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PREMATURITY

FRANCES C. SCHAEFFER, M.D., F.A.C.S.

In the United States in 1946 prematurity was eighth in the list of causes of death, being preceded by heart disease, cancer, apoplexy, nephritis, motor accidents, pneumonia and tuberculosis. In that year 10 percent of all deaths were listed as stillbirths or neonatal deaths. Of these, 49.2 percent were premature infants. Thus, to the physician interested in obstetrics, prematurity presents a major problem.

The incidence of the occurrence of prematurity varies as indicated by these records:

Johns Hopkins Hospital	11.7%
Eastman—private	5.3%
New York Lying-in	2.95%
Allentown General Hospital—1951	5.6%
Private Practice—1946-1951	5.4%

By definition, a premature infant is one whose weight at birth does not exceed 5.5 lbs. or 2,500 gms. Both the length of gestation and the length of the baby are too uncertain and variable to be of much value. Also, it has been found that the survival rate of premature infants varies directly with the weight of the infant at birth.

Why women go into premature labor, with or without premature rupture of the membranes, is not fully understood. Eastman believes that in at least 60 percent of the cases there is no demonstrable cause. However, there have been studies to show that certain factors tend to increase the incidence of prematurity. These factors include: poor prenatal care; previous infant loss; previous prematurity; previous abortion; bleeding during pregnancy; congenital malformation; obstetric abnormalities such as placenta praevia, premature separation of the placenta, toxemia, multiple births; acute and chronic disease in the mother, especially cardiac disease, nephritis, diabetes, pyelitis, syphilis, myoma, pneumonia; trauma; miscellaneous causes such as parity, youth, frequency of conception and constitutional make-up.

Brown et al have shown that one of the most important factors in the history of a woman who has a premature labor is some type of bleeding at any time during her pregnancy. They also point out that maternal illness appears to be associated either directly or indirectly with about 65 percent of single live-born premature infants and 80 percent of stillbirths.

The obstetric abnormalities enumerated frequently are the indication for an operative termination of the pregnancy. This is particularly true of severe toxemia and eclampsia. Moreover, these conditions, per se, increase the incidence of prematurity because of their high incidence of stillbirths. In the two series here studied there were 34 stillbirths and in nine cases there was associated toxemia. Toxemia associated with a medical complication is even more serious and frequently forces the obstetrician to deliver the patient prematurely. This was particularly true of our cases which had toxemia superimposed upon such conditions as rheumatic heart disease, severe hyperthyroidism, hypertension and diabetes.

There are several prematures in this series because of inductions without indication and two that are the result of elective repeat Caesarean section. There is no reliable way of accurately determining the size of an unborn infant.

Trauma as a factor is relatively unimportant. Occasionally surgery during late pregnancy will lead to premature labor and so should be avoided if possible. There is one case here of a ruptured appendix operated upon at seven months followed by premature labor.

Premature rupture of the membranes is a frequent complication of cervical amputation. This operation, therefore, should be reserved whenever possible for women past the child bearing age.

Tompkins and Wiehl, in an excellent paper entitled "Nutritional Deficiency as a Causal Factor in Toxemia and Premature Labor", have shown rather conclusively that "The patients beginning obviously underweight or overweight have an increased incidence of catastrophies, and those commencing pregnancy at standard weight but whose pattern of weight gain fails to follow the standard pattern, also have an increased incidence of catastrophies. The individual who is underweight at the time she becomes pregnant is the greatest obstetrical hazard, having the greatest possibility of both toxemia and prematurity."

In the series reported, the most frequent maternal complications were as follows:

MATERNAL COMPLICATIONS

	A.G.H.	Private
Total premature deliveries	121	90
Stillbirth	24	10
Toxemia	12	6
Placenta praevia	8	5
Premature separation	15	0
Medical	3	6

To further understand this condition we also must investigate the cause of death in the infants. This may be divided into stillbirths and neonatal deaths, and except for a few words the latter will be left to the pediatrician.

Many intrauterine deaths cannot be explained and so at present are not preventable.

INCIDENCE OF PREMATURE STILLBIRTH

	A.G.H. Private	
Prematures.....	121	90
Stillbirths.....	24	10
%	19.9%	11.1%

The most frequent cause of stillbirths in this series was toxemia with resulting premature separation of the placenta or placental infarction. Also important were severe erythroblastosis and congenital malformations.

The premature infant is born with certain physiologic handicaps which the physician must keep in mind. Lund, in his article "The Management of Premature Labor" has listed them as follows:

The respiratory system is anatomically immature. There is a layer of cuboidal epithelium overlying the capillaries in the alveoli and the capillaries are few in number. There is scant elastic tissue to aid in expansion of the lungs and the nervous system control is poor. The central nervous system reacts slowly to an increase in carbon dioxide in the blood. The cough and gag reflexes and the muscles and bones of the thoracic cage are weak.

The gaping fontanelles and suture lines expose the delicate brain tissue to trauma, and in these infants the brain tissues are softer and more friable than the full term infant. Also the membranes over the brain tear more readily.

In the circulatory system there is increased fragility of the capillaries, a decrease in prothrombin time and a decrease in the amount of elastic tissue around the blood vessels. The oxygen capacity of the blood is lessened by the presence of a large number of nucleated red cells and there is an iron deficiency. These handicaps increase the incidence of atelectasis, hyaline membrane disease, intracranial trauma and damage among other things.

