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All articles submitted *must be typewritten,* on one side of paper only, with double spacing and one and one-half inch margins on each side. Canadian Press (American) spelling must be adhered to. The format for references is as follows: *For books*: Author(s): title of book, publisher, place, year. *For journals*: Author(s): name of journal (abbreviated as in the World List of Scientific Periodicals), volume: page, year.

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# Symposium on Pediatrics

## Foreword

Medical writers have a very important contribution to make to society as a whole. Through their activities the recent advances and concepts in medicine are given wide circulation. All that is new and original is abstracted and reprinted in various medical and lay journals throughout the world. If a discovery has a practical application, in no time commercial manufacturers will take up production and society as a whole will benefit. This soon leads to increased employment and an indirect social benefit will result. From this concept, first advanced by Professor Lewellyn Barker in 1928, one realizes the power of the medical press, as well as the continuing need to train and produce medical thinkers and writers who will carry on the fine tradition which we have inherited.

All of this writing is under the control and rigid supervision of the medical editor—that demon with a blue pencil who reduces your carefully prepared manuscript to ribbons. And yet, his is a difficult job. He must improve and correct the English composition so that the subject may be understood by the reader. He must weed out all articles that are merely meretricious or poor and yet he must not reject that which has the glimmer of a new idea.

Because of this tremendous responsibility, it is with pride that I undertook to write the foreword to this issue devoted to Pediatric subjects. The editor has done a magnificent job and his corps of writers have not given him much opportunity to use his blue pencil. The papers themselves have lived up to the high standards set by their teachers—Doctors Collip, Noble, Stevenson, Barr and many others on the Faculty. I am sure that these embryo physicians will succeed in their careers for they have the gift of enthusiasm and a will to work. Their subject matter has been helpful for Pediatrics today is a rapidly changing scene, with discoveries in many fields opening up new avenues for progress in the development of healthier, happier children. In no branch of medicine is there greater hope for progress and so Pediatrics remains the most stimulating challenge to an inquiring mind.

Medical writers must describe, of course, experiments and research being performed around them. Thus, those who become infected with the desire to write, must undertake research in a subject, be it clinical, bibliophilic or basic. A heart-felt tribute must be paid here to Dr. Collip, who has instilled the idea of research into this school, which is producing daily more and more results in many fields.

I would like to dedicate this issue to Dr. Harold Little, whose many years of active teaching have made this special edition possible.

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# Perinatal Mortality

DOMINIC PANTALONY, '58

## INTRODUCTION

The medical profession may indeed be proud of the marked reduction in maternal mortality in the last twenty years. Another achievement is the significant reduction of infant mortality, and also that of early childhood. Our pride decreases when we fail to notice a similar reduction in the number of stillbirths and neonatal deaths in the same period.

Perinatal mortality is the collective expression now used to include both neonatal and fetal deaths (stillbirths). Mortality in this most important period of life accounted for more than 10% of all deaths in the United States in 1953!

## THE PROBLEM OF PERINATAL MORTALITY

In 1948, Sigismund Peller coined the term "Perinatal Mortality Rate" to include fetal death ratios and neonatal mortality. Their combination into one statistical entity is justified on the basis of similarity of the causes of death.

Perinatal mortality is defined as the number of deaths in fetuses and infants of 750 gm. and over up to the seventh day of extrauterine life. Perinatal mortality is a new concept; thus statistical analysis is somewhat impeded because of differences of opinion regarding definition, terminology, and principles. In general, though, the impact of perinatal loss has been felt by many. Because of the enormity of the problem many disciplines must be integrated to control the loss. These include medical scientists, clinicians, nurses, and public health workers. Its effect on socio-economic status involves political scientists, nutritionists, economists, sociologists and the general public. All must co-operate in acquiring information, and applying it to improve perinatal salvage.

There has been a decline in perinatal mortality but it is slow compared to that of maternal mortality. This decline has been the greatest in late fetal deaths (twenty-eight weeks and over), and least in the early infant period (under seven days old). A comprehensive New York study by Wallace has shown that gains have been made in:

1. Reducing maternal mortality from hemorrhage and infection.
2. Reducing postneonatal mortality.
3. Reducing neonatal mortality from birth injury, congenital defects and gastro-intestinal diseases.
4. Reducing the infant mortality in prematures born alive.

But no progress was shown in:

1. Decrease in ratio of fetal deaths to live births.
2. Prolonging pregnancy, thus reducing early fetal death and fetal death in the lower weight group.
3. Reducing the incidence of premature birth.
4. Reducing number of premature infants born in the lower weight group.

Potter of Chicago has devised a pathological classification of the major causes of perinatal death. It is hoped that further research in perinatal pathology will improve the groupings, since this type of classification aptly points out areas where knowledge is deficient. Eight major categories are used:

### 1. Anoxia

Anoxia is responsible for more deaths than any other etiological factor. Its classification depends upon common pathological lesions of anoxia. The greatest single cause of anoxic death is abruptio placenta. Other causes include placenta previa, cord pathology (such as prolapse), prolonged labor, maternal complications, and others.

### 2. No Abnormal State

The group of fetuses and infants dying with no abnormal state demonstrable pathologically is made up chiefly of fetal deaths *in utero* before labor with varying degrees of maceration. Fetal death due to maternal toxemia and diabetes are also in this category.

### 3. Birth Injury

Perinatal death due to birth injury, particularly intracranial hemorrhage, comprises the next grouping. Both traumatic and anoxic intracranial hemorrhage are included. The incidence of traumatic hemorrhage is greater in term infants. Anoxic hemorrhage is commoner in the premature infant. In the last five years the incidence of hemorrhage due to trauma has decreased while that due to anoxia has remained constant. According to Dill, only a small portion of birth injuries are due to obstetrical trauma in excess of the normal delivery pattern.

### 4. Congenital Malformations

These defects imply incompatibility with life, anomalies of the central nervous system being seen in one-half of these cases. The incidence is greater in prematures but the mortality due to malformations is greatest in the neonatal period. It is interesting that if the malformation is extreme in the early gestational period, abortion occurs.

### 5. Abnormal Pulmonary Ventilation

This class is one of the major causes of neonatal death, particularly in the premature infant. The primary pathology concerned here is hyaline-like membrane formation with resorption atelectasis along with other states such as infection, aspiration and the immature lung. According to Nesbitt, the amount of atelectasis present is the deciding factor in classification because other major pulmonary pathology may be present, accounting for neonatal death.

### 6. Infection

Infection is responsible for about 5% of perinatal death in Nesbitt's study at Johns Hopkins, pneumonia being the commonest non-syphilitic infection. Death usually occurs in the neonatal period. Pneumonia occurring in the first few days of life is usually the result of intrauterine infection. Bacterial contamination of the amniotic fluid is often associated with premature rupture of the membranes, long labor and intrapartum fevers. Outbreaks of gastrointestinal and skin infections in newborn nurseries are now uncommon causes of neonatal death.

### 7. Erythroblastosis Fetalis

Nesbitt's study in Baltimore revealed that erythroblastosis is not a major cause of perinatal death in his series. This was attributed to the larger Negro population dealt with, and, of course, to adequate knowledge and antepartum diagnosis of Rh and ABO antigen-antibody relationships.

### 8. Other Conditions and Causes

This miscellaneous group comprises a heterogeneous unrelated group of unclassifiable causes. These include advanced ectopic gestation, fetal hydrops of unknown origin, idiopathic increase of intracranial pressure, placental insufficiency secondary to massive infarction, and cord complications (vessel rupture, hematoma, etc.).

In the discussion of etiology of any disease, both tangible and intangible factors

are encountered. Thus, related factors in perinatal mortality become significant when taken in the light of the abovementioned specific causes. The age, race, and parity of the mother are interrelated factors influencing the reproductive outcome. Perinatal risk is lowest in the second pregnancy, increasing with subsequent pregnancies; mortality also increases progressively as maternal age advances. Maternal complications increase with age as does the incidence of fetal abnormalities.

Birth weight of the fetus is related to race, socio-economic status, and nutrition of mothers, these, in turn, influencing perinatal mortality in a complex manner. There are critical limits in birth weight for both male and female infants with points outside of them representing increased risk to the fetus. Similarly, decreased mortality rates may be found when gestation time lies betwen 275 days and 289 days. Statistical optima may be found relating birth weight to gestation time:

*for males*, 279 to 287 days and 7.43 to 8.27 lbs.

*for females*, 272 to 294 days and 6.64 to 9.04 lbs.

Further, the standard of obstetrical and pediatric care has a direct bearing on fetal and neonatal death, respectively. Such factors as operative procedures, management of premature labor, bleeding complications, etc., anesthesia and analgesia influence the neonatal outcome and reflect on the skill of the operator.

When discussing certain specific pathological causes of death related to perinatal statistics their significance may be somewhat lost. Thus they can be relegated to their proper status by discussing perinatal mortality under the following headings:

## EARLY FETAL DEATHS (ABORTION)

Fetal death is death prior to the complete expulsion or extraction from its mother of a product of conception regardless of gestation time. Early fetal death is classed as death before the twentieth week of gestation and, theoretically, does not enter the definition of perinatal mortality. The importance lies in the staggering amount of reproductive wastage represented by abortion. Estimates show that twenty-five per cent of all gestations terminate in abortion, spontaneous abortion accounting for ten per cent of the pregnancies. The difficulty in analysis lies in the understandably unsuccessful attempts to collect data because abortions may not be attended by medical personnel, may go undetected or may be illegal, and thus hidden.

## INTERMEDIATE AND LATE FETAL DEATHS

Intermediate fetal death (20 to 27 weeks gestation) and late fetal death (28 completed weeks gestation and over) has declined 45% in the United States from 1922 to 1952. But this combined group comprises one-half of perinatal mortality occurring *in utero*.

There is a higher percentage (no less than one-quarter of fetal deaths) due to unknown causes among those dying before labor than those dying during labor. Those unexplained deaths comprise the largest single factor of fetuses dying *in utero* and point out the lack of knowledge of this segment of fetal wastage.

### Known Pathological Causes

**1. Anoxia.** Of the known pathological causes of fetal death, 50% were classifiable as "anoxic" deaths. The most important single entity in causing anoxia is abruptio placenta. Abruptio is associated with maternal toxemia in about one-third of cases and this combination is instrumental in increasing fetal mortality. Many more deaths are ascribed to anoxia in the period during labor than before labor. The main contributory factors here are prolapse of the cord causing circulatory obstruction, uterine inertia, prolonged

labor, intrapartum fever, abnormal uterine contractions and mechanical dystocias. It should also be noted that the heavy sedation of toxemic mothers may contribute to anoxic insults in the fetus.

2. **Toxemia.** Fetal death in association with toxemia of pregnancy comprises the second largest group. But in the Baltimore study, 40% of the fetuses dying in association with maternal toxemia showed major pathology unrelated to toxemia, and 36% showed no pathology whatever. The latter group accounted for 8% of fetal deaths *in utero* before labor.

3. **Congenital Malformations.** This category comprises fetuses dying of malformations incompatible with life. Deaths were equally divided for the period *in utero* before and during labor, certain fetuses being unable to withstand the rigors of labor.

4. **Birth Injury.** Birth injury as a cause of fetal death during delivery has been minimized by the reduction of difficult vaginal deliveries. This has been achieved by improved obstetrical technique and judgement.

5. **Other Causes.** Proper antenatal case-finding has reduced markedly the deaths from erythroblastosis fetalis. Other infrequent causes include placenta previa, maternal diabetes, uterine rupture, prolonged second stage of labor, marginal sinus rupture, and syphilis. The unclassifiable causes, as mentioned previously, are advanced ectopic gestation, idiopathic fetal hydrops, marked increase in intracranial pressure with no demonstrable cause, and placental insufficiency with infarcation.

6. **Postmaturity.** British workers have found that fetal distress and death *in utero* increase in postmature pregnancies, the principle findings being a decrease in oxygen content and saturation of the cord blood as the pregnancy advances. Certain complications of labor show a striking relationship to postmaturity, including contracted pelvis, postpartum bleeding, uterine inertia, fetal distress, breech, and prolonged labor. The perinatal mortality in this group is increased threefold over the mature group, the greatest increase taking place in fetal deaths *in utero* during labor. Again, anoxia plays the leading role in etiology, the fetus being put in jeopardy by a combination of placental dysfunction and complications of labor.

## NEONATAL DEATH

Prematurity is the most important single factor influencing neonatal mortality and morbidity. It accounts for one-half of all perinatal deaths and one-third of all infant deaths under the age of one year. The importance of prematurity is further enhanced when we see that it ranks eighth among the leading causes of death in all age groups.

The premature infant is defined as a liveborn infant weighing under 2500 gm. (5½ lbs.) or with a gestation period under 37 weeks where weight is impractical. Other evidence such as total length, radiological examination of ossification centres, and estimation of fetal hemoglobin may be used to substantiate prematurity.

The major categories of perinatal death may be used in analyzing the specific causes of prematurity, but, of course, there is a marked difference in importance of the various pathological entities. The largest single entity associated with neonatal death in the premature is abnormal pulmonary ventilation. Hyaline-like membrane disease was found to be the most frequent significant cause. Various obstetrical factors predispose to the formation of hyaline-like membrane disease in the newborn. These include premature birth, maternal diabetes, caesarean section, breech, multiple delivery and maternal toxemia.

The major causes of premature perinatal loss are, in descending order of im-

portance, causes unknown, placental complications, abnormal pulmonary ventilation, toxemia, birth injury, malformation, and infection.

Related factors are important in evaluating the cause of prematurity. Birth weight has been shown to have a close relationship to race, sex, plurality of birth, and socio-economic status. The inverse relation between birth weight and perinatal loss due to prematurity is well known to all. Maternal dietary deficiency has recently been shown to take a large part in premature labor. The incidence is also increased in first-born infants and in the extreme maternal age groups. Thus it is seen that the quality and quantity of preconceptional and prenatal care is all important to the reproductive outcome.

Spontaneous termination of pregnancy occurs in about three-quarters of all premature births, defying explanation or demonstrable cause. The obstetrician must attempt to treat expectantly premature labor and rupture of membranes, and placenta previa. The pediatrician must improve on resuscitation and the follow-up care of the premature.

The subject of prematurity has been dealt with at great length in the foregoing discussion because it is the major underlying cause of neonatal death. Aside from hyaline-like membrane formation and/or prematurity the other most common causes of neonatal death are malformations, intrauterine anoxia, traumatic cerebral hemorrhage, and infection.

## GENERAL DISCUSSION

A general appraisal of the concept of perinatal mortality has been presented mainly to stress the existence of this entity as a most important segment of mortality in all ages. It is also hoped that from the discussion of causes it will be clear that much is to be learned in the field of perinatal pathology, and that much research is needed. Fully one-third of the deaths in the perinatal period are unexplainable, having no demonstrable cause. Therefore both obstetrical and pediatric care must constantly strive to improve, and deal with the problems as they arise. New discipline must come forth as more knowledge is gleaned.

