. Experiments with tobacco mosaic virus have shown that RNA alone, inoculated into a tobacco plant is capable of reproducing the virus. The infected plant manufactures a protein dictated by the RNA of the virus.

There are two types of RNA in the cell, messenger RNA (m-RNA) and soluble RNA (s-RNA). M-RNA is formed as the complement of RNA, in the nucleus, and then migrates to the cytoplasm where it attaches to the ribosomes. Thus m-RNA carries the genetic message from the nucleus to the site of protein synthesis in the cytoplasm. S-RNA, a low molecular weight polynucleotide takes amino acids from the cytoplasm to the ribosomes. There is a specific s-RNA for each amino acid. The four bases of DNA must be arranged in at least twenty permutations to code the twenty or more amino acids. Four bases taken two at a time gives sixteen permutations, three at a time gives sixty-four. Thus a sequence of three bases is required; however, an amino acid may occasionally be coded by two bases. Also, one amino acid may be coded by more than one triplet i.e. the code may be degenerate. The weight of evidence suggests that the code is a non-overlapping triplet code, heavily degenerate, and universal or

nearly so. The diagram, appended, illustrates how DNA codes the structure of a protein.

The amino acids are first activated by ATP forming AMP-amino acid compounds. These are incorporated into soluble RNA's specific for each amino acid. The soluble RNA's in turn become incorporated into the ribosomes where under the template influence of messenger RNA, synthesis of specific proteins takes place. Thus the cell's structure and metabolic activities are controlled by nuclear DNA with RNA acting as an intermediate.

As an embryo grows, its multiplying cells change into a variety of different kinds typical of the different tissues. In many cases, the divergence is known to be due to the transient exposure of the cells to particular local environments created by the neighbouring cells. Cells of one kind come to contain enzymes and proteins not demonstrable in another kind. Once established, each cell type is able to copy itself through many cell generations. Therefore, some persistent change has occurred in the replicating system for proteins. Yet all these divergent cell types of one organism have the same set of genes. It is evident that there must exist, in many organisms, mechanisms which can pick out certain genes and allow or prevent them from working, the selection differing according to the particular cell type. These inhibitory or promoting mechanisms must be accurately copied during growth. The nature of these mechanisms is an unfilled gap in current theory.

Between the primary activity of the gene and the final human characteristics that we may see, there are many steps; other gene-controlled processes and environmental influences participate in making the product. The advances in biochemical genetics are greatly adding to our insight in these matters. They are also opening a new chapter in medical history through



making it possible to correct many gene-produced defects in metabolism. One day these advances may allow the correction or replacement of defective or harmful genes.

The author wishes to thank Dr. H. B. Stewart for his assistance in the preparation of the article.

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## A Study of Serum Alkaline Phosphatase Levels

EDWIN FRAN CZAK, '66

During the past summer, a study was undertaken in the Paediatric Research Laboratory of the War Memorial Children's Hospital to determine the normal serum alkaline phosphatase levels of infants and children. This study was carried out as part of an investigation designed to compile accurate and statistically significant values for alkaline phosphatase in the blood serum for the ages from birth until 15 years. The results of the completed investigation will be incorporated into future experimental work requiring a high degree of accuracy.

#### General:

Alkaline phosphatase embodies an enzyme complex or group of enzymes with an optimal activity pH of 9.0 and is found in most tissues of the body. The measurement of serum alkaline phosphatase has definite diagnostic as well as research applications. Serum alkaline phosphatase levels reflect various pathological states as shown by some examples listed below.

#### Serum Alkaline Phosphatase Levels in Disease

Disease	Level
Osteolytic	
osteitis fibrosa cystica	rises
osteogenic sarcoma	rises
osteogenesis imperfecta	rises
Jaundice	
obstructive	rises
hemolytic	no change
Rickets	
infantile	rises
renal	rises
Chronic Nephritis	falls
Celiac Syndrome	falls
Cretinism	falls

#### Experimental Method:

The serum samples were obtained from venipuncture blood samples taken from pre-operative tonsil patients ranging from birth to the age of 15. These infants and

*Continued on Page 125*



# General Practice

## Preceptorship — A Report

DONALD W. ELLIOTT, 64

Among the changes being considered by the Curriculum Implementation Committee of the Council of the Faculty of Medicine, University of Western Ontario, is the introduction of short preceptorships in general practice during the undergraduate course.