These infants have poor body temperature control. It has definitely been shown that the prognosis of survival of a premature infant depends largely upon its weight at birth and the absence of

maternal disease or serious obstetrical complications. In spite of all the above factors it has been shown that the prognosis for survival is markedly improved if the infant survives the first 24 hours of its existence. The gastrointestinal tract is not capable of digesting food and feeding becomes a real problem.

There are certain complications which decrease the chance of survival of the child. These include immaturity; intracranial hemorrhage; congenital abnormalities; atelectasis and hyaline membrane disease; operative obstetrical procedures; improper use of anesthetics and analgesics; improper use of oxytocic; induction of labor; and hemorrhage and infection.

From this list it is evident that the chance for survival of the premature infant rests in great part on the skill and judgment of the attending obstetrician. Our aim in obstetrical care of our patients must be to prolong gestation and protect the fetus against such dangers as anoxia, obstetrical trauma, and infection to which it is so prone because of its physiologic handicaps.

Adequate pre-natal care is important. It has been shown that the incidence of prematurity is definitely higher among patients of the poorer class with their poor diet and inadequate pre-natal care. The detection of anemia in the mother will help to decrease the amount of anemia in the infant. Proper instruction in diet is more important than pills. Tompkins et al have shown that an underweight individual needs to gain at least three pounds in the first trimester and five pounds in the second trimester to decrease her chances of prematurity. These cannot be compensated for in the third trimester because of the possibility of precipitating toxemia. Thus nausea and vomiting during pregnancy should be controlled as early as possible. Likewise he has shown that the overweight patient is better with a weight loss on an adequate diet.

As has been mentioned, a previous history of abortion, prematurity and stillbirth is important. These patients need careful supervision. Smith and Smith in Boston have decreased the incidence of prematurity by 20 percent with the use of Stilbesterol in indicated cases.

With a routine Wasserman, syphilis can be detected early and adequately treated, thus decreasing almost to nothing the premature births caused by this disease. Early pre-natal care makes possible the detection of serious medical complications and their careful supervision during the entire pregnancy. This is true of cardiacs, diabetics, hypertensives, etc. Adequate treatment of pyelitis, hypo or hyperthyroidism and other chronic diseases will help to lower the incidence of prematurity and also produce healthier infants even though they are premature.

The importance of the early detection of toxemia cannot be over-emphasized. Immediate control and then delivery of the infant is imperative. After the 36th or 37th week, the advantage of increased birth weight gained by waiting is offset by the possibility of intrauterine death from premature separation of the placenta and toxemia.

Of special interest in recent years is the complication of hyaline membrane disease, particularly frequent in premature infants born by Caesarean Section. Every effort possible should be made by the accoucheur to allow repeat Caesarean Sections to wait until as near term as is deemed safe for the mother.

In all types of obstetrical complications it is well to try to delay delivery until after the 35th week. In the treatment of placenta praevia there will be fewer neonatal deaths if delivery is delayed until the 35th or even 37th week. Traut, in an excellent paper on "The Conservative Management of Third Trimester Bleeding", outlines the following: With the first bleeding he hospitalizes the patient at once. Blood is made available and the patient is put at complete bedrest. No rectal or vaginal examinations are done. The patient is watched carefully and blood replaced as necessary. When the bleeding has stopped for at least 24 hours, the patient is X-rayed to determine the cause of the bleeding. If the infant is small he waits. If not, and if the patient is near term, he makes his diagnosis by vaginal examination with a double set up. He and others have shown that the maternal mortality is not increased by this method but that fetal survival is markedly increased. He bases his treatment on the fact that only about 20 percent of all third trimester bleeding is due to placenta praevia and that this bleeding, even when it is due to placenta praevia, will cease spontaneously in 24 hours in almost all cases with bedrest and mild sedation. Often it will not recur under these ideal conditions.

Premature rupture of the membranes is a common complication of premature deliveries. Its etiology is not known and it may be serious because of the danger of infection to both the infant and the mother. However, the liberal use of antibiotics, along with hospital care, has minimized this complication and thus it is safe to maintain the pregnancy. There are good reports of delaying labor with the use of large doses of progesterone. This, however, is expensive.

As we have shown, the premature infant is sensitive to any central nervous system depressants and easily injured by unnecessary trauma. The management of labor, delivery and the infant at delivery is therefore most important. The less analgesia used, the better. Demerol in small doses with moderate doses of Scopolamine have given good

results in our hands. Morphine is contra-indicated and should never be used to stop premature labor. It is ineffectual and if labor progresses may severely affect the infant. There is an unbroken chain between pain relieving drugs, general anesthesia and neonatal death. These must be avoided.

With the use of the various conduction anesthetics, very little or no analgesia is necessary. There is rapid dilation of the cervix and good relaxation of the perineal floor in second stage, thus preventing pressure on the brain. However, the drop of blood pressure, sometimes seen when these anesthetics are given, may be injurious to the infant by decreasing its oxygen supply. We therefore prefer local anesthesia for delivery of the smaller premature because it has no effect on the infant whatsoever. Liberal use of 100% oxygen is of value during the second stage of labor and during delivery.