To achieve any results one must be specific as to what is to be done. Since anoxia was found to be responsible for more deaths than any other factor, maternal-fetal oxygen relationships need thorough research.

To the investigative mind the anoxia-producing pathological states, both maternal and fetal, are very inviting. Abruptio placenta, uterine muscle physiology and histochemistry (and indeed of all smooth muscle) in relation to premature labor, uterine inertia, and prolonged gestation are indeed fruitful fields. The subject of intrauterine anoxia and its effect on brain cell injury presents a virgin pathological field to clarify birth injury deaths and the sublethal neurological sequelae, the "continuum of anoxia".

Further examples such as hyaline-like membrane disease, placental degeneration, petechial hemorrhages, and cerebral edema give the problem of perinatal physiopathology an almost philosophical connotation —research at the capillary level!

We must study preconceptional care, environmental pathology, and endometrial insufficiency. Prenatal care must be maintained at a high standard, attempts being made to include women in all socio-economic strata. In intrapartum and postpartum care, skilled obstetrical, pediatric and anesthetic consultation and teaching are required. Autopsies should be sought and their quality improved by special training for pathologists. Thus, definitions and classifications may be further clarified. The establishment of perinatal mortality conferences should be developed. Frank discussion between obstetrician, pediatrician and pathologist will increase the stan-

dard of perinatal care. These conferences, established at the hospital and community level, represent the ultimate in integration of those disciplines which are affected most by perinatal mortality.

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"That which pretends to be big, is always small; that which boasts of its strength, tries to cover up its well-known weakness by noise. He who is secure in himself loves peace, for he has no occasion to disturb it. He who wantonly seeks to disturb the peace is unsure of himself and dares not remain at peace himself!"

Alcuin, Charlemagne's tutor, 8th century.

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"God give me unclouded eyes and freedom from haste.

God give me a quiet and relentless anger against all pretentious work and all work left slack and unfinished.

God give me a relentlessness whereby I may neither sleep nor accept praise till my observed results equal my calculated results or in pious glee I discover and assault my error.

God give me strength not to trust in God!"

Martin Arrowsmith's prayer in "Arrowsmith",
Sinclair Lewis, 1925.

# The Pulmonary Hyaline Membrane Syndrome

GERALD J. A. CROPP, '58

## INTRODUCTION

This pathological condition has received increasing attention in the past few years because it has been recognized as a very important cause of neonatal mortality. It must be remembered, though, that this condition is not an established disease entity yet. The existence of hyaline membranes in newborns dying shortly after birth was recognized by Hoccheim in 1903. Johnson and Meyer correlated the pathological findings with a clinical picture, thus establishing it as a syndrome (1925). Since that time much research has been devoted to discover the etiology and pathogenesis of this dreadful condition which causes approximately 50% of premature deaths.

It must be noted that pulmonary hyaline membranes occur in many diseases affecting adults as well as children. Burns and Shields list the following diseases as having pulmonary hyaline membranes as part of the pathological picture:

1. Radiation pneumonitis
2. Influenzal pneumonia
3. Aspiration of amniotic sac content
4. War gases and HCl
5. Rheumatic pneumonitis
6. Sulfonamide anaphylactic pneumonitis
7. Plague
8. Septicemia and chronic infection
9. Atypical pneumonia
10. Metastatic chorionepithelioma
11. Acute and chronic glomerulonephritis
12. Oxygen poisoning
13. Cadmium chloride aerosol
14. Oxides of nitrogen

This communication will limit itself to a discussion of the pulmonary hyaline membrane syndrome as it occurs in neonates.

The pulmonary hyaline membrane syndrome is a pathological condition which almost always causes death in very early life after respiration has been normal for at least one hour, and is characterized by progressive respiratory distress, leading to cyanosis and eventually asphyxia. Pathological examination reveals hyaline membranes in alveoli, alveolar ducts and bronchioles. As will be seen later, there is a rather definite clinical and pathological picture associated with this state so that a diagnosis can usually be established prior to death.

## INCIDENCE

Different authors agree fairly well that 5-20,000 babies die every year in the U.S.A. from this condition. It is the most commonly found pathological finding in premature infants dying during the early neonatal period. Potter found that this condition caused 40% of premature deaths, while Neustein and Van Breemen found it in only 25% of their series. Laufe and Stevenson stated in 1955 that one out of 400 live births at the Elizabeth Steel Magee Hospital died of this syndrome. Miller and Jennison found the incidence

to be highest in the weight bracket from 1000-3000 gm. 55% of infants who died and belonged in the above stated weight range showed hyaline membrane formation. Deaths outside this range showed only an 8% incidence of membrane formation. The peak incidence lies in the group of prematures between 1000 and 2000 gm. 47.3% of neonatal deaths were caused by this syndrome in their study. Blystad, Landig and Smith hold hyaline membrane syndrome responsible for about half of their premature deaths. In their series 22% of membrane formations occurred in full-term babies. Miller and Jennison found this condition in 13.6% of stillborn infants. When it does occur in stillborns, membrane formation is usually minimal. Minimal membrane formation is insufficient evidence for a diagnosis of hyaline membrane formation. When comparing white with negro populations it was found that whites showed a slightly higher incidence of this condition. Rogers, Gables and Gruenwald state that 91% of pulmonary hyaline membrane syndrome occurs in prematures.

## PREDISPOSING FACTORS

The true etiology of this condition has not been established. I shall discuss two important factors which predispose to the development of pulmonary hyaline membranes:

1. *Prematurity.* This is the most significant of the predisposing factors. It will be recalled that the peak incidence of this condition is in infants from 1000-2000 gm. 91% of hyaline membrane syndrome occurs in prematures.

2. *Maternal complications during pregnancy.* While there exists no agreement on the relation of maternal complications during pregnancy, labor or delivery to the development of pulmonary hyaline membrane formation, recent reports mention the following factors as significant ones:

(a) Antepartum hemorrhage, especially placenta previa.
(b) Caesarean section.
(c) Maternal general anesthesia.
(d) Diabetic and prediabetic mothers.
(e) Fetal distress.

Blystad, Landig and Smith found that 88 out of 93 mothers whose infants subsequently died of the hyaline membrane syndrome had one or more complications of pregnancy, labor or delivery.

## EXPERIMENTAL PRODUCTION OF PULMONARY HYALINE MEMBRANE

Innumerable substances have been used in the attempt to produce hyaline membranes in experimental animals. Intratracheal administration of soaps, lysol, egg albumin, amniotic fluid and fibropurulent exudate and many other substances produced more or less typical histological changes. Only some of the more interesting experiments will be discussed here.

1. *Oxygen concentration*

Although the evidence is only experimental, it may be of import once the understanding of this condition has been advanced. Burns and Shields produced typical hyaline membranes in guinea pigs by exposing them to 98% oxygen at atmospheric pressure. If this pressure was lowered to 200 mm. Hg no membrane formation could be produced. These investigators could not demonstrate any influence on the fetuses of pregnant guinea pigs no matter to what oxygen concentration they were exposed.

2. *Amniotic fluid*

It is well known that amniotic fluid contains thromboplastin-like substances, which are important in the sealing of maternal blood sinuses after delivery of the placenta. Fresh amniotic fluid will cut plasma clotting time one-half. Laufe and Stevenson postulate that there is some endogenous serous exudate present in the lungs of afflicted infants. It is produced

by vagal injury, irritation from amniotic fluid, administration of oxygen, anoxia or other injurious influences. The aspiration of amniotic fluid causes the serous exudate to clot. The supernatant fluid is reabsorbed and the cloth remains behind. The clot develops into a membrane plastered against alveolor walls, etc. Some plugs occlude the airways and cause atelectasis. The mode of death is asphyxia. The authors successfully reproduced not only the pathological pulmonary lesions but also the clinical syndrome in the guinea pigs by introduction of a mixture of plasma and amniotic fluid through a tracheotomy opening. Animals which did not die within 48 hours were killed and underwent post-mortem examination. No membranes were found but interstitial leucocyte infiltration was present. It seems entirely possible that these cells exerted a proteolytic and phagocytic action as that described by Potter in lungs of neonates dying of the syndrome under discussion within 48 hours.

## ETIOLOGICAL THEORIES

For many years pediatricians believed that the hyaline membrane syndrome was produced by aspiration of amniotic sac content. Numerous experiments seemed to prove that amniotic sac content with its high content of squamous cells would produce hyaline membranes. This is possible but it has been shown that the typical hyaline membrane found in infants dying of the hyaline membrane syndrome shows only very few squamous cells. Rosenthal mentioned in 1935 for the first time that degenerative changes in the epithelium of the respiratory passage caused the membrane formation. He called the condition a "desquamative anaerosis". Miller and Hamilton more recently renewed the doubt in the aspiration theory and postulated that the membranes were a result of some injury to the lung. They did not know what this injury was. Miller and Jennison speculated that it may be infectious because of the similarity between membranes seen in certain infectious diseases and those in this condition. These investigators made the much quoted statement: ". . . facts suggest that the lungs of the fetus are peculiarly susceptible to some type of injury at a certain stage of development and that possibly the agent which causes the pulmonary injury also precipitates labor and birth. The injury occurs *in utero* since hyaline-like material was found in the lungs of a few stillborns."

In 1951 Blystad, Landig and Smith once more presented evidence in favor of the aspiration theory. They showed that typical hyaline membranes could be produced by introduction of human amniotic fluid into tracheae of rats. Small amounts would not produce membranes but when the lungs were moved through respiratory phases for a long enough time and sufficiently large quantities of amniotic fluid were introduced they would develop definite membranes. They theorized that the anoxic fetus goes through vigorous respiratory movements thus aspirating amniotic sac content. Whether hyaline or squamous cells predominated in the membranes so produced depended on the time of gestation when anoxia occurred. Squamous cells in the amniotic sac content increase markedly as term is approached. Protein content is highest in the 4th, 5th, 6th and 9th calendar month.

In 1956 Gitlin and Craig presented most fascinating evidence as to the composition and pathogenesis of hyaline membranes in newborns. They obtained 2 sets of sections from all lungs included in their study. From one set all albumin, gamma globulin and fibrinogen was removed but fibrin was left behind. The second set was examined for soluble plasma, and tissue proteins. Both sets were stained with antibodies which were labelled with fluorescein isocyanate, capable of fluorescing under ultra-violet illumination. Antisera containing those antibodies were prepared in rabbits. They also stained amniotic sedi-

ments by the same method. Results of this study indicated that the hyaline membranes in infants dying early in life consisted primarily of fibrin; the fibrin is derived from pulmonary capillaries, not aspirated amniotic fluid. Insoluble fibrin cannot be transported across cellular membranes and therefore must have formed in situ. Fibrinogen travelled across capillary walls and was precipitated in the alveoli. Fibrin formation may well have been accelerated by some aspirated amniotic fluid with its high levels of thromboplastin-like substance.

A purely theoretical but most promising hypothesis was forwarded by Lendrum. He explains the whole pathogenesis on a cardiovascular basis. The clinical findings (increasing dyspnea; cyanosis; dilatation of the right heart, especially the right atrium; congestion of lungs with extreme capillary engorgement; resorption atelectasis; pulmonary edema) suggest acute left heart failure. The X-ray evidence also indicates pooling of edema fluid in the dependent area of the chest (the child lies on his back and radiolucency is greatest in the anterior part of the chest). Post mortem findings in the lungs are not like atelectasis at all, but rather those of heart failure. Prematures have an underdeveloped pulmonary circulatory bed and heart when they are born. The right heart does less and the left more work. The 3 structures taking the greatest burden are:

1. Pulmonary vascular bed.
2. Muscular wall of left ventricle.
3. Circular muscle of ductus arteriosus.

Either the left heart fails or the ductus arteriosus does not close. Either mechanism overloads the pulmonary circulation with consequent rise in pulmonary blood pressure. Respiratory failure is not immediate; therefore, death does not occur for at least one hour. The increased pulmonary blood pressure and pulmonary blood volume results in transudation into the alveoli. This makes oxygenation of blood more difficult. Anoxemia increases and left heart failure is aggravated. A vicious cycle is established. The difference between adult paroxysmal dyspnea and this state of affairs is:

1. The weight of the left ventricular muscle is equal to or less than that of the right ventricular muscle in newborns.

2. Fetal circulatory channels may be reopened under appropriate conditions of pressure and anoxia.

3. The heart of the newborn can continue to function in extreme states of anoxemia, longer than in later life. Glycolysis is probably much more intensive than later in life.

If pulmonary blood pressure and right ventricular pressure increase sufficiently the old fetal circulation may be re-established. Blood flows through the foramen ovale and ductus arteriosus. This lowers pulmonary blood pressure. Some of the previously transudated fluid is reabsorbed from the alveoli but the proteinaceous material is left behind and coagulates, forming a membrane. Surface tension of the wet alveolar lining may contribute to the developing atelectasis.

Progesterone may be involved in some cases of hyaline membrane formation. Progesterone levels do not fall when infants are delivered by caesarean section. It is an accepted fact that progesterone has a relaxing effect on smooth muscle; whether such high progesterone levels may affect the fetus and prevent closure of the vascular shunts (ductus arteriosus and venosus) after delivery remains to be proven.

## PATHOLOGY

The infant is cyanotic.

The characteristic pathological findings are restricted to the lungs. Gross: the lungs are large, heavy, purplish-red, firm and edematous. Microscopic: intense capillary congestion; many alveoli are collapsed and appear solid. With H. and E.

stains there is a homogenous eosinophilic membrane lining alveoli, alveolar ducts and bronchioles. In humans, pulmonary atelectasis is also present. Electron-microscopic studies showed that the hyaline membranes consist of fibrils representing fibrin and cell debris overlying the epithelium of alveolar ducts and some alveoli.

## CLINCAL PICTURE

The child suffering from this syndrome is usually premature and the prenatal and puerperal course may have been complicated. Infants dying of this condition rarely, if ever, die in the first hour of life. Most deaths will occur between the first and 24th hour. This syndrome accounts for 47% of neonatal deaths during this period. 40% of deaths on the second day of life are caused by this disturbance. As the child gets older his chances of dying from the hyaline membrane formation steadily decline. Between the 6th and 14th day only 10% of deaths are accounted for by pulmonary hyaline membrane formation.

In the survey conducted by Rogers *et al* only 10% of babies dying subsequently of the condition were in good health at birth. 52% had a delayed onset of respiration. 84% developed cyanosis before or shortly after arrival at the nursery. 84% had a weak and/or delayed cry.