The members of the Curriculum Implementation Committee are Dr. H. B. Stewart, chairman, Dr. G. H. Valentine and Dean O. H. Warwick.

### Purpose

The purpose of the preceptorship, as outlined briefly by Dr. Warwick, is to give students, during their undergraduate course, an opportunity to see something of the life which a general practitioner lives, and the nature of his work.

### Plan

Students, individually or in pairs, are sent to small communities where each is to accompany a general practitioner in all his activities for a period of ten or twelve days. It is preferred that the student live at the home of the practitioner to whom he is assigned. The student is present as an observer and it is not intended that he attempt to acquire any skills during his stay. However, it is to be hoped that he will share in any of the usual recreational activities to which his preceptor is accustomed.

Arrangements are made in advance by the committee, usually through the chief of medical staff of each local hospital.

### Execution 1963

Last spring the committee asked members of the third year class to participate in the plan on a voluntary basis, and made contact with practitioners in several West-

ern Ontario towns. In many cases members of the committee made personal visits to the hospitals involved.

Thirteen students took part, going to communities ranging in population from 500 to 28,000. The visits were all made during the summer vacation with early June and early September being the times chosen most frequently.

Many of the students lived in the homes of the practitioners to whom they were assigned. Some lived in the local hospitals, and others made private arrangements. Some spent the entire period with one doctor while others divided their time among three or four.

The group met with Dr. Stewart early in the fall and made their reports to him. All thirteen students were most favorably impressed with the welcome they received from the co-operating practitioners.

In addition to the reports to the committee the participating students answered an unofficial questionnaire concerning various aspects of the project. The questions and the answers given by the thirteen students follow on the next page.

### The Future

Although the committee is still gathering information, the hope has been unofficially expressed that the number of participating students and practitioners will grow each year until an entire class can take part at the same time.

From the answers to the following questionnaire it is apparent that those who took part in the first project feel that a general practice preceptorship would be a valuable addition to the undergraduate curriculum.



## Questions

Questions	Answers		
	Yes	No	Do Not Know
1. Did you embark on the preceptorship with a <i>definite</i> interest in general practice?	7	6	
2. Did the preceptorship increase or inspire interest in general practice?	10	2	1
3. Did the preceptorship cause you to lose interest in general practice?	1	12	
4. Do you feel that such a preceptorship should be part of the undergraduate curriculum?	12		1
5. If so, when would be the ideal time?			
	during school year .....	8	
	immediately after examinations.....	3	
	immediately before final year.....	1	
	do not know.....	1	
6. What is the ideal length of such a project?			
	10 days .....	7	
	2 weeks .....	3	
	1 week .....	1	
	3 or 4 days per doctor .....	1	
	4 or 5 days per doctor .....	1	

*Continued from Page 123*

children were chosen to eliminate patients with disease states that would yield abnormal values. Normal adults were used as experimental controls in this study.

The serum alkaline phosphatase levels were measured, using a method outlined by Taussky and Shorr<sup>1</sup> which utilizes the Bodansky substrate, a glycerophosphate compound. To attain the desired degree of accuracy, the inorganic phosphorus determinations were done in duplicate and the incubated alkaline phosphatase activity was measured in triplicate. The enzyme activity liberates the free inorganic phosphorus from the glycerophosphate substrate per unit of time. The naturally occurring and the liberated phosphorus in the blood samples were measured by a colorimetric method.

## Results:

The work done during the summer indicates that the level of alkaline phosphatase in the blood serum may be as high as 15 Bodansky units\* at birth. The level drops steadily until approximately the age of 15 where a distinct levelling off occurs to between 2 to 4 Bodansky units. On the basis of these results an inverse relationship is evident between age and alkaline phosphatase activity, up to the age of 15. Thus a serum alkaline phosphatase range of 4 to 15 Bodansky units is indicated by the graph, based on the results obtained this summer.

*Continued on Page 127*



# Antenatal Prediction of Hemolytic Disease of the Newborn

MARY ELLEN KIRK, '64

When a gravid, Rh negative patient comes to her doctor for a prenatal visit, the question of potential hemolytic disease of the newborn is always raised. If there is a history of an affected child or of an incompatible blood transfusion, and if the patient has demonstrable antibodies, the possibility of an erythroblastotic infant or an intra-uterine death must be considered. Certainly the patient's obstetrical history and the dilutions and trend of her antibody titres are of considerable prognostic value, but the possibility of an anamnestic reaction and the presence of a heterozygous husband make the problem complex and the best management equivocal.