Intracranial hemorrhage and trauma are frequent among premature infants. These may be prevented by preserving the membranes as long as possible, by the use of liberal episiotomy and by either spontaneous or low forceps delivery. With Dana and other authors, we believe that low forceps tend to protect the head of the infant as it passes over the perineum and also prevent precipitous deliveries. Rapid or operative deliveries are too traumatic to the delicate infant.

Malpositions, especially breeches, are frequent in premature labors. In 1951 at the Allentown Hospital in 2,139 deliveries there were 58 breech deliveries or 2.3 percent. Of 121 premature deliveries there were 10 breech or 9.3 percent. In the private series reported, the incidence of premature breech delivery was 8.9 percent. Conservative management of these malpositions has given the best results. In breech deliveries it is especially important to wait for complete dilatation of the cervix and here again the use of aftercoming head forceps, we believe, will prevent brain damage. Caesarean Section is done in most cases in the interest of the mother. Premature infants born by Caesarean Section frequently do not do well and are especially susceptible to hyaline membrane disease. We still do not know how to prevent this fatal complication.

Premature labor is often prolonged and ineffectual. Exhaustion in the mother is reflected in the infant and thus must be avoided. Acidosis, ketosis and dehydration must be prevented by the use of fluids fortified with glucose by mouth when tolerated, or intravenously. The use of intravenous vitamins may be of value in long labors. Although we believe that stimulation of labor by the use of pituitary extract is bad because of potential trauma to the infant, still it may be used occasionally with caution. Caesarean Section may have to be employed in a few studied cases.

Anemia developing in these infants is often a problem. They can be given increased iron by delay in clamping the cord after birth. The cord should be allowed to pulsate as long as possible and be clamped late. Remember, however, during this time the infant should be kept warm and the airways kept open.

The question of the value of Vitamin K in the prevention of hemorrhage is not answered. Some men prefer to give it to the mother during labor—remembering that it must be repeated at least every eight hours. Others give it to the infant at birth.

All premature infants should be handled gently. The actual delivery is extremely important and should be handled by an accomplished obstetrician. I prefer to have a pediatrician present at the time of delivery and let him supervise the immediate care of the infant.

We obstetricians must admit that more has been done to decrease neonatal mortality from prematurity by the pediatricians than by ourselves. With good obstetrical care, however, we can give the pediatrician better babies and fewer prematures with which to work. I feel this important subject demands more study and attention by all of us.

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PEDIATRIC ASPECTS OF PREMATURITY

FORREST G. MOYER, M.D., F.A.A.P.

MORTALITY rates for all ages have shown a steady decline throughout the world for the past 50 years. The total death rate in the USA has fallen from 17.6 per 1,000 estimated population in 1900 to 10.0 in 1947. With the decrease in the number of deaths has come a shift in the relative frequency of various causes. Prematurity, which was not among the 10 leading causes of death in 1900, is now in eighth place. It is surpassed only by heart disease, cancer, apoplexy, nephritis, motor accidents, pneumonia and tuberculosis. The rate for death from prematurity in 1946 was 28.8 per 100,000 estimated population.

Prematurity, according to data on death certificates, accounted for 22 per cent of the deaths under 1 year in 1920 and for 32 per cent of the deaths in 1946 despite the fact that during the same period mortality from prematurity declined from 19.4 to 12.1 per 1,000 live births. This means that prematurity has decreased less than have other conditions responsible for fatalities in this age period.

We have reviewed the cases of prematurity at the Allentown General Hospital in 1951.

BIRTHS AND STILL BIRTHS - ALLENTOWN GENERAL HOSPITAL 1951

Births	Stillbirths	Deaths
2139	35	37
	of which prematures make up	
107	24	36

In our series the incidence of prematurity in relation to the total number of live births was approximately five per cent, which compares favorably with those rates reported in other studies.

Age at Death	Allentown General Hospital	Boston Lying In
0 to 7 days	96%	96%
8 to 21 days	2%	4%
21 plus	2%	0%

It will be noted that the majority of deaths occurred within the first 48 hours of life. Even those infants of less than 7 months gestation will live for 18 to 24 hours before death occurs. Few live more than 48 hours. The miniature respiratory and circulatory systems seem incapable of sustaining life beyond that time.

Time of Death	Number	Time of Death	Number
within 24 hours	19	within 120 hours	1
within 48 hours	6	within 144 hours	3
within 72 hours	3	later	2
within 96 hours	2	Total	36

Birth Weight	No. of Prematures	Mortality	
		Altwn Gen.	Bos. Lying
0 to 1,000 Grams	14	100%	92%
1,000 to 1,500 Grams	11	63%	58%
1,501 to 2,000 Grams	29	31%	13%
2,001 to 2,500 Grams	61	9.8%	5%

The fatality rate is inversely proportional to the birth weight, and our mortality rate compares with those reported in other series. The mortality rates of the Boston Lying In Hospital are included for comparison.

CAUSES OF DEATH

Prematurity	18
Respiratory	11
Spina Bifida	1
Congenital Heart Disease	3
Duodenal Stenosis	1
Monstrosity	1
Intracranial Hemorrhage	1
Total	36

What is listed as prematurity in the table of causes of death is usually assigned to deaths during the first day. The majority of these deaths were in infants weighing less than two pounds and are the deaths which are most difficult to prevent.