The striking signs are due to respiratory distress. The respiratory rate gradually climbs and the respiratory pattern becomes irregular and grunting. Eventually there is supra- and infra-sternal retraction. Cyanosis develops soon. There may be rales and poor air entry over both lungs early, but they become quite definite as the clinical state deteriorates. First there is tachycardia, but terminally bradycardia is evident. The baby becomes hypotonic, hyporeflexic, hypothermic and may show hepatomegaly. It should be remembered that tachycardia, cardiac enlargement and hepatomegaly are the classical signs of heart failure in neonates. Cardiomegaly is seen on the X-ray. The infant exerts four to ten times the normal amount of energy used in respiration. A respiratory acidosis develops slowly because of the increasing alveolar barrier. Carbon dioxide combining power drops, pH falls and blood carbon dioxide content rises. The X-ray is quite typical. All fatal cases show constant changes. The thorax is normal in size and shape and the diaphragm is in normal position. The lungs give a ground-glass or granular appearance throughout, becoming very opaque terminally. Air content is definitely decreased. The bronchi contain a normal amount of air. The heart shows slight enlargement. If the infant should survive the X-ray will clear in a few days. Complications such as pneumothorax or mediastinal emphysema are rare. They occur in infants surviving beyond 24 to 48 hours. If aspiration or infection become superimposed the appropriate changes will be seen. Fever may develop once complications are present.

## TREATMENT

There is no specific treatment for this clinical state, namely because the basic cause is unknown. Prevention has little to offer since prematurity is in over one-half of cases a totally unexplained abnormality and therefore cannot be prevented.

Lendrum suggests that heart failure can be prevented to some extent by keeping the head of the baby up so blood can gravitate below the diaphragm and not encroach on the breathing space and congest the lungs. This is opposite to the accepted position for the premature. Experiments make it appear that high concentrations of oxygen under atmospheric pressure are detrimental to the newborn and should therefore be avoided.

The once popular wetting agents have completely lost their place.

Symptomatic treatment consists of frequent nasopharyngeal suction, and stimu-

lants such as sodium benzoate or niketha-mide during periods of distress. Placing the baby in an incubator gives temporary relief only. The ultimate outcome is little affected by these sometimes heroic measures.

## PROGNOSIS

Prognosis is extremely bad. Only very few mild cases survive. Many apparent survivals may not have suffered from pulmonary hyaline membrane syndrome at all. An increasing respiratory rate which becomes irregular in a premature suggests the diagnosis of pulmonary hyaline membrane syndrome.

## SUMMARY

1. Pulmonary hyaline membrane syndrome is a relatively common condition and accounts for almost half of early neonatal deaths. Hyaline membranes occur in adults and children in a multiplicity of clinical states.

2. The true cause of this condition is not known. Pulmonary transudation, possibly on the basis of cardiac decompensation, is responsible for the membrane formation. Prematures account for the vast majority of cases. Amniotic aspiration may enhance membrane formation but is not the basic cause.

3. The pathological triad is hyaline membrane formation, capillary congestion and atelectasis.

4. There is no definite treatment.

5. Prognosis is practically hopeless.

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"Every race, every art has its hypocrisy. The world is fed with a little truth and many lies. The human mind is feeble: pure truth agrees with it but ill: its religion, its morality, its states, its poets, its artists, must all be presented to it swathed in lies. These lies are adapted to the mind of each race: they vary from one to the other: it is they that make it so easy for them to despise each other. Truth is the same for all of us: but every nation has its own lie, which it calls its idealism: every creature therein breathes it from birth to death: it has become a condition of life: there are only a few men of genius who can break free from it through heroic moments of crisis, when they are alone in the free world of their thoughts."

Romain Rolland, "Jean-Christophe", 1910.

# Enuresis as a Psychosomatic Problem in Pediatrics

IAN D. GRAHAM, '58


## INTRODUCTION

The enuretic child is a common pediatric problem, and a complex one to understand and manage. The psychosomatic approach is defined and applied in an endeavor to present a frame of reference in which its pathogenesis, diagnosis and treatment may be discussed on a comprehensive, rational basis.


## DEFINITION

Enuresis may be defined as the repeated involuntary discharge of urine occurring after the age when nocturnal bladder control is usually acquired. This age is arbitrarily set by most authorities at three years. Enuresis must be differentiated from the diurnal incontinence of urine which may be associated with neurogenic bladder, epilepsy, urethral strictures, urethral or bladder infection or on the basis of increased urinary volume secondary to diabetes mellitus or insipidus, excessive fluid intake, or the consumption of diuretic beverages.

## INCIDENCE

General incidence is probably within the range of 1 to 5%. Figures rise in selected groups. For example, pediatric out-patient departments report 1 to 25%, children's institutions 10%, and psychiatric consultants that not less than 26% of their patients are enuretic. There is a marked male predominance, but a fairly even distribution over the I.Q. range. The complaint is nocturnal in 63%, diurnal in 30% and purely a daytime problem in only 7%. Most enuresis is life-long in duration, 9% relapsing completely after acquiring control and 13% relapsing after entering psychiatric clinics for other difficulties (Kanner). In one series, a positive family history of enuresis was acquired in 63% and a sibling history of 21%.

## APPROACHES TO THE PROBLEM

A review of the literature on enuresis is an interesting illustration of the historical development in theories on the causation of human disease. It reflects the cultural background, attitudes, training and experience of each investigator, be he pediatrician, neurologist, academic psychologist, urologist, general psychiatrist or child analyst. In turn, various probings have involved the child's lower genito-urinary tract, presacral plexus, tonsils, modes of learning, unconscious motivation, fluid intake, the bedroom temperature and so on. There has been understandable fluctuation in insight and bewilderment, success and frustration, and most of all, in total therapeutic effectiveness. Much of the relatively common difficulty in managing the situation lies not with a lack of knowledge as in the need for a comprehensive intelligible frame of reference adaptable to theoretician and general practitioner alike. This holds, as well, for certain gastro-intestinal disorders, certain forms of obesity, migraine, asthma and so on, which are less commonly found in the pediatric age group.

The psychosomatic concept may be considered as an attempt to put more of the ancient "art" of medicine on a scientific basis by adding the insights and techniques of dynamic psychiatry and integrative neurophysiology to established principles of organic pathophysiology. It is a systematic attempt, not to study the "soma" less but rather to evaluate how much the psyche, and how much the soma are involved in causing diseased states and what relationship exists between them. Admittedly the two-part term "psychosomatic" is contradictory to the purpose for which it is used, but to the extent that it perpetuates the confluence of psychological and physiological investigation it serves a useful purpose.

What value has the psychosomatic approach for the practising pediatrician? By integrating newer concepts of the effects of interpersonal factors and psycho-physiologic mechanisms with familiar pathogenic ones, this approach expands his capacity to supervise the health of the child as a whole. As his own understanding broadens, the education of parents in child care and earlier recognition of pathogenic influences in the child and his environment becomes relatively easier. Thus the correction of these processes before the disease process is fixed and refractory to treatment, is simplified. When specific psychosomatic disease entities arise, he has a frame of reference for their management. Finally, by minimizing the emotional reactions to overtly organic disease and hospitalization, these principles enhance the ease and effectiveness of such somatic therapies as insulin, dietary measures or prolonged bed rest. They facilitate an earlier return to normal living and diminish the likelihood that the patient, as an adult, will seek somatic illness as an escape from stressful situations.

## ENURESIS AS A PSYCHOSOMATIC PROBLEM

1. The normal development of bladder control in relation to total personality evolution consists of three continuous phases, separated for description as:

(a) The stage of becoming conscious of urination. During early infancy the bladder functions in a simple reflex manner. Following the pleasure principle, distension is immediately relieved by reflex evacuation of the bladder and discomfort is exchanged for relief at frequent intervals.

(b) The stage of daytime control begins towards the end of the first year. The child is more aware of the act but has little conscious control. Periods between urination exceed one hour. Concurrently the personality is learning to differentiate between the confines of its own self and the external reality of parental figures and inanimate objects.

(c) The final stage is the development of night-time control and this takes place over the second and third years. During this time it must be incorporated as an unconscious cerebral control and as such implies a satisfactory resolution of the conflict between innate biological drives and the demands of the culture as interpreted by the parents.

2. Pathogenic factors. In many of these children, enuresis is only a symptomatic complaint in a disturbed parent-child relationship and as such is as nonspecific as a fever. Moreover, according to Kanner, it is rarely "monosymptomatic". Direct cause-effect relationships are obscured by cycles of emotional reaction to the symptom which serve to increase the conflict. Each individual situation may be compounded of any combination, in varying proportions, of the following elements:

(a) Primary failure of the mother to meet the emotional needs of the child such as for affection, security, self-respect, and autonomy. The causes may be external in the form of unusual physical, economic or marital stresses which would be difficult for even the most stable person to withstand. More often internal factors,

operating at various levels of the mother's awareness, may be at fault. Rejection of the child for various reasons may be overt, or in the form of domination or over-protection. Anxiety from any cause, however, is quickly transmitted to the child.

(b) Inappropriateness of the learning situation arises from any of the following:

(i) misunderstanding by parents of the normal variations in the age at which the child is emotionally and physically capable of each stage of bladder control;

(ii) carrying over from their own childhood training, rigid or overlax attitudes regarding child guidance;

(iii) failure to realize the effect their emotional reactions and over-emphasis have upon the child's development;

(iv) simple inattention to such details as regards adequate bedroom and bathroom facilities.

3. The reactions of the child which are predominantly to the mistrust, frustration and guilt feelings provoked, including resentment, rebellion and anxiety — both overt and internalized. Frequently, boys are seen to take on a passive role while girls tend towards the active "tom-boy" one. Behaviour often returns to more immature patterns.

4. Reactivation of the habit under situations of emotional stress: progress made in bladder control may be lost temporarily under stressful conditions. Whether the process in the case of enuresis is a conversion symptom or a pure psychosomatic phenomenon in the limited sense used by Alexander and French is an unresolved theoretical point. The situations include:

(a) Birth of a sibling with loss of some maternal attention.

(b) Somatic illness, especially if hospitalization is necessary.

(c) Separation from one or both parents.

(d) Phases such as entering school, starting at a summer camp, or moving to new environment.

## MANAGEMENT

### 1. Diagnosis.

The principle of psychosomatic diagnosis is the evaluation and correlation of the somatic and psychic factors in pathogenesis. Life situations are juxtaposed in the doctor's mind with symptom formation. The classical medical history-taking is enlarged to include personality study (here including to some extent, both parent and child). The former "query-session" with the mother is replaced by an interview in which the patient is allowed more freedom to ventilate the emotional aspects spontaneously, while the physician listens, observes attitudes in verbal content and interview behavior, and carefully induces relevant topics or necessary historical data. The physical examination is appropriately thorough to rule out organic incontinence and coincidental physical disease. This should include a careful palpation of the lower abdomen for bladder distension and examination of sphincter tone and integrity of the motor function and sensation of the sacral segments. Repeated urinalyses are necessary. Full neurologic and urologic procedures should be reserved for cases in which the history demonstrates lack of daytime control, frequency, polyuria or inability to produce a copious stream on daytime voiding. Intravenous pyelography, cystometery, cystoscopy and lumbosacral X-rays should not be allowed to replace clinical thoroughness. These procedures tend to compound the psychological trauma to the child and add expense and physical pain out of proportion to the confidence it supplies to the attending doctor.

### 2. Treatment

Treatment, to be specific, aims at correction of the disturbance in the parent-child relationship, facilitated, where neces-

sary, by auxillary procedures to interrupt the vicious cycle of symptom and reaction. Therapy must primarily consider the child's total development, not his bladder function alone. Time and effort expended on the various elements present in the individual case is proportionate to their relative intensity and the practitioner's ability to cope with them.

(a) *Interpersonal Aspects*

Time is well spent with the mother in interviews of a re-educative and supportive nature. Simple, well-timed explanations regarding the child's developmental needs and the proportionate significance of the symptom are more readily accepted if the parent is allowed to express, and is given insight into her own reactions to the situation. Informed and supported, she is more capable of, and willing to cooperate in treatment. The same holds true where the father is, and should be, concerned. Against this background, environmental influences are handled on a more rational basis.

The older the child involved, the greater is the necessity to guide him directly, and separately. Ignoring the wetting conflict initially, the doctor endeavors to establish a friendly "partnership" with the child by taking an active interest in him, reassuring him of his worth and "de-sensitizing" his anxiety over the symptom. If this can be done, the problem may be discussed and then approached as one which the child can handle on his own, to discuss directly only with the doctor. Where necessary, adjunctive procedures are explained to the child and handled by him alone. Security and self-reliance, instilled in the child, are an integral part of any therapy.

(b) *Adjuvant Procedures*

If the "emotional air" can be cleared, symptomatic relief begins proportionately rapidly, and this may be enough, if all concerned can be patient and optimistic. When the practitioner feels that a simple symptom-reaction-symptom cycle exists, he may prescribe tincture of belladonna, 5 drops t.i.d., increasing the dose at the rate of one drop per dose per day until signs of atropism appear, and maintain a slightly lower dosage, if effective, for an additional 2 to 3 weeks, during which it is gradually tapered off. Sedation, such as elixir of phenbarbitone may be indicated.

With an older, relatively stable child, the procedure of setting his own alarm clock to coincide with the probable hour of bedwetting to allow him to awaken completely and go alone to the bathroom once a night, has been effective. Moderate fluid restriction in the evening and having the child void h.s. is advisable. Coincidental physical disease is treated as indicated at any time and divorced from the enuretic problem in the child's mind.

(c) *Referral*

If, during the initial appraisal or subsequent visits, moderate or severe manifestations of emotional disturbance appear in parent or child, referral to a child guidance clinic or psychiatric consultant is indicated. The availability of, and parental desire for expert help should be considered before advice is given. Furthermore, explanation and reassurance by the referring practitioner about these sources can do much to promote their effectiveness when they are required.

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"Nor is the striving for self knowledge altogether without prospects, since there exists a factor which, though completely disregarded, meets our expectations halfway. This is the unconscious *Zeitgeist*. It compensates the attitude of the conscious mind and anticipates changes to come. An excellent example of this is modern art: though seeming to deal with esthetic problems, it is really performing a work of psychological education on the public by breaking down and destroying their previous esthetic views of what is beautiful in form and meaningful in content. The pleasingness of the artistic produce is replaced by chill abstractions of the most subjective nature, which brusquely slams the door on the naïve and romantic delight in the senses and their obligatory love for the object. This tells us, in plain and universal language, that the prophetic spirit of art has turned away from the old object relationship and towards the—for the time being—dark chaos of subjectivisms."

Carl G. Jung, "God, the Devil, and the Human Soul."
Atlantic Monthly, 100th Ann. Issue, 1957.

# Epilepsy

GARY J. O. WELSH, '58

## INTRODUCTION

The term epilepsy is derived from the future tense of the Greek verb "to seize, to lay hold of, to overtake". The derivation of the word encompasses the note of uncertainty and the threat of the future.

The major consideration of this paper is the therapeutic facet of the disease. The description and classification are briefly presented to facilitate the understanding of the therapy while the psycho-social aspects of the disease are omitted. This in no way lessens the importance of the psycho-social approach.