## Purpose of the Study:

The value of amniotic fluid analysis in cases of suspected hemolytic disease of the newborn has been recently demonstrated by Liley (spectrophotometric curve method)<sup>1</sup> and by Watson (chemical method).<sup>2</sup> The aim of this research project was to determine whether these two methods could be standardized and allow better obstetrical management of sensitized patients. If the results so indicated, amniotic fluid analysis would be incorporated as a routine hospital laboratory test.

## Case History:

The following case is presented to illustrate one of the problems in which amniotic fluid analysis may prove of value.

Mrs. M. is a 22-year-old Rh negative para 2002 who was referred to the prenatal clinic at Victoria Hospital. Her first

pregnancy is recorded as normal; her second child was erythroblastotic and exchanged immediately after birth. Both children are now alive and well. The date of Mrs. M's last normal menstrual period was November 21, 1962, making her expected date of confinement August 23, 1963. There was agreement between the clinical estimate of gestation and her dates until late June, when the uterus appeared larger than that expected on the basis of her history. Serial antibody titres were done using the indirect Coombs technique with the results shown in Table I. Mr. M's blood type was reported as Rh positive (cDe/cDE). Amniocentesis was carried out on three occasions and the results are also shown in Table I.

Table I

Date	Gestation (Weeks)	Anti-D Titre	450 Peak (OD Units)*	Bilirubin mg%*
May 2	23	1/512		
June 12	29	1/256	0.34	0.40
July 4	32	1/256	0.27	0.30
July 18	34	1/2048	0.28	0.30

\*With bilirubin levels over 0.10mg% and 450 peaks over 0.05 units, erythroblastosis is likely; where the respective values are over 0.20mg% and 0.25 units, a severely affected baby is anticipated.

X-ray investigation on July 18 showed signs suggestive of hydrops fetalis and the fetal age was estimated between 34 and 35 weeks. On July 19, Mrs. M was surgically induced and delivered a 7 pound 6 ounce edematous male infant with an APGAR rating of 5-6. The cord blood was Coombs +++++; cord hemoglobin was 5.2 mg% and cord bilirubin was 6.8 mg%. Immediate exchange transfusion was carried out and subsequently



repeated five times. Babe and mother were later discharged from hospital in apparently satisfactory condition.

#### Discussion:

In this particular case, each of the history, the homozygous husband, and the antibody titres indicated an affected fetus. Amniotic fluid analysis confirmed this and strongly suggested that the fetus would die in utero<sup>1,2</sup> probably several weeks before full term. The only chance for a live baby lay in radically early induction (34 weeks) followed by expert pediatric assessment and care. These hypotheses were emphatically confirmed at the time of delivery.

Based upon the literature and upon the small series of patients studied here this

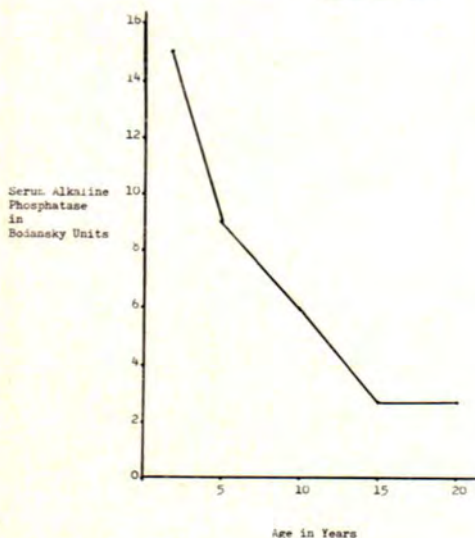
summer, it may be said that spectrophotometric and chemical analysis of amniotic fluid provides an aid in assessing whether or not a fetus is affected by a hemolytic process and secondly, suggests the severity of the process when present. Combined with evidence obtained from past history, paternal genotype, and antibody titres, a better obstetrical management is possible, and fetal and neonatal wastage from hemolytic disease should be decreased.

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Continued from Page 125

Fig. 1 - Changes of Serum Alkaline Phosphatase at Various Ages (Male and Female).



\*Bodansky unit is the amount of phosphatase that liberates 1 mg. of phosphorus from a buffered glycerophosphate substrate (pH of 8.6 for alkaline phosphatase) at 37°C. in one hour.

This work will be continued in the outlined manner until sufficient data has been compiled to make the results of the investigation statistically significant.

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