Potter has shown that abnormal function of the lungs is the most common cause of death in prematures.

The lungs are slow to develop in utero and in the infant at birth are proportionately less mature than most other organs. Except for the vascular system, the lungs are the part of the body whose satisfactory function immediately after birth is most essential for survival. They are the only organs that take on an entirely new function after birth. Even though respiratory movements are normally made before birth they serve no purpose in oxygenating fetal blood. After birth for the first time air is drawn into the lungs and O_2 and CO_2 are exchanged across the capillary membrane that separated the pulmonary blood supply from the alveolar oxygen.

In the fetus of less than four or five months, transfer of inspired air to the blood vessels in the lungs is impossible because the pulmonary tree is lined by a continuous layer of cuboidal cells and the blood vessels lie in the intervening interstitial tissue and have no direct contact with the potential air spaces. A live born fetus of this age will draw air into its lungs and dilate the lumens of the air spaces but the cuboidal cells persist and form an impenetrable barrier to the exchange of oxygen and carbon dioxide.

Early in the fifth month ingrowth of capillaries marks the beginning of an alveolar differentiation and by the end of the seventh month enough capillaries are present in direct contact with the potential air spaces to permit adequate oxygenation of the infant's blood. The principal reason that the end of the seventh month, when the infant weighs about 1000 grams, generally marks the beginning of the period of independent viability is that at this time the lungs begin to be able to function in a manner capable of supporting life.

The more immature the infant at birth, the fewer the alveoli and alveolar capillaries that have developed and the less the pulmonary reserve on which it can depend. Consequently any factor interfering with pulmonary function will be much more hazardous for a small premature than an older one and more hazardous for both than for an infant at term.

Since proper aeration is so important for the premature infant, one might well allow two or three minutes of posterral drainage and catheter suction before the premature infant is transferred from the birth canal to the oxygen filled incubator. Even the smallest of the premature do not die quickly and perhaps unnecessary haste has been devoted to getting these babies into extra warmth and oxygen in the least possible time. A few moments devoted to gentle suction and drainage might prevent the deep advance into the lungs of aspirated material never again so easily removable as immediately after birth.

We prefer the suction bulb and Arnold aspirator for this purpose. A motor driven aspirator has too much suction for small tissues as evidenced by the hemorrhage and edema so frequently seen in the throats of the new born. Direct laryngoscopy and bronchial aspiration is technically difficult and to my mind, the danger of trauma outweighs its advantages unless done by trained personnel. Unfortunately such personnel is not readily available at the time of greatest need. Blossom has devised a mechanical lung with varying pressure of O_2 . Great success has been claimed for this device but its value has been questioned.

In the past few years more and more has been written of a pathologic condition found in the lungs of a large number of premature infants,

and a smaller number of mature infants, especially those born of Caesarean section. It has been called "Hyaline Membrane Disease", "Resorption Atelectasis with Hyaline Membrane" or "Potter's Disease". The infants affected by this disease have a typical clinical story and its presence can be foretold before autopsy. The typical history is that of spontaneous breathing immediately after birth followed by an interval of normal breathing lasting from a few minutes to several hours. Only rarely is the respiration poor from the time of birth or of an irregular apneic type. After a varying interval the expiration is groaning or whining and on inspiration a deepening furrow appears at or below the costal margin or between the ribs. In small infants the whole sternum is caved in. They appear grim and anxious and seem unable to sleep, as though all of their powers are required for the task of breathing. Physical examination of the chest shows the lungs sometimes emphysematous at the first but soon presenting increasing areas of dullness and fine rales. If these infants survive for four days they almost always recover rapidly and completely. More often death occurs within a few hours.

This condition may be found in premature infants following all methods of delivery. It has no relation to any type of material complication and is not proportionally more frequent among infants of similar weight groups born to mothers with premature separation of placenta, placenta previa, etc. It is not related to type or degree of anesthesia or analgesia, to time of rupture of membranes or to any other known condition. Recently we have used oxygen tents saturated with water and have felt this method to be of some value. More recently the acquisition of Isolette incubators with special humidifiers has made the use of oxygen enriched humidity more available and efficient. We feel the incubators have proven of great value.

Premature infants are not given anything by mouth for at least 24 hours and at times we may wait 72 hours before starting feeding. General appearance is used as a guide for parental fluid therapy.

Provided that the airways are clear and that no congenital defects are present, the babies' future depends on nursing care more than on any other one factor. Increased oxygen, controlled warmth and protection against infection are essential in premature survival, but the care of a skilled nurse far overshadows any of these.

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HEPATO-LENTICULAR DEGENERATION (Wilson's Disease)

PETER MIRALDO, M.D.

THIS condition is characterized chiefly by its involvement of the nervous system and the liver. There is degeneration of the basal ganglia producing disturbances in stereotyped movements and in the postural mechanism which is easily recognized clinically. In contrast, no signs of liver damage are apparent, but a marked cirrhosis is always found at autopsy. Yet in the case cited here, the liver had been investigated primarily and only later were the patient's neurological symptoms stressed. Perhaps there are many patients discharged from the hospital with another diagnosis, because this syndrome was not considered. In this hospital the files from 1932 to 1953 did not reveal any cases of "Hepato-lenticular Degeneration" except that mentioned below. None have been reported in the Neurology Clinic.