## HISTORIC BACKGROUND

Epilepsy is older than man himself for it affects other members of the animal kingdom. The work of Hughlings Jackson divides the history of epilepsy. Written records date the beginning of the pre-Jackson era at 1500 B.C.; however, the trephined skulls found in caves of the Neolithic period bear mute testimony to a search for a radical treatment to cure the intracranial demons.

The early Greeks attributed the seizure to a soul-racking visitation of divinity and correlated the various forms of the disease with individual deities.

Hippocrates maintained that the disease was hereditary and of cerebral origin. His writings denied a supernatural cause, and recognized an idiopathic and symptomatic form. An aphorism of the day which remains untarnished by time is "Those cases of epilepsy which come on before puberty may undergo a change, but those which come after twenty-five years of age for the most part terminate in death."

Bound by superstitions and religious dogma, little was accomplished in the field of epilepsy other than description. It was not until Thomas Willis re-emphasized that epilepsy had its seat in the brain that the dawn of a new era appeared. With Hughlings Jackson came the transition from a chaotic demon-filled era to the modern era. The simplicity and completeness of his definition of epilepsy epitomizes the transition, "Epilepsy is the name for occasional, sudden, excessive, rapid and local discharges of grey matter".

The history of anticonvulsant therapy closely parallels the history of the disease. Prior to the transition, chants, charms and prayer were "therapeutic". It was not until 1857 that specific therapy, in the form of bromide, was prescribed. In 1912 phenobarbital was introduced. The cadence of advance steadily increased until at present eighty-five per cent of epileptics can be offered some relief.

## INCIDENCE

Lennox calculated the incidence of epilepsy in the general population to be 0.5 - 0.6%. He also estimated that 1 out of 10 persons has a dysrhythmic electroencephalogram. No obvious sex differences were apparent.

## ETIOLOGY

In general, two kinds of epilepsy are recognized — primary or idiopathic, and secondary or symptomatic. The idiopathic variety is the commonest and probably has a biochemical basis. Heredity is related in many cases as an incidental factor.

Secondary epilepsy results from specific structural changes within the brain and may be associated with a variety of pathological conditions. Careful history, examination and follow-up frequently alters the diagnosis of idiopathic epilepsy.

**Suggested Causes of Seizures Beginning at Various Ages**

0 to 1 year –

| | |
|---|---|
| Idiopathic | 50% |
| Birth injuries | 18% |
| Infections | 18% |
| Congenital defect | 10% |
| Misc. (tumors) | 4% |

2 to 4 years –

| | |
|---|---|
| Idiopathic | 75% |
| Infections | 12% |
| Birth injuries | 5% |
| Congenital defect | 5% |
| Misc. | 3% |

5 to 9 years –

| | |
|---|---|
| Idiopathic | 80% |
| Brain injuries | 12% |
| Infections | 8% |

10 to 14 years –

| | |
|---|---|
| Idiopathic | 60% |
| Puberty | 20% |
| Brain injury | 12% |
| Brain infection | 8% |

## CLASSIFICATION

The following classification divides epilepsy into two main groups, generalized and partial, on the basis of clinical and electroencephalographic manifestations.

### A. Generalized Epilepsy

Characterized clinically by a loss of consciousness (not just an alteration in the state of awareness as may occur in partial epilepsy), and electrographically by bilateral seizure discharges from both cerebral hemispheres during convulsions.

1. *Grand Mal* is familiar to all, may or may not have an associated aura, and is characterized by a sudden loss of consciousness, followed by rigidity and, seconds later, generalized intense clonic jerks. Bowel and bladder incontinence, frothing at the mouth, tongue biting, cyanosis, and gnashing of the lips and tongue, are but manifestations of the generalized muscle involvement. As convulsions end, the muscles relax and consciousness returns. The entire episode lasts four to five minutes. Disorientation, muscle pain, throbbing headache and a period of sleep may follow the seizure.

2. *Petit Mal* is seen in childhood but rarely in adulthood. The attack occurs as a brief loss of consciousness during which time the child is oblivious to his surroundings. Occasionally the eyelids and extremities exhibit fine slow rhythmic jerks. Characteristically, seizures occur many times a day, last less than twenty seconds and appear simply as a "lapse" in which the child hesitates in carrying out some motor or intellectual function. Such children are often labeled "day-dreamers".

### B. Partial Epilepsy

Termed "focal" or "local", the clinical picture is entirely dependent of the area of brain involved. Loss of consciousness does not occur. Both motor and sensory seizures are recognized. Although focal in origin, the process may spread to adjacent areas through fixed pathways to involve the entire cortex and end in a generalized convulsion.

1. *Motor seizures* originate in the precentral area of the frontal lobe.

(a) Clonic type is a unilateral rhythmic jerking most commonly beginning at the thumb, great toe, or corner of the mouth, spreading to adjacent areas in what is described as a "Jacksonian march".

(b) Tonic type consists of spasm of extensor or flexor groups. The clinical picture is dependent on the predominating group.

(c) Versive type consists of turning the eyes, head and body to the side of the

focus. Movements arise in premotor portion of the frontal lobe.

2. *Aphasic seizures* arise from speech areas of dominant hemisphere. They may constitute a simple arrest or may leave the patient groping for suitable words with which to express himself. Usually encountered as a portion of a more diffuse focal seizure.

3. *Sensory Seizures*

(a) Somatosensory seizures, originating in the parietal lobe, produce peculiar sensations such as warmth, cold, abnormal position of one part of the body in relation to the rest, and are frequently mistaken for hysteria.

(b) Seizures of special senses present a clinical picture dependent on the cortical area involved.

(c) Psychic arise in the temporal lobe and are most often encountered as a part of the general seizure. The seizure takes the form of hallucinations, illusions, compulsive ideas or changes in mood. The hallucinations are like dreams and may involve any of the senses. Illusions may refer to changes in size, shape or form of objects near at hand; or the peculiar sensation of re-experiencing a situation as if it had previously occurred (déja vu), or the opposite, when the patient fails to recognize people, places or things previously familiar to him (jamais vu).

(d) Automatism is also most often encountered as a part of the more diffuse focal epilepsy. The action varies from simple gesticulations to complicated ambulatory automatism. Smacking of the lips, disrobing, etc. are common examples of such seizures.

## DIAGNOSIS

The diagnosis of the specific type of seizure may escape the general practitioner but he must recognize epilepsy in its general sense. In referring such cases to the neurologist, it is the duty of the practitioner to provide as much information as possible. A useful outline for obtaining this information is as follows:

1. Description:
   (a) aura
   (b) manifestations of seizures
   (c) post-seizure state.
2. Duration of each component of above.
3. Frequency of spells:
   (a) date of onset
   (b) seizure cycle frequency
   (c) precipitating or ameliorating influences
   (d) effect of medication.
4. Childhood and family history.
5. Functional capacity in seizure free period.

Idiopathic epilepsy is a diagnosis of exclusion; it must not be made while some possible secondary cause exists.

## THERAPY

Only the medical aspects of therapy are considered in this presentation. The application of surgical technique to epilepsy is limited and for the most part discouraging.

The ideal therapeutic agent would be easy to dispense, cheap, without side effects and one hundred per cent effective. Today our agents are far from ideal but do control 80% of epileptics with grand mal, and about 60% with partial seizures.

### A. Criteria for Treatment

1. *Absolute Indications*

(a) Recurrent seizures whether primary or secondary.

(b) A single seizure if it has been a prolonged episode of convulsive activity.

(c) If seizure occurred within one year of brain trauma, infection or vascular injury.

(d) After a single grand mal seizure if electroencephalogram is abnormal.

2. *Questionable Indications*

A single seizure of less than fifteen minutes duration, not accompanied by postictal signs, which has occurred during a reversible metabolic abnormality. An example of such is the common febrile convulsion seen in children.

**B. Rationale of Therapy**

Aside from inconvenience and embarrassment the following factors make treatment imperative. Although a paroxysmal disorder, the changes of future convulsions increase with each seizure. Brain damage is observed to occur in frequent seizures. Such areas of damage may be the seat of new foci of discharge, producing an endless chain.

**C. Specific Measures**

1. *The Seizure.* No drugs need be administered during the usual seizure.

Protect the patient from harm by removing sharp objects.

Once teeth are clenched attempts to prevent biting are impractical.

Postural drainage is effective following tonic phase.

Prolonged attacks may be terminated using intravenous amobarbital.

2. *Interseizure Management.*

(a) Drug Administration in Major Seizures (Grand Mal and Partial Seizures).

For all seizures, except petit mal, the initial drugs of choice are diphenylhydantoin sodium (Dilantin) and/or phenobarbital. Their high therapeutic index with a minimum of untoward effects have made these standard anticonvulsant drugs. In patients with infrequent seizures phenobarbital may suffice by itself. In patients with more frequent attacks diphenylhydantoin sodium is the drug of choice. Best results are often obtained by using the two in combination; their synergistic actions allow effective administration of lower doses.

*Phenobarbital.* The initial dose for children over the age of 2 years is usually 0.1 gm. a day given as a single dose at bedtime. The dose for children under the age of 2 years is computed on the basis of body weight. Untoward effects are: (1) Drowsiness and lethargy with initial doses. If this effect fails to disappear spontaneously 5-20 mg. of amphetamine sulfate will alleviate the symptoms. (2) An allergic maculopapular rash may appear at any time. (3) Higher dose ranges may produce ataxia of gait, vertigo and blurring of vision.

*Diphenylhydantoin Sodium.* In children under 6 years of age, the starting dose is 32 mg. t.i.d.; in those over 6 years, 0.1 gm. b.i.d. Minor untoward effects are: (1) Gastric distress and nausea, which may be minimized by taking drug at mealtime or with sodium bicarbonate. (2) Transient nervousness and sleeplessness. (3) Nystagmus, which if associated with ataxia requires restriction of the drug. (4) Hypertrophy of the gums, commonly seen in children. Good dental hygiene and massage may retard the process. (5) Hirsutism, occasionally seen in children and usually mild; withdrawal of the drug is not a cure and therefore is not indicated unless the condition is progressive. Major untoward effects are allergic phenomena which constitute an absolute indication for withdrawal of the drug.

The newer anticonvulsants include some with serious irreversible side reactions and others with less potential in controlling seizures. Their use is indicated after an adequate trial of diphenylhydantoin and/or phenobarbital has failed. Adequate trial indicates the use of the drugs alone and in combination in increasing doses until seizure control or toxic reactions to the drug result.

*Methylphenylethylhydantoin* (*Mesantoin*). In children under 6 years of age, 50 mg. t.i.d.; over 6 years, 100 mg. t.i.d. Untoward effects are: (1) Drowsiness. (2) Allergic skin reactions similar to those sen in diphenylhydantoin. (3) Agranulocytosis, pancytopenia, and aplastic anemia. For this reason a complete cell count once a month is mandatory.

*Mephobarbital.* Mainly used as a substitute for phenobarbital. Its therapeutic dosage is twice that of phenobarbital; its side effects are similar.

*Primidone.* The starting dose in children is 0.15 gm. daily, increasing the daily dose by 0.15 gm. weekly. Daily doses of 0.45-0.90 gm. are necessary to be effective. Untoward effects are nausea, vomiting, ataxia and dizziness. It is usually used in combination with diphenylhydantoin sodium.

*Combined Drugs.* Commercial combinations of one of the hydantoins and barbiturates have an exceedingly limited use in that the dosage of one cannot be adjusted without affecting the other.

(b) Drug Administration in Petit Mal.

The successful treatment of petit mal is dependant on distinguishing it from the partial seizure types. Drugs used in the treatment of petit mal are not effective in the treatment of other types of seizures. When petit mal co-exists with other seizure types adequate therapeutic doses of phenobarbital as well as diphenylhydantoin sodium are indicated.

*Trimethadione.* In children under 2 years of age 0.15 mg. b.i.d. or t.i.d. is the initial dose with increments of 0.15 mg. until therapeutic levels are reached. Children over 2 years receive double the initial dose and increment. Minor untoward effects are photophobia, drowsiness and nausea, which are usually transient. Toxic dermatitis is not uncommon and is an absolute indication for withdrawal of the drug. Major untoward effects are aplastic anemia, agranulocytosis and nephroses. Kidney dysfunction calls for immediate withdrawal of the agent. Frequent blood cell counts are mandatory.

*Paramethadione.* The dosages and untoward effects are identical with those of trimethadione. Its use is found in the cases refractory to treatment or who develop toxic reactions to trimethadione.

*Phensuximide.* Indicated when trimethadione and/or paramethadione have proved ineffective. The starting dose is 0.5 gm. t.i.d. with gradual increments of 0.5 gm. Therapeutic levels are usually found with a dose near 2.0-3.0 gm. daily. Limited side effects are nausea, vomiting, dizziness, drowsiness, and dream-like states. Urinalysis and blood counts at regular intervals would seem indicated until more is known of the untoward effects of the agent.

**Treatment of Status Epilepticus**

1. Patient should be heavily sedated for twenty-four hours. This is best accomplished using amobarbital sodium 1.0 gm. in 20 cc. of saline given slowly intravenously (at a rate of 1-2 cc./min.) until seizures stop and deep sleep results.

2. Sleep is maintained with intravenous drip of 0.5 gm. amobarbital sodium in 500 cc. isotonic saline.

3. The patient must be turned half-hourly to prevent hypostatic pneumonia (Stryker frame).

4. Mild Trendelenberg is maintained.

5. Frequent mechanical aspiration is necessary.

6. Oxygen through nasal catheter when required.

7. Added sedation may be obtained without increased respiratory depression by using paraldehyde.

## PROGNOSIS

It is unlikely that any other major chronic disease has such a favorable prog-

nosis as epilepsy. Looking back a few decades, one finds a great contrast to the productive life now enjoyed by the epileptic. Refinements in diagnosis and control of the untoward effects of today's drugs will bring us within sight of the 100% effective management of seizures.

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"Can anyone explain in mere prose the wonder of one note following or coinciding with the other so that we feel that it is exactly how those notes had to be? Of course not. No matter what rationalists we may profess to be, we are stopped cold at the border of this mystic area. It is not too much to say mystic or even magic. No art lover can be an agnostic when the chips are down. If you love music you are a believer, however dialectically you try to wriggle out of it."

Leonard Bernstein, "Speaking of Music",
Atlantic Monthly, Dec., 1957.

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"Christ gave only one Commandment—and that was Love."

Albert Schweitzer.

# Pediatric Virology

## INTRODUCTION

The purpose of these three articles is to outline some of the current concepts regarding the new viruses and to link them with pediatric illnesses. To accomplish this end, one must appreciate (1) the nature and characteristics of the viruses under study, (2) the presence of disease with its distinctive clinical features, and (3) the fact that the association of virus and disease is more than mere chance. It is obvious that one must evaluate new information as virologist, clinician, and epidemiologist. Thus the pediatrician, working as a team within himself, establishes the relative importance of such information to his own practice of medicine. Fortunately, the great technical advances taking place in virology at present are providing useful diagnostic aids in easier and more rapid laboratory tests. Soon the pediatrician will not rely on clinical evidence alone to establish his diagnosis.

# The Coxsackie Viruses

JOHN B. DALTON, '60

## HISTORY

The Coxsackie viruses derived their name from the Hudson River town, Coxsackie, N.Y., where they were first isolated during screening tests for polio virus in 1948. At that time Dalldorf and Sickles inoculated suckling mice with the virus and found that these mice developed a fatal paralysis. Within a year so many strains of these peculiar C viruses had been isolated that a classification was proposed and later approved by the International Congress for Microbiology at Rome in 1953. Consequently, they have been divided into two groups, A and B, and each group is further subdivided into types 1, 2, 3, etc. From the time of their discovery, the etiologic role of Coxsackie viruses in human disease was doubted. However, in 1956, direct isolation from cerebro-spinal fluid plus serological evidence established that Coxsackie B is an important cause of aseptic meningitis.

## VIRUS CHARACTERISTICS

The Coxsackie viruses are relatively small spheres with a diameter of 6 mu. to 37 mu. depending on the strain and method of isolation. They are found in feces and sewage, and less often in the throat. They remain stable at –70° C. for months without loss of infectivity, and are killed by heat of 55° C. for 30 minutes. Their outstanding characteristic is their unusual pathogenicity for and lesions in suckling mice. Since 1948 at least 26 antigenic types have been isolated and these have been divided into Groups A and B depending on the histologic changes induced in these mice. Lesions induced by Group A are characterized by acute myositis (hyaline eosinophilic degeneration of voluntary muscle fibres, associated with acute inflammation and repair). Lesions of the B group usually show focal myositis, fat necrosis, and acute inflammatory infiltration. Furthermore, Coxsackie B viruses give rise to C.N.S. lesions, whereas Group A give rise to signs of flaccid paralysis only by the degenerative changes which they cause in striated muscle.

## DIAGNOSIS

Accurate specific diagnosis of Coxsackie diseases is now very important to medicine and public health. Unfortunately, simplification of the differential diagnosis has not been attained. Therefore, a definite diagnosis of Coxsackie virus infection can be made only by laboratory methods. The continuing development and improvement of tissue culture techniques have proved of great value in the study of these diseases.

Specimens containing Coxsackie A or B are found in the throat and feces of cases.

### Laboratory Procedure

1. Preparation and purification.

2. Inoculation into litters of 1-day-old baby mice, into cultures of human cells, or into cultures of monkey cells.

3. Two-week observation of the mice for tremors, weakness, paralysis, and other signs of illness.

4. Infected mice killed with ether.

5. Portions of organs fixed and histological sections prepared.

Demonstrations of cytopathogenic changes reveals multiplication of the virus. Antibiotics are used to prevent contamination with micro-organisms. The characteristic histologic lesion establishes the *group*, and since Coxsackie virus disease stimulates the production of type-specific neutralizing and complement-fixing antibodies, the virus *type* can be verified and the serologic response to infection detected.

The differentiation of enteric virus diseases (poliomyelitis, ECHO, and Coxsackie) where clinical manifestations are similar, is made by comparing the morphological and growth characteristics of the plaques produced on monkey kidney monolayer cultures.

## CLINICAL FINDINGS

### Coxsackie A

There is good evidence that Coxsackie A is the etiologic agent in herpangina. This is characterized (in children) by sudden onset, fever to 105° F. lasting 3 days, sore throat, and difficulty in swallowing. There may also be vomiting, muscular aches, and headache. The characteristic gray-white papulovesicular lesions (1-2 mm. diam.) appear mainly on the anterior pillars of the tonsils. Most cases show diffuse pharyngeal erythema. Other conditions found in association with Coxsackie A virus infections are acute lymphadenitis, meningo-encephalitis, Guillain-Barré syndrome, Bell's palsy, and summer diarrhea. Cases of a syndrome of herpangina and parotitis have been reported. Coxsackie A viruses have been isolated in association with poliomyelitis virus but have not been implicated in any C.N.S. disease, although they may play a part in the visceral complications of poliomyelitis.

### Coxsackie B

Coxsackie B virus infection has been shown to be causal in pleurodynia, meningo-encephalitis, and myocarditis neonatorum. Pleurodynia (Bornholm's disease) is characterized by a sudden onset of pain in the region of the diaphragm not associated with rigidity, but aggravated by breathing, causing protective splinting of lower chest and upper abdomen. There is pain and tenderness of muscles, fever, rapid pulse and frontal headache. The symptoms associated with the second condition, meningo-encephalitis, are sore throat, abdominal pain and vomiting, and 1 to 7 days later, fever, vomiting, severe headache, and generalized muscle pain. The outstanding sign on examination, however, is marked stiffness of the neck and back. Myocarditis neonatorum is an acute febrile illness ending in circulatory collapse and occurring soon after birth. Post-mortem examination shows the cause of death to be acute heart failure from extensive myocarditis. In the British epidemic of 1951, illnesses simulating infectious mononucleosis, acute appendicitis,

sinusitis and influenza proved to be infections of Coxsackie group B virus.

## EPIDEMIOLOGY

Coxsackie viruses have a world-wide distribution, being isolated from sewage, humans, and flies. In the human disease there appears no sex or race differences. However, there are important age differences; the disease occurring most frequently in the 6 mo. to 8 year age group. There is a greater frequency of the A group in childhood, and it has been suggested that adults who have escaped childhood infection may suffer more dramatic group A infections later. The seasonal distribution is similar to that of poliomyelitis and shows a higher incidence in late summer and in temperate climates. Dissemination occurs by feces, droplets, and contact.

Epidemiological studies have shown some peculiar characteristics of these organisms. For instance, they are heat stable if suspended in dairy products. Current sanitary methods do not regularly destroy them. Due to their bizarre clinical manifestations, some epidemics have been noted only in retrospect. Although Coxsackie and polio viruses have been seen together in patients during epidemics, it has not been established whether or not this is merely chance. On the other hand, certain non-paralytic poliomyelitis epidemics have shown a preponderance of Coxsackie and only a few poliomyelitis viruses. However, it has not been shown that Coxsackie viruses can cause paralysis in man or influence the course of a simultaneous infection by poliomyelitis virus.

## IMPORTANCE

Coxsackie viruses are important etiologic agents in human disease. Awareness of this will lead to discovery of more information about the viruses in the future. At present, it is difficult to relate isolation of the virus to the pathogenesis, and hence clinical manifestations. Nevertheless, certain characteristics are appreciated already. Firstly, prenatal infections of Coxsackie viruses sometimes cause meningo-encephalitis and/or acute myocarditis, and with other virus infections may contribute to unexplained congenital anomalies (especially when infection occurs during the first trimester of pregnancy). Secondly, when a major childhood illness (endemic or epidemic) is contracted and is thought due to Coxsackie infection, the recent virus laboratory techniques enable isolation and identification of the virus. Although establishment of the diagnosis does not determine any specific treatment, the clinician who can recognize the disease (e.g. herpangina) can give a good prognosis to parents, reassuring them that another more serious illness is not present. Finally, since Coxsackie infection may produce only a minor illness which may be overlooked, it must be considered when healthy persons display abnormal electrocardiograms.

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# The Echo Viruses

GLENN L. OLIVER, '60

## HISTORY

The recovery in different laboratories of large numbers of new cytopathogenic viruses from the human intestinal tract has led to the recognition of a new group of viruses. There now exist 14 different antigenic types. Types 4, 6 and 9 have been correlated with the syndrome of aseptic meningitis in children.

The earliest isolations were largely from patients with a clinical diagnosis of mild or non-paralytic poliomyelitis. Cultures and serological tests, however, yielded no evidence to support such a diagnosis. Recently more isolations have been made from subjects diagnosed as aseptic meningitis or having milder nondescript febrile illnesses without manifestations of meningeal irritation, as well as from healthy children.

These viruses, some of which have been referred to as orphan viruses and others as the human enteric viruses, are now classified as the enteric cytopathogenic human orphan (ECHO) group.

## VIRUS CHARACTERISTICS

1. They are cytopathogenic for monkey and human cells in culture.

2. They are not neutralized by pools of the 3 types of poliomyelitis antisera.

3. They produce paralysis, usually of the hind legs, in day-old suckling mice.

4. They are not related to other groups of viruses recoverable from the alimentary tract by inoculation of primate tissue cultures, such as the viruses of herpes simplex, influenza, mumps, measles, varicella and the A.R.D. (acute respiratory disease) or A.P.C. (adenoidal-pharyngeal-conjunctival) group.

5. They are neutralized by human globulin or individual human sera, indicating that they infect humans.

6. All viruses tested are ether-resistant.

7. Unlike the clear round poliomyelitis plaques, the plaques of the ECHO viruses have irregular diffuse boundaries and healthy cells can be found within the degenerated areas of the plaque.

## LABORATORY DIAGNOSIS

### A. *Recovery of the Virus*

Specimens of feces and cerebrospinal fluid should be obtained from the patient between 2 and 7 days after onset of the illness. The specimens are then inoculated into the plates of monkey kidney epithelium or human cells in which the virus produces characteristic lesions.

### B. *Serology*

The significance of any isolation in tissue culture can be confirmed by a rise in titer or a high titer of neutralizing antibody in the convalescent serum. The cerebrospinal fluid may show a pleocytosis of 12 to 300 cells (mainly lymphocytes) and also a reltaively slight increase in protein.

## CLINICAL PICTURE

The syndrome of aseptic meningitis has been recognized for decades and it can not be sharply differentiated clinically from non-paralytic poliomyelitis. The cases under study have not differed materially from the old familiar picture. This is described as a benign febrile illness mainly limited to children. It begins abruptly with a severe headache, followed shortly by malaise, stiffness of the neck, often weakness of the muscles, pain in the back and anorexia. Occasionally the patient may

be subject to vomiting and complain of a sore throat. These symptoms subside within a week without sequelae and in particular without presenting muscular paresis.

Type 9 of the ECHO viruses in addition produces a rubelliform rash in about 40% of patients. The rash is finely maculopapular and appears 1 or 2 days before the onset of the major illness and persists for 8 or 9 days. It covers the face, trunk and extremities but no lesions occur in the mouth. The rash does not scale and usually clears without complications.

Neurological examination is usually negative except for stiffness of the muscles commonly subsiding within a few days. Often there is a diminution of the reflexes and some transient localized muscular weakness. The milder cases without stiffness of the neck and back show no adequately distinctive features, although there is often a pleocytosis in the CSF. In both groups specific complement fixing and neutralizing antibodies are produced although often less actively and in lower titer than in poliomyelitis.

## TREATMENT

As there is no specific therapy, treatment is entirely symptomatic together with good general care. Recognition and isolation of the virus strains will add much to basic knowledge of these infections.

## IMPORTANCE

As many as 10% or more of young children, apparently in good health, may harbor one of the ECHO viruses. The incidence of carriers is 3 times as great among children living in poorer surroundings than in those living in upper class districts with good environmental sanitation. The recent reports make it reasonably certain that at least 3 types of ECHO (4, 6 and 9) can cause active infection with involvement of the meninges, but thus far, fortunately, there have been no mortalities or definite permanent sequelae.

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# The Adenoviruses


V. CECIL WRIGHT, '60


## HISTORY

In the last 2 or 3 years a family of viruses known variously as the APC, AD, ARD, and RI viruses have been discovered. The field was opened in 1953 by Rowe and his associates. These investigators studied the tissue culture growth of bits of adenoids surgically removed from normal children. Immunization of rabbits with tissue-culture fluids containing the agent resulted in serum antibodies capable of neutralizing the agent in the culture. The agent was called "adenoid degeneration agent" or AD agent. The AD agent was later found in nasopharyngeal swabs and conjunctival swabs, hence

the name "adenoidal-pharyngeal-conjunctival" or APC virus. The ARD virus was associated with the acute respiratory diseases in military troops. This was due to RI-67 virus, or adenovirus type 4. A committee of investigators has recently agreed on the term adenoviruses. Rowe reported recently that the adenovirus family consists of at least seventeen serologically distinct viruses having similar properties. Three of these strains have been isolated from primates and are not associated with human disease.

## CLASSIFICATION OF ADENOVIRUSES

Types 1, 2, 5 adenoviruses occur chiefly in infants and young children. Type 3 adenovirus is associated with pharyngoconjunctival fever in children. Type 4 and 7 adenoviruses are associated with disease in adults only. Adenovirus type 4 is associated with acute respiratory disease in military recruits.

## PROPERTIES OF THE VIRUS

**A. Size.** The infective virus particles are 90 millimicrons in diameter as determined by electron microscopy.

**B. Reaction to Physical and Chemical Agents.** The viruses are ether-resistant but are heat labile, being destroyed at 56°C for 30 minutes. They are resistant to penicillin, streptomycin, and the sulfonamides. The viruses are stable in the pH range from 3.1 to 9.4. They are destroyed at pH 2.0 or below and at pH 10.0 or above. The viruses are usually stored frozen.

**C. Animal Susceptibility and Growth of Virus.** The virus does not produce disease in any known laboratory animal. It is cytopathogenic for human cell cultures, including HeLa cells, and for monkey kidney, and rabbit trachea cell cultures. The viruses are epitheliotropic, growing and causing changes in human epithelial cells more rapidly than in fibroblasts.

**D. Antigenic Properties.** The APC viruses, while immunologically distinct in neutralization tests, produce complement-fixing antigens which are exclusively shared. Infection of humans with a single APC virus stimulates a rise in complement-fixing antibody to antigens of all types. The complement-fixing antigen produced by the APC viruses was separable from the infective virus particle illustrating a soluble antigen.

## PATHOGENESIS AND PATHOLOGY

At least 5 of the virus types have been demonstrated in the tissues of adenoids and tonsils removed in surgery, by growing epithelium from such tissue for prolonged periods in the culture. The viruses could not be isolated from nasopharyngeal swabs or from suspensions of adenoids and tonsil of the same persons by the method of inoculating such material into highly susceptible cell cultures. An explanation for this is that the patients who yielded these viruses have usually possessed serum antibodies against the virus type later recovered from them. Such antibodies have been demonstrated in adenoidal and tonsillar tissue. The question has been raised whether these agents play a role not only in the acute diseases but also in chronic diseases (hypertrophy of tissues) of the nasopharynx that result in the necessity of surgical removal of adenoids and tonsils.

The viruses of these groups have been isolated from surgically removed adenoids and tonsils. No conclusions can yet be drawn as to the prevalence of the viruses in children lacking the clinical indications for tonsillectomy or adenoidectomy.

## TYPE 1, 2, 5 ADENOVIRUSES

Type 1, 2, 5 adenoviruses were in the majority of surgically removed adenoids and tonsils of children. Ninety-one percent of all the viruses recovered were of types 1, 2, 5 but strains of types 3, 4 and

6 were likewise recovered. Types 1, 2 and 5 are associated with producing an acute illness in children, sometimes called febrile catarrh.