Dr. Wilson first described this condition in 1912, and up to 1940 he had reported 130 cases. In his original paper he gives a classical picture of the disease, describing the tremors, postural state, contractures, dysphagia and the psychotic changes. It is a familial disease usually affecting several children in the same family although no symptoms of cerebral or hepatic disorder are present in the preceding generation. In addition, there is a history in many cases of marriages between relatives. It is a disease of early life, occurring in the second decade and found more often in males than in females. The earliest reported case began at four years of age. The life expectancy is estimated to be four years. The exact cause of the disease is unknown and there is no effective treatment.

CASE REPORT

This 17 year old white male was readmitted on July 11th, 1952 with pain and swelling of both legs. Six months previously he had similar complaints, but no definite diagnosis was made during his hospitalization. There is a history of crampy pain in the lower legs for the past several years, but recently this has become more severe. Associated with the pain there is edema which becomes more pronounced when he is on his feet for long periods of time.

Other symptoms are referable to the chest and G.U. System. He is conscious of his "heart-beat" and is aware of an increased heart rate. There is no chest pain, but the patient is easily fatigued. There is no orthopnea, cough, or hemoptysis present. In reference to the G.U.

system, his chief complaint is frequency with nocturia, three to four times. No dysuria or hematuria is present. His appetite is good, and he has no food intolerance.

The patient's parents both died of cancer. A sister died of tuberculous meningitis. There are no known nervous disorders in the family. He is now living in a charitable institution, attending a public high-school where he has above average grades. There are no serious illnesses. The only childhood diseases were measles, mumps and chicken pox.

The patient is a thin, well developed male in no apparent distress. His blood pressure was found to be 130/70. Nothing remarkable was found on physical examination. A one plus pretibial edema was noted. No swelling or tenderness of joints was evident. There was some question as to what was present clinically in the precordial area, but a consultation ruled out any pathology. Repeated E.K.G.'s, X-rays and fluroscopic examination of cardiac shadows did not reveal any abnormalities. The first impression on both admissions was rheumatic fever with congestive heart failure, or rheumatoid arthritis. All sedimentation rates were normal and the temperature was not elevated. However, occasionally on repeated examinations a mid-diastolic murmur seemed to be present and a rough pulmonic systolic murmur.

In the right base, dullness was noted, but no fluid was found in the right pleural cavity on X-ray. The liver edge was found just below the right costal margin, so the dullness was assumed to be due to an enlargement of that organ. Laboratory tests determining liver function indicated pathology. The thymol turbidity on two occasions was 35 and 22 units and the cephalin flocculation was 4-plus in 48 hours. The serum protein was below normal with reversal of the a/g ratio:

Proteins	5.6 grams; a/g	1.1/1
	5.4 grams; a/g	.7/1
	5.8 grams; a/g	.8/1
	6.0 grams; a/g	.73/1

Six months ago the serum protein was 6.2 grams with an a/g ratio of 1.5/1. At that time the liver function tests were in the lower limits of normal. During this admission, intravenously injected Bromsulfalein indicated a 10 per cent retention in 30 minutes. No clinical jaundice was present at the time of the tests, however the total bilirubin was elevated 1.6 mgs. per 100 cc. In the absence of liver disease, less than 10 per cent of the dye is retained after 30 minutes. In 45 minutes only 6 per cent remains. Here no 45-minute determination was carried out, but it can be assumed, having other positive liver function test, that there is a delayed excretion of the dye by the liver. The cholesterol

and cholesteresters were normal. However, in Wilson's Disease, the laboratory tests do not indicate marked liver damage. There are only two tests usually consistently positive. These are the thymol turbidity and cephalin flocculation tests, but at autopsy a far advanced nodular cirrhosis is found. Thus far it is established that there is liver damage in a young individual and edema due to hypoproteinemia. The patient was placed on a high protein and a high vitamin diet with nourishment between meals and also given whole blood and crude liver. The edema disappeared and the patient stated he felt better.

Another finding during the patient's hospitalization was a persistent low white count, ranging from 2,000 to 5,000 per cu. mm. One observer noted a slightly enlarged spleen and some petechiae around the ankles. Because of these findings, with the edema and arthralgia, one of the collagen diseases was suspected. A sternal marrow puncture did not reveal any "L.E." cells. The platelet count was found to be normal. The erythrocyte count is expected to be below normal, but this patient did not show any anemia.

The kidney was studied thoroughly without significant findings. Repeated urinalyses, blood urea nitrogen, intravenous urogram, urinary concentration tests, and phenolsulfanphthalein tests were all normal.

While in the hospital, some awkwardness of the patient was noted. His movements were slow, but no particular gait abnormality was present. He remained at the bedside not seeking the companionship of the other patients. He spent most of his time reading good books, and he expressed a desire to go to college. He did not participate in any activities of the institution nor did he want any responsible job. He was content drying dishes. Several times he was caught taking other people's articles, although they were not of any great value. While at the hospital, he frequently became emotionally upset and cried because he wanted to go back to the Home or gave the excuse he was missing too many days from school. Tremors became more marked when he was upset. His speech was nasal and he showed difficulty in bringing out his words. Cog-wheel rigidity of the upper extremities was present. He had a masked facies. His writing was poor, the letters were small and not very legible. No abnormal reflexes were found. Spinal fluid studies were normal. With these findings hepatolenticular degeneration was suspected. A slit-lamp examination revealed Kayser-Fleisher rings.