The acute illness is characterized by fever, chills, generalized aches and pains, hoarseness and an irritated or scratchy throat. Cervical lymphadenopathy is frequently present. Pneumonitis is occasionally seen.

## TYPE 3 ADENOVIRUS

This virus was isolated almost exclusively from nasopharyngeal and conjunctival sections and anal excretions, the majority of isolations being obtained from persons with acute febrile pharyngitis and conjunctivitis. Type 3 adenovirus is associated with pharyngo-conjunctival fever in children. The illness is acute, characterized by fever, pharyngitis, conjunctivitis, malaise and cervical lymphadenopathy.

Total white cell counts taken early in the illness in some cases ranged from 7,400 to 16,400. During the early period of illness there was a slight neutrophilia. As symptoms progressed, differential counts returned to normal and mild leukopenia developed in most patients.

## IMMUNITY

Studies in human volunteers contributed the following information. Type-specific neutralizing antibodies protect against the disease of the adenovirus group, but the protection is not absolute. The cumulative occurrence of neutralizing antibodies against one or more types in different age groups shows that antibodies may be present in over 50% of the infants from 6 to 11 months of age. In one study a substantial increase in antibodies occurred in persons 2 years of age, but very little additional increase occurred in children 3 to 5 years old. Marked increases in 6 to 15 and 16 to 34 age groups were recorded in which the majority of persons had antibodies to 3 or more types.

The antibodies of types 1 and 2 were found prevalent in younger age groups. Antibodies to type 3 were found in 35 to 50% of children. Antibodies to types 5, 6 and 7 are less prevalent and children have no antibodies to type 4. Infants are usually born without complement-fixing antibodies but develop these by 6 months of age.

## TREATMENT

No specific treatment is known.

## IMPORTANCE

Man is commonly infected with these agents, the virus being readily spread from person to person. Members of the adenovirus group have been prominently associated with the latent infections of human tissues of the upper respiratory tract, epidemic diseases of children referred to as pharyngo-conjunctival fever, and epidemic respiratory illness of military recruits. Apart from their importance in the genesis of acute illness is the question of their possible role in the chronic diseases of the nasopharynx that result in surgical removal of the adenoids and tonsils. Although there is at present no convincing evidence that the persistence of these agents in such tissues represents a factor in disease and hypertrophy of those tissues, investigation of this seems warranted. Since infection by the adenoviruses is associated with respiratory diseases, attention is called to the role of the eye both as a site of primary infection and as a portal of entry for the infection.

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# Pediatric Pharmacology

THEODORE N. SILLER, '59

## INTRODUCTION

At present in pediatrics there is a swing from the use of apothecary's weights in drug dosage to the more accurate metric system. This transition has been gradual until the last few years and now the metric system seems to have come into its own. Reorganization in thinking, the great mass of factory-compounded drugs, and increasing knowledge allowing a more practical type of therapy all have contributed to this new uniformity of dosage measurement.

The change is not complete, however, and the following material is designed in an attempt to give the present picture, emphasizing its confusing nature and thus implying justification of the use of the metric system solely.

## HISTORY OF WEIGHTS AND MEASURES

From the known beginning of history, man found that the many facets and objects in his life had to be measured. This was done at first by comparing things to the nearest object at hand such as his finger length or bits of grain, accuracy not being essential as only the individual was concerned. As society grew the tendency was toward uniformity and the development of trade added to the idea of equability. The realization that the interests of all would be best served by a single system in a tribe was acted upon by adopting a mean or standard. The standard was fixed by the ruler in an arbitrary manner, such as the length of the English yard being fixed by the length of Henry I's arm or the grain by the size of seeds from a certain part of the head of grain.

With the development of geometry and astronomy a more mathematical approach was to result and with the continued improvement of these sciences the improved accuracy of the weights and measures was to coincide. Standards of various metals were set up and continually re-standardized with the growth of need and knowledge. Although these standards improved, they were only copies of the originals handed down through time.

The earliest reference to the metric system was the establishment of the metre as being equal to the ten-millionth part of the earth's meridian-quadrant, and the fixing of a relationship between units of weight (kilogram), capacity (liter) and unit of length (metre). Although this was not wholly accurate, scientific achievement has brought it up to a high degree of perfection.

## PEDIATRIC DOSAGE ESTIMATION

Several "rules of thumb" exist in determining the dosage of a given drug for infants and children. No arbitrary rule is completely satisfactory, being varied with the drug, individual and situation. Generally the therapeutic dose of most drugs is determined by pharmacological evaluation, initially in animals and subsequently in human adults. The quantity of a drug prescribed per unit body weight for an obese child should be somewhat less than for a thin one, suggesting the potential abuse of drug therapy and inadequate data for the determination of drug dosages for infants and children.

The newer and most popular rules include:

1. Fried's Rule: (for age group under 2 years)

$$\frac{\text{adult dose x age in months}}{150}$$

2. Clark's Rule: (for age group over 2 years)

$$\frac{\text{adult dose x weight in lbs.}}{150}$$

3. Young's Rule:

$$\frac{\text{adult dose x age in years}}{12 \text{ x age in years}}$$

4. Surface Area Rule:

$$\frac{\text{surface area of patient in sq. metres x adult dose}}{1.73}$$

The advantages of certain rules for particular situations seems inevitable and no one rule can be considered steadfast. Here again the measuring system can be confused in that the prescribed dose is given in amount of drug per unit body weight, the drug measured in metric units and the body weight in the avoirdupois system. Studies by various groups have been made on the three major criteria (age, weight, surface area) possible in determining dosage.

**Age**

Dosage according to age seems practical to many who feel that the infant or child is more susceptible to some drugs while more resistant to others. Morphine at blood concentrations producing analgesia in an adult may result in deep coma in a very young infant. The newborn infant may be deeply narcotized from an analgesic dose of morphine given to the mother prior to delivery. Atropine on the other hand seems to be tolerated by infants to a greater degree than by adults. The limited applicability of dosage based on age would seem apparent when one considers the appreciable error when the patient deviates from the norm as to size.

**Weight**

This seems to be the most practical criterion as it takes into consideration the range of size from the premature infant to the adolescent child. The weight also bears a fairly regular relationship to blood volume, thus allowing reasonable blood concentrations to be maintained. The drawbacks include the factor of obesity and differences in susceptibility at various ages where size may be constant. An example may be the decreased effectiveness of sedatives and digitalis when given according to adult dosage.

**Surface Area**

With the view that size variations are wide at certain ages, this method seems to be the most accurate and therefore satisfactory according to some authors. It is known that many of the fundamental physiologic processes of mammalian organisms are essentially constant when expressed per unit of surface area. An example cited is the energy output of the rat compared to a steer when expressed in calories / Kg. / unit time but is more comparable as calories / square metre of body surface. The accuracy of this method is immediately offset by the impracticability of measuring the patient and calculating, from normograms, the surface area.

## ANALGESICS AND BARBITURATES

Acetylsalicylic acid is probably administered to patients more frequently than any other drug and often without discrimination. It frequently causes poisoning in children. This drug is antipyretic and will alleviate headache, myalgia and arthralgia, one of its big uses being found in the treatment of rheumatic fever. Morphine, related alkaloids, and newer synthetics (Demerol) can produce addiction in infancy. Morphine in particular will depress peristalsis by increasing muscle tone, while stimulating the medullary emetic centre and causing marked respiratory depression. Except preoperatively, the opiates, other than codeine, produce a most effective analgesia.

The barbiturates have become increasingly popular for mild sedation. The in-

fant is more tolerant to these and therefore dosage according to age is the rule. Phenobarbital has been found to be satisfactory and occasionally, when very prompt sedation is required, intravenous phenobarbital sodium is found to be very effective. These dosages vary but in general the more excited the child the greater the initial dose required. Hypnotic doses are used to control convulsions or to supplement local anesthesia during the performance of painful procedures. They are contraindicated in the presence of any respiratory infection, obstruction or impairment of pulmonary ventilation. Other sedating agents used in pediatrics include secobarbital, paraldehyde and chloral hydrate.

## ANTIBIOTICS

These are defined as substances possessing anti-bacterial activity and, as in adult treatment, their use in pediatrics is very great. Penicillin, streptomycin, chloramphenicol, aureomycin and terramycin are the most widely used.

It is becoming well known that these antibiotics are effective against a great number of organisms but the potency varies with the organism and resistance to certain antibiotics can be found even at the level of strains of an individual group. This warrants precise knowledge of degrees of activity and methods of determining effective concentrations. The use of the metric system is indicated here. Penicillin dosage given in units persists but even here a transition seems inevitable as the drug is useful only when millions of units are given. The degrees of absorption and distribution from various sites of administration as determined by blood concentration levels, which in turn gives the picture of the effective amounts, all require a universal means of measurement. Rates of excretion and methods of maintaining high levels of concentration, both in the acute and prophylactic use, all show the need for a standard type of measurement, the metric system.

This requirement of precision must be even more emphasized in pediatrics where smaller quantities are required. Here the physiological systems may not all be completely developed, thus being more prone to damage.

## DIGITALIS

Although the indiscriminate use of digitalis in congenital heart conditions is to be deprecated, the wise use of the drug can be life-saving. Indications are the same as for the adult, including (1) cardiac failure, (2) dilatation of the heart and a gallop rhythm, (3) excessively rapid heart action, and (4) the more serious cardiac arrythmias. Any carefully tested stable preparation may be used. The dose is given in proportion to body weight, both dose and weight being given in metric units. The extreme care required is due to the fact that full therapeutic effects are attained in the child before any evidence of toxicity. Moreover, minor toxic effects are difficult to detect in young persons and the drug is usually needed for several years until the heart has adjusted to its load, then allowing discontinuance of therapy. The advantages of a uniform system of measurements in this type of therapy can be readily appreciated.

**Digitalis**

| Drug | Digitalizing Dose (Daily) |
|---|---|
| Digitalis leaf | 10 mg./lb. |
| Lanatoside C | 0.01-0.02 mg./lb. |
| Digoxin | 0.03 mg./lb. |

(Maintenance dose is 10% of digitalizing dose).

## SUMMARY

In the embryonic development of drug discovery and therapy the methods of measurement were those closest at hand. Prescriptions containing eight to ten drugs

with only one or two being of any use were written. Now only the essential constituents are used, requiring a precision never seen before. As the field has grown a more definite, universal method is needed, not only for the dosage measurement but more so in the experimental investigation and evaluation of a drug.

The older compounds such as acetylsalicylic acid and the belladonnas are still prescribed in "grains" to a great degree but the majority of compounds have turned to the metric system. The change has been especially noted with the advent of sulphonamides, antibiotics and newer sedatives.

Drug houses now market their products almost solely in metric units. The latest manuals and textbooks have to be well scanned to find a deviation from this new trend. The change to more uniformity is especially evident in pediatric practice where more delicate mechanisms and a great amount of variation deemed the use of the metric system in drug therapy as inevitable.

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"Clinical wisdom in its essence is case memory."

W. Heneage Ogilvie, Surgery Orthodox & Heterodox, 1948.

# Current Research in Pediatrics at U.W.O.

LAWRENCE A. BURK, '59

The majority of pediatric research now underway at the University of Western Ontario Medical School is in basic biochemistry. The work being done by the Pepartment of Paediatrics under Dr. John C. Rathbun has been greatly facilitated by the wide personal inter-departmental co-operation which is unique at this university. Elsewhere, basic science and clinical departments are separated, but under Dr. J. B. Collip a team approach toward research has been developed.

A series of investigations under the Department of Paediatrics are handled on a budget of $5,000. This is in contrast to the Hospital for Sick Children in Toronto where a budget of $500,000 is followed. However, despite financial difficulties, a varied program is being undertaken.

Two years ago a study began, with Mrs. Helen Robinson as technician, of glucose and galactose levels in the newborn infant. They were interested in discovering the changes that occurred in these carbohydrates in the first few weeks of life. During the past year two papers have been published on the techniques and methods of microanalysis. The method of sugar determination involved estimations on single drops of blood taken from the infant's heel. The analysis of these determinations is just being completed.

Now under way is a study which emphasizes the team approach to research. The departments of pediatrics, physiology, and obstetrics are combining in the investigation to find a relationship between fetal distress due to anoxia and certain conditions of the mother and the baby, the type of delivery, and observed chemical changes. Those factors which are found to produce fetal distress will then be reproduced experimentally in pregnant sheep and dogs. Under controlled conditions carbohydrate metabolism will be studied in normal animals as well as those under stress as evidenced by acidosis or anoxia.

Just beginning is a statistical study on all the factors involved in peri-natal mortality. It has been considered in the past that peri-natal mortality was unprofitable as far as scientific results were concerned. Consequently, nobody has really looked at the subject closely until the past two years. Spearheaded by Dr. John S. McKim, the departments of obstetrics, anesthesia and pathology, and the nursery will record 79 different factors on a check-type record sheet. The factors include time of first pre-natal visit, obstetrical history, presentation, duration of labor, infant resuscitation, anesthesia, infant feeding, congenital malformations, and affections of the newborn, to mention only a few. All these facts will be gathered together on I.B.M. cards and run through an I.B.M. machine. Any correlations between the factors and fetal deaths will then become apparent. With this information, the obstetrician and pediatrician will then know where we are going wrong, and may point the way to further research.

A small but interesting study concerns phenylpyruvic oligophrenia, a rare condi-

tion in which the amino acid phenylalanine is not properly converted to tyrosine. Tyrosine is the precursor for thyroxine, nor-adrenaline and thence adrenaline, and the dark melanin pigments of the hair and skin. A family under investigation had three children afflicted with this upset. One child died without treatment, one is in mental hospital, and the youngest is now under care at War Memorial Children's Hospital. This child, now 22 months old, is learning to walk and talk, making remarkable progress. The treatment is a phenylalanine-poor diet, one which is very difficult to obtain. The effects of this treatment are being studied, and to date it appears that early treatment, in the first few weeks or months of life, can lead to good results.

The Department of Paediatrics works closely with the Collip Medical Research Laboratory, where Dr. E. R. Plunkett and Dr. Rathbun are investigating endocrine disturbances. The War Memorial Children's Hospital also supplies much of Dr. M. L. Barr's clinical material in his work on sex chromatin.

The team approach leads to greater efficiency of research as has already been demonstrated by Dr. Barr's research, in which the departments of medicine, obstetrics, and histology co-operated. The study of carbohydrate metabolism was only possible through the co-operation of the departments of physiology, biochemistry, pathological chemistry, and pediatrics. The Department of Biochemistry under Dr. R. J. Rossiter has given considerable technical advice in the development of the methods of micro-blood determinations and the electrophoresis of free sugars in blood.

## THE RELATION OF VITAMIN K TO HYPERBILIRUBINEMIA

**E. Asteriadou-Samartzis, and S. Leikin, Pediatrics, 21:397, 1958.**

The authors wanted to find a preparation of Vitamin K which did not have a hyperbilirubinemic effect. This report consists of observations concerning the effect of various preparations of Vitamin K on the concentration of bilirubin in the serum of new-born premature and full-term infants. Attention was directed to the fact that Vitamin $K_1$ did not have the hemolytic action of water-soluble Vitamin K in experimental animals.

The investigators observed 119 infants divided into 7 sets (5 premature and 2 full-term groups). Serum bilirubin levels were determined on the 5th day of life on all premature infants and on the 3rd day of life on the full-term babies. The mean concentration of bilirubin for the premature group which received large doses of water-soluble Vitamin K was significantly higher than in the untreated premature group. The mean concentration of bilirubin for the premature and full-term group given Vitamin $K_1$ I.V. was below their controls.

The study indicated that 25 mg. of Vitamin $K_1$ I.V. could be employed for prophylaxis or therapy, and would not have the same dangerous effect of producing hyperbilirubinemia as water-soluble Vitamin K.

—Steve Radin, '59

# Some Medico-Legal Aspects of Flexion-Extension ("Whip-Lash") Injuries of the Neck

FRANK RIGALL, M.A., M.D., F.R.C.P. & F.R.C.S. (Edin.), F.R.F.P.S. (Glas.), Chief of Staff, Elizabeth Hospital, Prairie Grove, Ark.

The internal combustion engine has brought benefit and pleasure, but there is no pleasure without pain in this life. One of the pains brought by that engine is in the neck, caused by flexion-extension injury and widely known by the surgical slang term "whip-lash". Though not unknown in the horse drawn era, the condition lacked a specific name until its frequency increased with the advent of bigger, heavier, faster automobiles. There is a definite connection between automobile speed and weight and this injury. Its occurrence in European countries where big automobiles are used is more than in those countries where smaller, lighter cars predominate.

The most important and neglected study in medicine is the history of medicine. (1) It teaches us that where the cause of a condition is unknown the void of ignorance cannot be borne by medicine's disciples. They hasten to fill that void with theory and speculation, disregarding a rule that the greatest of scientific crimes is to pretend to knowledge where there is none. Flexion-extension injury of the neck has been no exception; medico-legal confusion has been the result; and this study proposes to dispel that confusion.

The injury here discussed has been a medico-legal no-man's-land (2 & 3). Lawyers, like St. Thomas, look for signs that they might believe, but they call them demonstrative evidence. The patient-clients with whom this paper deals present few or no signs. Most of them have been treated by orthopedists rather than neurologists because the trouble was considered to be musculo-skeletal and because there are more orthopedists than neurologists. The result has been to squeeze patient-clients into wrong categories and to try to make wrong categories fit the patient-clients. Between lawyers who wanted signs and doctors who could not supply them, unfortunate patients-clients have often been deprived of their medico-legal rights. Before post-mortem examinations and studies were made and a human volunteer used, the condition was a mystery. Much anatomical and pathological nonsense was created, and genuinely injured patients have been called neurotics, hysterics, malingerers, or seekers after the cure by gold.

Typically, but not solely, flexion-extension injuries of the neck occur when a car in which the patient is riding is struck from behind. The ramming car may hit dead on or at some side angle. The angle of ramming may alter the clinical picture; therefore, if possible, it is helpful to ascertain the positions of the cars at impact.

The victim's neck is first violently extended then flexed before equilibrium is restored. Extension is the villain in the event. (4)

Anatomically, the neck is a straightforward exercise, but there are important variants from the "normal". (5 and 6) High or low brachial plexus fixation, with possible alteration in the cervical plexus, is most important. The reported cases do not warrant dogmatism on the percentage of people afflicted by these congenital aberrations.

The yellow elastic tissue ligaments (Ligamenta Flava) of the neck are unique in their action. Strong pieces of tissue, they are powerful aids to the extensor muscles. They are out of harm's way in flexion. When extension occurs so unexpectedly that nature's guardian reflexes are not brought into play, the yellow ligaments are forced between the laminae, with curve convex forward, to crush the spinal cord against the vertebral bodies. For anatomical reasons this occurs only in the neck. It is the crux of this medico-legal problem.

Chance often illuminates dark corners in medicine. A totally unexpected experimental result in Wohler's laboratory in 1828 gave birth to organic chemistry. Processions of ants in Minkowski's laboratory pointed to the role of the pancreas in diabetes. (7) A chance remark of a veterinarian to a clinical experimenter revolutionized treatment of pernicious anemia. Gastric physiology had its foundations laid in the happenstance of a gunshot wound. Flexion-extension injuries of the neck share the romance.

Taylor tells the story. (8) An elderly man walking along with his hands in his pockets was kicking a golf ball. He stumbled, fell forward, and sustained a flexion-extension injury to his neck, paralysing him below the level of C6 and 7. He was quickly conveyed to hospital where X-rays were negative. In nine weeks he died of urinary infection. Death certificate requirements demanded post-mortem examination to explain the accident. The spinal column was uninjured, but the spinal cord was damaged. It had been crushed from behind forward at C4-5 segmental levels. Gross and microscopic examinations of the cord were illuminating, and convincing. They answered "What?" and "Where?" but not "How?".

In a brilliant series of studies on cadavers and a human volunteer done in the department of neurosurgery at Edinburgh Royal Infirmary it was shown conclusively that the damage was caused by the yellow ligaments. Knowledge resulting from these studies (9) solves a medicol-legal puzzle.

A useful classification of neck tissues injured in flexion-extension is:

1. Hard tissues—the neck bones
2. Soft tissues
   - A. Muscles and fasciae
   - B. Nerves and their meningeal sleeves
   - C. Blood vessels
   - D. Spinal cord
3. Combined hard and soft
   - A. Intervertebral discs
   - B. Intervertebral joints
4. Combinations of 1, 2, and 3.

Flexion-extension neck injuries are analyzed as follows:

**1. Hard tissues**

Neck bones rarely cause medico-legal problems. Their injuries are catalogued, X-rays reveal fractures and crushes, treatment is well defined, and prognosis known. In flexion the usual injury is compression. Extension breaks the arches. Cervical bodies 4, 5, and 6 are most frequently the site of flexion damage. Extension involves atlas and axis more frequently than 3, 4, 5, 6, and 7. (10 and 11). Subluxation can occur, may cause death, and has been reduced by surgeons, but

the theory of rapid subluxation and spontaneous reduction can today be dismissed as a fairy tale.

**2. Soft tissues**

*A. Muscles and fasciae*

Anatomy of muscles and their actions, and anatomy of fasciae are well known. Neither muscles nor fasciae refer pains widely. "They hurt where they are." If anatomy and pathology are sound, musculo-fascial injuries do not come within the problem.

*B. Nerves and their meningal sleeves*

If variations from "normal" are borne in mind, injuries to these parts are straightforward. The guide is this: though the injuries produce multum, they do not produce multa. Distributive fields can be plotted against pain and paresthesia descriptions by the patient. Injury may result from crushing or tearing, but most trouble comes from end results of inflammation due to trauma. If the capsule picture of inflammation be remembered, viz., Hemorrhage; Exudate; Organization; Adhesion; Contraction, the rest is simplified.

*C. Blood vessels*

Large blood vessels may be dismissed from consideration. Small blood vessels may be torn, or crushed, and, especially in the spinal cord, do severe damage via tissue necrosis.

*D. Spinal cord*

This site accounts for most of the pain and disability of patient-clients making up the problem. Their syndrome is strikingly different from those whose flexion-extension neck injuries have not included spinal cord damage. A catastrophe to victims has been a conundrum to doctors who have been unable to explain complaints anatomically or pathologically. Strong mental discipline is required to overcome that natural tendency of the normal human mind to deny what it does not understand. Unfortunately, that discipline has not always been used; consequently, lawyers have been angered and frustrated by denial or belittlement of sufferings they believe to be real.

The cord is injured in rapid complete extension by yellow ligaments infolding between laminae. Though cord crushing in this way happens most often and most severely at the summit of the curve, damage can occur from end to end of the curve. Consequently, the clinical picture may include segments C2 to C7 with C4-5-6 predominating. This area extends from occipito-parietal to lower scapula. Directions of impact force explain differences between sides.

Yellow ligaments and spinal cord do not show on X-rays. Because damage is to the posterior portion of the cord no disordered reflexes are produced. There is no demonstrative evidence for the lawyers. However, doctors who build their work on rock foundations of anatomy and pathology will have very little difficulty. Basic knowledge, and the ability to talk about it in a workmanlike manner, can marshall evidence for injured patient-clients for juries to understand.

Physiotherapy and common medicines relieve neck injury patients who have no cord damage. Such measures can be used as therapeutic tests to assess pain and disability. They do not relieve victims of cord injury; the pain is too severe and the paresthesias too distressing. Patients minus cord damage improve and get well according to the usual prognosis for the injuries they received. Spinal cord injury does not get well in the same time as damaged muscles and fasciae, bones or joints, or nerves and their sleeves.

Knowledge of the injury mechanism guides treatment. Fixation in mild or moderate flexion must be used. Extension did the damage and will perpetuate it. Traction is useless. Much longer rest is required than has been customary because

the prognosis is that of injured central nervous system tissue. An example is the anterior horns in poliomyelitis; another is nerve suture. From 18 to 24 months must elapse before the end result can be assessed except in the fortunate.

**3. Combined hard and soft**

*A. Intervertebral discs*

Discs have been blamed for much they cannot cause. Neck nerve roots pass directly laterally to their foraminal exits. Segment nerves emerge above the level of their corresponding vertebrae, e.g. C6 nerve passes out just above the body of C6 vertebrae. Each cervical nerve is in relation with only one disc.

Either by trauma or degeneration discs may bulge, lift the longitudinal ligaments and periosteum off the adjacent bone edges, carrying their blood vessels with them. Grieg proved that bone is laid down along the lifted vessels if the periosteum is not quickly replaced (12). Such new bone is the "osteophyte", a term of art invented by the radiologists. Posterior longitudinal ligament osteophytes lessen the available space in the spinal canal, thereby aggravating effects of flexion-extension. Osteophytes are protective in Nature's design. By limiting excursion of aging joints many a patient is spared pain and disability. (13)

Bulging discs may protrude centrally or laterally. Central protrusions affect the anterior portion of the cord. Symptoms so produced differ entirely from those being discussed. Lateral bulges cannot reach the nerve root without first pressing on half the anterior portion of the cord to cause a complete or partial Brown-Sequard syndrome (14). Only a ruptured disc with extruded material pushed laterally can affect a nerve root and nothing more. Symptoms so produced are distinctive, definite, and confined to the distribution of the root.

Multiple root involvement attributed to discs has origin in the osteophytes of spondylosis. Because nerve roots occupy only about one-third of space available to them in their foraminal passages, osteophytes have to be large to press upon nerves. When that stage is reached, there is indubitable X-ray evidence of spondylosis elsewhere.

*B. Intervertebral joints*

Large joints between vertebral bodies have been discussed adequately under their discs and longitudinal ligaments. Apophyseal joints, the small joints, are synovial. They resemble muscles and fasciae since "they hurt where they are". That they do not refer pain to wide areas is a fact observable in rheumatoid arthrithis. Spondylosis causes pain, sometimes severe, and aggravated by neck movements. Wear and tear of age with its osteoporosis, degeneration of discs and forward drooping of the neck puts a strain on the small joints with production of aching localized pain of a type distinguishable from pain of posterior cord trauma.

**4. Combinations of 1, 2 & 3.**

To reduce the problem to its least common denominators neck injuries have been described singly. In practice they occur in combinations, but, clearly, analysis of the combination is feasible. The problem cases will be the hard core left after single entities have been recognized; moreover, it is clear that only one of the denominators gives the extensive clinical picture produced by posterior cord involvement. There is a vagueness, indescribable and indefinable, about that involvement which in itself is part of the diagnosis and is explained by the anatomy of tracts and fibres affected. Cases differ because forces and extent of injury are different; yet, in measure, they all display the same factors. It follows that anatomical and pathological knowledge of possibilities eliminates impossibilities.

When estimating damages the long view must be taken (15). Doctors ought to be

taught the "once and for all" concept of damages awards. Many doctors do not know that when a case is settled there can be no further award to the patient for aggravation of his condition by normal, natural aging. Posterior cord damage present two years after injury will be permanent, and, with any other permanent disability present, will be made worse when bones shrink from osteoporosis and when soft tissues lose their supportive elasticity. It is, therefore, imperative in order to do justice that life expectancy and life's trials play their part when considering percentage disability (16).

It is hoped that this presentation of flexion-extension injuries of the neck will aid understanding of the problem. Better understanding will improve relations between medicine and law. Such improved relations will benefit patient-clients.

In closing, these words from Montaigne's "Essays" seem appropriate.

"I have gathered a posie of other men's flowers, and nothing but the thread that binds them is mine own."

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# Abstracts and Book Reviews

## HEMATOLOGIC STUDIES OF CHILDREN WITH LEAD POISONING

**R. Watson, E. Decker and H. C. Lichtman**

**Pediatrics, 21:40-46, 1958.**

Lead poisoning is known to produce anemia, basophilic stippling of the erythrocytes, porphyrinuria, and an increased concentration of free protoporphyrin in the erythrocytes. The pathogenesis of the anemia is believed to be a combination of increased hemolysis and a decreased marrow production of erythrocytes; of the porphyrinuria, a defect in the tissue metabolism of porphyrin rather than a result of increased hemoglobin degradation.

In an attempt to learn more about the exact pathogenesis of the anemia involved, complete hematologic studies were made of a group of thirteen children, ranging in age from 16 - 36 months, admitted to Kings County Hospital, with severe lead poisoning.

Diagnosis was made on a history of ingestion of plaster and paint, vomiting, and convulsions; on roentgenographic evidence of lines of increased density in the long bones; and on elevations of blood concentration of lead to 0.06 mg./100ml. or more.

### Results of Hematologic Studies

The anemia was microcytic and hypochromic in type, with a mean hemoglobin of 7.6 Gm/100 ml. There was moderate aniso- and poikilocytosis. Target cells were extremely numerous and reticulocytes were above 2% in nine cases. The plasma iron and percent saturation were low in all cases. However, the total iron-building capacity (TIBC) was variable, with a normal mean value of 285 ug/100 ml. The most striking finding was a marked elevation of free erythrocyte protoporphyrin (FEP), 1040-6620 ug/100 ml. of erythrocytes. The anemia, therefore, was similar to that seen in iron deficiency.

A comparative study was done in a group of children with iron deficiency anemia in which microcytosis, hypochromia, low plasma iron, and percent saturation were all found to approach the values demonstrated in the group with lead poisoning. However, reticulocytosis was almost absent, the TIBC values tended to be higher, and the values of FEP lower. Target cells were present in only moderately increased numbers, and there was no basophilic stippling in the iron deficiency group.