If this syndrome is considered, the diagnosis is easy in a fully developed case; however, other conditions must be ruled out such as multiple sclerosis and paralysis agitans. The chief features of hepatolenticular degeneration are as follows:

- (1) Its occurrence in a young individual.
- (2) Familial nature of the disorder.
- (3) The insidious onset and its fluctuating course.
- (4) The presence of striatal symptoms, such as tremor and postural disorders.
- (5) Cirrhosis of the liver.
- (6) Presence of Kayser-Fleisher rings. This is a green-brown ring in the cornea. The pigment is found in Descemet's membrane and believed to be due to deposits of urobilin.

Pseudosclerosis has similar symptoms as found in progressive lenticular degeneration, but is claimed to be a separate entity. The onset is the same and the Kayser-Fleisher rings are also present. However, at autopsy the findings are more diffuse resulting in less severe symptoms and a not too rapid death. Here too, the cirrhosis is a late feature. Wilson has included the pseudosclerosis in his group. Andre tabulated 144 cases of Wilson's disease, all proven either by Kayser-Fleisher ring or by family history and found that 110 cases fell in the group of "latent cirrhosis". Twenty-seven had marked hepatic symptoms associated with the neurological findings. This was 18.5 per cent of the group and only 5 per cent or 7 patients had no neurological findings with the hepatic symptoms, yet it is felt that the liver is involved first.

At autopsy the liver grossly appears shrunken and finely nodular. Microscopically there is a typical portal cirrhosis. Connective tissue has replaced the liver cells and moderate amount of infiltration with lymphocytes has taken place. The spleen is also frequently enlarged. If death occurs early, the central nervous system might not show any lesion microscopically except for fatty degeneration. The findings are marked when the disease has been present for some time. There is bilateral softening of the putamen nucleus. In the globus pallidus and caudate nucleus the changes are not as marked. At first discoloration is evident, followed by atrophy and softening, and finally disintegration and cavitation. Microscopically there is glial overgrowth with the production of giant astrocytes. The normal nerve fibers and cells disappear.

Many laboratory studies have been done to help make a diagnosis, especially in trying to detect the presence of cirrhosis. These, however, have been of little value. The severity of the disease is only realized at autopsy and its progression is best followed by repeated physical examinations. The cephalin flocculation and the thymol turbidity have been of some value. It is sometimes the first indication that a cirrhosis is present. A constant finding in these patients is an excessive amount of amino acids in the urine. In Wilson's disease it is two and a

half times that of a normal individual. Yet, is the disturbance a primary factor producing part of the picture or is it secondary? Recently large amounts of copper have been reported to be present in tissues of those with hepatolenticular degeneration. Thus far there does not seem to be a relation between the copper and the amino-aciduria.

An increase in urinary output of amino acids occurs chiefly in conditions associated with hepatic disfunction and in situations where there is extensive tissue destruction. The increased excretion is partly due to decreased deamination of amino-acids in the liver and also to autolysis of proteins of the liver itself. However, it is noted that 90 per cent of the liver must be damaged before deamination is significantly impaired. Elevated values in the urine are found in acute yellow atrophy phosphorus poisoning, arsphenamine and hepatitis. But in this disease the increased excretion is found before any laboratory test shows liver damage. Even biopsy of the liver did not show the cirrhosis found at autopsy. It should also be mentioned that there are other diseases of the liver and of the basal ganglia that do not show an increased amino aciduria. Therefore it was concluded that it is not primarily a liver disease, but a defect in the metabolism of amino acids and in turn producing liver damage. There is also a renal theory, either a renal anomaly or a lowered renal threshold to the amino acids. However, if an infusion of amino acids is given to a normal individual and one with Wilson's disease, there is no significant change in the levels in the blood or in the kidney excretion.

Although Uzman and Denny Brown had also postulated the renal theory they now feel that the cirrhosis of the liver is a result of a chronic loss of amino acids brought about by some disturbance in metabolism. They believe there is a deficiency in the tissue of peptides having a terminal dicarboxylic amino acid and found in increasing amounts in the urine. The increased amount of these peptides in the urine is not due to faulty reabsorption by the renal tubules, but depend on the type of peptides in the circulating blood and the glomerular filtrate. There is a "competitive reabsorption of such peptides in preference to, and to the partial exclusion of free amino acid". A family of eleven in which four had died of Wilson's disease was studied. All members showed an amino-aciduria, concluding it is a "familial generalized metabolic disturbance". In some families a cirrhosis of the liver occurred later where some member had hepatolenticular degeneration. The lesions found in the basal ganglia are not explained.

At necropsy, Spillane found an increased amount of copper in the brain and the liver in addition to the persistent amino aciduria. The quantity of copper in the brain and the liver with Wilson's disease was

approximately ten times as much as found in normal individuals. The increased content is not found in other diseases of the basal ganglia. The following are the results of a study by Cumings on three patients with hepatolenticular degeneration.