### Discussion

Lead is thought to injure the surface of the erythrocyte, thus increasing its fragility and decreasing its life span. The ribonucleoprotein of the young erythrocyte injured by the lead is precipitated by the stain to give the appearance of stippling. The authors cite the findings of McFadzean, Goldberg *et al* and their theories concerning the precise sites of lead action. But previous studies of lead poisoning have not shown that lead can produce an iron deficiency type of anemia.

Since the age of peak incidence of lead poisoning corresponded with that of nutritional iron deficiency, it is assumed that the nutritional anemia antedated the lead poisoning, and perhaps predisposed the victims to pica and the ingestion of paint and plaster.

The seasonal incidence of lead poisoning, in summer months, resulted in some speculation concerning the role of sunlight in the development of symptoms. In their rat studies, Rapoport and Rubin

found that both sunlight and cod liver oil enhanced the absorption of lead.

**Treatment**

The patients responded to Calcium Versenate intravenously, and Elixir of Ferrous Sulphate, 0.6 gm. daily.

—M. Jeanne Ferrari, '59

## SURVEY OF GENETICS AS IT APPLIES TO PROBLEMS IN MEDICINE

**B. Childs and J. B. Sidbury, Pediatrics, 20, July 1957**

In a not too technical, yet authoritative and complete manner, the authors have reviewed the fundamental concepts of genetics, and its applications to medicine. An increasing interest in the metabolic aspects of disease has led to the present recognition of their genetic control, although its practical impact has been little in the past. It is shown how genetics may be understood in biochemical terms and emphasis is made on the complexity of the mechanisms and the limitations of present knowledge.

Because genes with negative reproductive values tend to affect fertility adversely, early death or disability is the rule. It is for this reason that genetically determined diseases figure so prominently in the field of pediatrics.

**The Hereditary Material**

The concept proposed suggests that the DNA of the nucleus transmits its highly specific information to the RNA in the microsomes, possibly by governing the nucleotide sequence within the latter's molecule. The latter then acts in the synthesis of proteins (cheifly enzymes), and in this way the function of each gene is to control an enzymatically catalyzed reaction. Pauling, in accordance with this concept, suggests that all hereditary diseases are due to some abnormal product of an altered gene. Others maintain that genes express themselves through their influence on the balance of reaction rates, thus assigning to genes the responsibility for the fundamental mechanism of homeostasis.

These studies, as well as newer ones on mutations, positional effects, and pseudoalleles all confirm that the genetic unit is not independent of other loci. The day when one could consider the gene as an invariably discrete, simple kind of independent particle is obviously ended.

**Medical Applications**

While there are undoubtedly more conditions of medical interest due to dominants, it is often difficult to state if these are completely dominant since in most cases we never see the heterozygote. These genes are so rare that a mating of two heteros seldom occurs. In either case the phenotypic expression of the genes is its manifestation in its particular environment. It is for this reason that genes show the quality of pleiotropy, having a number of different effects on the various systems. The problem in human genetics is usually to try to explain these disparate effects in terms of metabolic actions consequent upon a single gene mutation.

Diseases due to genes in the heterozygous state include Marfan's syndrome and Osteogenesis imperfecta, both of which are characterized by defects in connective tissue fibres, late age of onset, and fairly mild clinical manifestations. The lack of severity may be attributed to the fact that the mutant genes are present in the genotype together with a normal allele, which ameliorates its phenotypic effects.

Diseases due to genes in the homozygous state include most of the "inborn errors of metabolism". These generally are more severe, earlier in onset, and the victims less likely to reproduce, than the above. Microbial genetics has shown that

whenever there is evidence of reduced enzyme activity with an accumulation of some percursor substance (or a deficit of some other protein substance) there is a mutant gene at work. In phenylketonuria, the synthesis of tyrosine from phenylalanine is blocked as a result of loss of an enzyme. Galactosemia has the same basis, and shows as well the relationship between gene and environment—in any society in which milk is not used, the gene and the disease would be unknown. Glycogen disease may take any of four types, each of which can be differentiated clinically.

Diseases due to genes of intermediate dominance are exemplified by the hemoglobinopathies. Here, a minor manifestation is distributed in families as if due to a dominant gene and vice versa. Thus in a large group of sibships the distribution should be Mendelian.

Heterogeneity of clinical manifestations within a syndrome, if genetically determined, will be more pronounced between rather than within families. This may be due to genes at different loci causing different biochemical defects or to alleles at a single locus. In Virilizing Adrenal Hyperplasia the clinical and chemical variants suggest that each type is the result of a different mutant gene acting from an unique locus. Cretinism with goitre, although homogeneous clinically, has been shown to be due to any one of three specific enzymatic blocks in the synthesis of thyroxine.

Genetic effects may also be modified by the action of other genes or by environmental effects. In premature baldness the sex-linked gene's capacity for expression is wholly dependant on the hormonal environment, whereas in Hemochromatosis the apparent male predominance is merely a reflection of the protective effect of menstrual iron loss.

In other situations such as Rheumatic fever, Erythroblastosis Fetalis, Mongolism and Diabetes, the situations are more complex and definite evidence is lacking.

—Ivan B. Pless, '58

## TONSILLECTOMY AND THE RISK OF POLIOMYELITIS

**P. Barsky and R. Lauer,**
**Canad. Med. Ass. J., 77: 576-578, 1957**

During 1953, a total of 2,371 cases of poliomyelitis were reported to the Manitoba Department of Health. The epidemic was unique because of the high incidence and severity of the forms of bulbar poliomyelitis. The present report is an analysis of the incidence of tonsillectomy among these patients.

The present enquiry differs from previous ones in that the incidence of tonsillectomy in the various forms of poliomyelitis has been correlated with the incidence among an exposed control population in whom the disease did not develop.

It was found that persons with bulbar and bulbospinal poliomyelitis are more likely to have had their tonsils removed than those with the spinal or nonparalytic forms. The family contact controls of bulbar and bulbospinal types are also more likely to have had tonsillectomy than the family contacts of the other groups.

This suggests that there may be some underlying factor that determines both tonsillectomy and bulbar infection. There is a greater incidence of tonsillectomy in patients with all forms of poliomyelitis than in the family controls in whom the disease does not develop. When these patients are compared with the population exposed to poliomyelitis, but remaining free from the disease, it can be seen that there is a similar increase in the incidence of tonsillectomy among these controls. There may be some local condition of the pharynx which, on the other hand, makes a child more liable to bulbar poliomyelitis after the operation.

—Martin Taylor, '59

# News and Views

### Catching Cold

Epidemiological observations in the field have confirmed the common view that one may catch a cold from another sufferer, probably by direct contact, the frequency and intimacy of contact being important factors. Age is important, and it is clear that children are more susceptible to infection than adults and are more often responsibile for introducing infection into the home. Some people regularly catch more than their quota of about two colds per season. Despite seasonal prevalence and the observed coincidence of outbreaks with low temperature and humidity, experimental chilling has not been found to induce colds or to reduce resistance to small doses of virus.

### Animal Experimentation

At a lecture given to the Research Defence Society in London, England, Lord Cohen of Birkenhead waded through the still not clear antivivisectionists' views on animal experimentation. This latter group's confusion through the years seems to reside in the following three aspects. Firstly, the contribution of this experimentation to the understanding of disease, and its cause, prevention, cure and alleviation; secondly, the assurance by legislation that needless suffering was prevented; and lastly, the question of ethics and morals of using animals experimentally in the attempt to ease human suffering.

The eminent lecturer cited the discovery of insulin and its great aid in prolonging the life expectancy of the diabetic. Equally strong arguments lay in examples of vaccines and sera whose production, virulence and potency testing in animals could not be dismissed, even by antivivisectionists, as not a true need. For the legislative end of the matter, it was cited that in England's House of Lords where the subject had recently been debated, no specific indictment was laid despite full opportunity.

The ethical defensibility of animal experimentation, like all such questions, must be answered by the individual, although of significance was the overwhelming acceptance of a questionnaire sent to the religious heads of the community.

A final controversial point lay in the antivivisectionists' feelings that these experimentations are useless because the final experiment has to be made in man. To this, the point was made that although animals differed in many respects to man, the similarities are more marked and in selecting an animal suited to the purpose, one is able to define whether the results are applicable to man and safe for human experiment.

### Congenital Malformations

A very interesting study to follow through on the antivivisection question is that of exposure to hypoxia of pregnant female mice with subsequent congenital malformation of the offspring. These malformations were mostly skeletal and were induced in mice by simulating high altitudes for appropriate periods of time. The extent of deformity varied according to altitude simulated and length of time mothers were kept within the chamber.

The nature and extent of skeletal malformations were also dependent upon the precise stage of somite differentiation at the time when maternal stress was induced. A cephalocaudad sequence of maldevelopments emerged corresponding to the cephalocaudad sequence of skeletal somite formation.

Independently, workers and investigators in the United States, Germany, and

Japan have brought together their observations. They indicate clearly the importance of minute and sharply timed, environmental circumstances in determining variations generally thought to be of genetic origin.

### Communicable Diseases

A point of interest, in our decreasing incidence of communicable disease, is the fact that the State of Georgia, U.S.A., has had 200 to 300 cases of diphtheria each year from 1949 to 1954. These rates are three times the national average for the year. The persistent localization of such reported diphtheria cases has resulted in a further study. The state is thought to have a good public health system and good laboratory facilities. The constant awareness of such situations in medical practice need not be emphasized further.

# Recent Acquisitions in the Library

ALTSCHULE, M. D.: Roots of modern psychiatry. 1957.

ANDERSON, W. A. D.: Pathology. 1957.

ASKEY, J. M.: Systemic arterial embolism. 1957.

CANTAROW, A.: Biochemistry. 1957.

CHATFIELD, P. O.: Fundamentals of clinical neurophysiology. 1957.

DILL, L. V.: Modern perinatal care. 1957.

EVANS, R. W.: Histological appearances of tumours. 1956.

FOLLEY, S. J.: The physiology and biochemistry of lactation. 1956.

FROBISHER, M.: Fundamentals of microbiology. 1957.

GELVIN, E. P.: Obesity. 1957.

GREEN, G.: The last angry man. 1956.

GREENFIELD, J. G.: An atlas of muscle pathology. 1957.

Gt. Britain. Royal commission on the law relating to mental illness and mental deficiency, 1954-1957.

GUYTON, A. C.: Textbook of medical physiology. 1956.

HANLEY, H. G.: Recent advances in urology. 1957.

HARTMAN, F. W.: Hepatitis frontiers. 1957.

HEWITT, R. M.: The physician-writer's book. 1957.

Houston Neurological Society. Brain mechanisms and drug action. 1957.

KEULEMANS, A. I. M.: Gas chromatography. 1957.

LAWLER, S. D.: Human blood groups and inheritance. 1957.

MEDAWAR, P. B.: The uniqueness of the individual. 1957.

MOORE, T.: Vitamin A. 1957.

MONTAGU, A.: The direction of human development. 1955.

National Research Council. The physiology of induced hypothermia. 1956.

New York Academy of Medicine. Freud and contemporary culture. 1957.

PEARSON, O. H.: Hypophysectomy. 1957.

PIGMAN, W. W.: The carbohydrates. 1957.

QUICK, A. J.: Hemorrhagic diseases. 1957.

RCA Service Company, inc.: Atomic radiation. 1957.

REYNOLDS, A. K.: Morphine and allied drugs. 1957.

ROBBINS, S. L.: Textbook of pathology. 1957.

SENTURIA, B. H.: Diseases of the external ear. 1957.

Society for general microbiology. Mechanisms of microbial pathogenicity. 1955.

SOLOMONS, B. A. H.: One doctor in his time. 1956.

STOKES, E. J.: Clinical bacteriology. 1955.

SWANSON, C. P.: Cytology and cytogenetics. 1957.

WELSH, A. L.: The dermatologist's handbook. 1957.

ZINSSER, H.: Bacteriology. 1957.

# Alumni and Faculty News

We are sorry to lose Dr. Lyle Jentz (Meds '51) who has gone to the Brantford General Hospital as chief pathologist. Dr. Jentz was on the University staff as a Teaching Fellow in Pathology and on the staff of St. Joseph's Hospital in this city.

By devious means (hiding under the pool table in the interns' quarters) we have managed to find out what most of the UWO '57 grads from Victoria Hospital are going to do next year.

(* indicates Victoria Hospital, London.)

Dr. Ron Armstrong — General Practice Course at University of Toronto.
Dr. Don Campbell — General Practice Internship at Montreal General Hospital.
Dr. Tom Code — General Practice Internship at Hamilton General Hospital.
Dr. John Collyer — General Practice Internship at Hamilton General Hospital.
Dr. Keith Johnston — General practice.
Dr. Mas Kawasaki — Residency in Otolaryngology at Washington University, St. Louis, Mo.
Dr. Don Killinger — Senior Intern in Medicine*.
Dr. Charles Knight — Royal Canadian Navy.
Dr. Dave Lawson — Royal Canadian Air Force.
Dr. Bill MacDonald — General Practice Course at University of Toronto.
Dr. Bob MacLachlan — Surgery at Winnipeg General Hospital.
Dr. Ian Malcolm — General practice in Hamilton.
Dr. Don McGee — Senior Intern in Medicine*.
Dr. Don Mills — Research Associate in Pharmacology at Queen's University, Kingston.
Dr. Reg Ort — Senior Intern in Surgery*.
Dr. John Platt — Medicine and Surgery (six months each) at Westminster Hospital, London.
Dr. Vince Quinlan — Senior Intern in Medicine*.
Dr. Ed Rawling — Senior Intern in Surgery*.
Dr. Don Robinson — Obstetrics and Gynecology, (Junior Fellow in Pathology)*.
Dr. Marcia Smith — Senior Intern in Medicine*.
Dr. Newel Smith — Residency in Ophthalmology at University of Michigan, Ann Arbor, Mich.
Dr. John Spears — Senior Intern in Medicine at Kingston General Hospital.
Dr. Paul Walsh — Neurophysiology, Dept. of Physiology, U.W.O.
Dr. Benny Waxman — Obstetrics and Gynecology, (Junior Fellow in Pathology)*.

Their classmates now at St. Joseph's Hospital also have varied plans.

Dr. Ronald Berry — General practice in St. Thomas, Ont.
Dr. Norm Burt-Gerrans — General practice in Woodstock, Ont.
Dr. Bill Butler — General practice in Ailsa Craig, Ont.
Dr. Jim Goodwin — Royal Canadian Navy.
Dr. Joe Hackney — General practice in St. Marys, Ont.
Dr. Lyall Howlett — Royal Canadian Air Force.
Dr. John Lohstoeter — Surgery at University of Arkansas.
Dr. Lewis Milburn — Anesthesia at Receiving Hospital, Detroit, Mich.
Dr. Eric Palmer — General practice in Woodstock, Ont.
Dr. John Patten — General practice in London, Ont.
Dr. Joe Schisler — General practice.