COPPER IN MG./100 GM. OF DRY TISSUE

	18T	2nd	3rd	Normal
1. Cortical white matter	10.9	14.7	12.9	1.1- 8.7
2. Cortical gray matter	4.6	27.6	46.5	2.4- 9.9
3. Caudate nucleus	10.1	13.8	13.8	3.4- 9.4
4. Thalamus	31.9	20.7	31.9	13.1- 2.4
5. Putamen nucleus	-	60.5	69.3	6.1- 1.2
6. Globus pallidus	8.4	23.0	39.9	10.5-10.8
7. Liver	156.4	55.0	39.4	3.7-17.2

The increased copper found in hepatolenticular degeneration is believed to be due to an increased absorption of the metal from the blood stream. It is not due to the liver damage, although most of the copper is excreted in the bile. The content of copper in the bile is the same in patients with Wilson's disease and normal persons.

Since BAL is known to increase the excretion of some of the heavy metals, it has been used to mobilize copper from patients with hepatolenticular degeneration. Urinary excretions of copper were increased twenty to seventy times per twenty-four. No toxic effects were noticed with its use, except for some nausea, dizziness, vomiting, and blurring of vision. No further liver damage occurred, nor is there an excretion of any of the other heavy metals from the body. The amino-aciduria present is not affected. Experimentally, BAL (dimercaptol) has been administered to five patients, but repeated courses were necessary to maintain the patients in remission. They gave 2.5 mg. 1 Kg. of body weight twice daily intramuscularly in a 10 percent solution of peanut oil. Improvement in the neurological symptoms were evident after two weeks of therapy.

Cortisone and ACTH have been tried for many nervous disorders. In all cases of extrapyramidal diseases no improvement occurred. The improvement on the cirrhosis is questionable. There are series where a high protein diet is helpful showing an improvement in the cephalin flocculation test and the thymol turbidity. These became negative over a period of a year. The diet should consist of 25% protein, 70% carbohydrate, and 5% fat, amounting to 3000 to 4000 calories a day.

During hospitalization this patient improved on a high protein and a high vitamin diet. After discharge, gradual regression was again

evident. His speech became more slurred and he had more difficulty writing. Tremors and rigidity increased. The patient made an attempt to use a typewriter to do his school work, but his fingers were not sufficiently flexible. Again edema of both lower extremities occurred. Four months after his discharge from this hospital he was taken to a Philadelphia hospital. He died three weeks after admission. BAL was tried but they did not get the results that Brown and Porter did. This patient excreted from two to three times the copper found in normal individuals. Cortisone and ACTH were not helpful.

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GALLSTONE ILEUS

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THE purpose of this paper is to review the literature* on Gallstone Ileus, and to describe an extremely interesting case treated at the Allentown Hospital.

REVIEW OF LITERATURE

Bartholin (1) in 1654 is credited with the first report of a gallstone perforating into some portion of the intestine. **Von Wagner** (2) in 1914 presented an analysis of 334 cases which were found in the available literature at that time. **Foss** (3) reported in 1942 on 10 personally treated cases and **Nemir** (4) presented eight complete studies in 1952.

The incidence of Gallstone Ileus is rare. Figures range from three to five per cent of all intestinal obstructions. **Foss and Summers** (5) tabulated an incidence of four per cent, while **Fulin and Petersen** (6) reported in a ten year period, 5.3 per cent. Most busy surgeons can expect to see but a few cases of Gallstone Ileus during their lifetime. Mortality is extremely high. Statistics show 20 to 50 percent as compared to 5 to 7 per cent in cases of obstruction due to adhesions, strictures, carcinomas or hernias. The obstruction usually is simple, and as a rule there is no compromise of the circulation. Size of the gallstone that causes intestinal obstruction is usually one inch or more in diameter. The site for the lodgement of the stone that causes obstruction, is the lower ileum. Out of 239 cases of Gallstone Ileus collected by **Wolfer and Lieblein** (7) ninety were present in the lower third of the ileum. Gallstones, however, are known to have become lodged in Meckel's Diverticulum according to **Hauke** (8). Obstruction may result from gallstones in the intestinal mesentery. **Wakefield et al** (9) cited two instances in which the gallbladder had perforated into the mesentery of the small intestine and subsequent tumefaction and abscess formation were sufficient to produce the clinical signs and symptoms of Gallstone Ileus.

The majority of the patients developing gallstone ileus are obese, elderly females, with associated diabetes or organic heart disease. Frequently they will give a definite history of gallbladder disease. **Rigler, Borman and Noble** (10) found that in 75 per cent of the cases of obstruction caused by gallstones, the age of the patients was 60 years, while **Hinchey**, (11) reported an average of 66 years in his series. **Wortmann** (12) however, reports a gallstone ileus in a woman of 25 years, the youngest age at which this type of obstruction has been observed.

There are two possible ways by which a gallstone may enter the gastro-intestinal tract. The first would be for the stone to transverse the cystic and common ducts to enter the duodenum. The second way would be to rupture the fundus of the gallbladder and enter the intestine by means of a fistulous tract. The latter is the most common route. Most authorities feel that the stone must be at least one inch in diameter to cause intestinal obstruction. It is difficult to believe that a large stone could possibly transverse the cystic and common ducts. **Murphy** (13) reports a stone measuring 4.5 x 2.7 cm. transverse the common duct. Gangrene and perforation of the gallbladder according to **Heuer** (14) occurred in 20% of cases of acute cholecystitis in which the pathological process was not interrupted by surgical intervention and more than 90% of these cases of perforation occurred in a gallbladder which contained stones.

The location of the fistula may vary. **Wakefield, Vickers and Walters** (15) in a study of 176 cases of cholecystoenteric fistulas at the Mayo Clinic, found that the fistulous communication occurred between the gallbladder and the duodenum in 101 cases. In 33 cases the fistula occurred between the colon and the gallbladder, and in 7 cases between the stomach and the gallbladder. In 1952, Dr. T. Yamashita, of the Allentown Hospital Staff, reported an extremely interesting case of Choledochoduodenal Fistula. A subtotal gastric resection was performed on that case which rendered the patient symptom free.

The symptoms of gallstone ileus may be less typical than in the usual case of obstruction due to common causes. There may be a history of gastric distress and epigastric pain. In 10% of the cases there is jaundice. There may or may not be a past history of gallbladder disease. The early symptoms of obstruction may simulate biliary colic, but if there has been a previous history of cholelithiasis, the patient will normally describe the present episode of pain as being of a much different character. At first the obstruction is but partial, but may be absolute; this is usually characteristic and with frequent remissions of symptoms.

Roentgenologic examinations offer help in the diagnosis of gallstone ileum. **Rigler, Bowman and Noble** (16) have the largest series of cases correctly diagnosed pre-operatively by this means. The three criteria that they use are (1), Air or contrast medium in the biliary system. (2), Direct visualization of the stone. (3) Roentgenologic evidence of intestinal obstruction. X-rays are essential for diagnosis and also aid in the planning of surgery. Valuable signs are disappearance of gallstones noted on a previous film; the presence of a gallstone

in the gastro-intestinal tract, and most important, the regurgitation of gas or barium in the biliary tract which the roentgenologist attempts to elicit by abdominal compression or by directed injection of air or barium through a tube. Accumulation of gas in the biliary tract is most striking and is always seen in gallstone ileus. This, therefore, should be looked for in all cases of intestinal obstruction.

In considering the differential diagnosis of gallstone ileus, the following conditions must be ruled out.

- (1) Intestinal obstruction due to adhesions.
- (2) Perforated peptic ulcer.
- (3) Mesenteric thrombosis.
- (4) Acute pancreatitis.
- (5) Acute appendicitis.
- (6) Biliary colic.
- (7) Renal colic.

The prognosis in a case of gallstone ileus must be guarded. As mentioned previously, most of the patients are elderly, obese females with either diabetes or organic heart disease. The mortality rate is high because of the patient's delay in coming to the hospital. **Balch** (17) has shown that but one out of eight patients operated upon, after the third day of obstruction, survives.

The operation to correct gallstone ileus is best performed under spinal anesthesia. The incision may be either lower median or a right paramedian. The entire small intestine is carefully inspected and palpated. The actual pathology may be found by following the distended bowel downward, or the collapsed upward. After the involved segment is located, it is brought out through the wound, walled off, and rubber shod clamps employed across the bowel proximally and distally. A longitudinal incision is made over the anti-mesenteric border and the stone delivered. However, it should be mentioned that many surgeons milk the stone into the normal bowel before making the incision. The opening in the bowel should be sutured transversely so as to avoid constriction of the bowel lumen.

CASE RECORD — GALLSTONE ILEUS

1. Allentown Hospital No. 284, 801, M.H. Female Age 62.

CC: "Pain in abdomen". Three days before admission patient had diarrhea for 24 hours. The next day she became nauseated and vomited. The day before admission she did not have a bowel movement, but vomited material that had odor of feces. Developed rapidly increasing weakness with abdominal distention.

Physical Examination

T 101 P 100 R30 B.P. 130/90

Patient acutely ill; no jaundice. Abdomen markedly distended. No engorged veins or visible peristalsis. Tenderness over entire abdomen. Percussion revealed hyperresonance to tympany over all. No borborygmus heard or auscultation.

Survey film of the abdomen showed several loops of small bowel, indication of gaseous distention and several fluid levels suggestion of small bowel obstruction.

Preoperative Diagnosis: Intestinal Obstruction.

Operation:

Performed under spinal anesthesia. Upon opening the abdomen, distended coils of the ileum were encountered, which were found to lead to a point of obstruction in the lower third of the ileum, below which the intestine was collapsed. A faceted calculus measuring 3.5 cm. x 3 cm. was found to be the cause of the obstruction. The intestine in this area was extremely dark and gangrenous. Resection of this segment of bowel was performed and an end-to-end anastomosis established. Palpation of the gallbladder revealed the presence of another large stone. Due to the poor condition of the patient no attempt was made to correct that condition.

Patient made an uneventful recovery and was discharged 10 days later. She remained symptom free but returned to hospital three months later, at which time a cholecystoduodenal fistula was excised, and a cholelithotomy performed. Again patient made a good recovery.

This case is extremely interesting and unusual in that the gallstone ileus was complete, the bowel was gangrenous, and a resection was required with end-to-end anastomosis. In addition, palpation of the gallbladder revealed another large stone. The patient was too ill to attempt correction at this time, however, at a later date the gallstone was removed by cholelithotomy and repair of cholecysto-duodenal fistula.

* List of references furnished on request.