PROGRESS IN PEDIATRICS

RECENT ADVANCES IN ANATOMY, PHYSIOLOGY, AND PATHOLOGY OF CHILDHOOD*

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N. Pende¹ has described what he believes to be a new endocrinal gland. The structure has been found by him in puppies and in infants under 1 year of age. It occurs in the form of fifteen to twenty solid "epithelial islets," scattered around the parathyroids, thyroid and upper pole of the thymus, occasionally, also, at the lower pole, and more especially in the connective tissue of the superior outlet of the thorax.

These structures were found in making serial sections of the neck organs from the tongue downward. The author thinks it is not improbable that the glands have also a wider distribution.

In newborn infants the largest masses may be seen, at times, as grayish red points that through their richness in vascular capillaries stand out against the suprathymic or periparathyroid connective tissue.

The conformation of the islets is said to be microscopically quite characteristic. They consist of a mass of closely packed cells pierced by a rich capillary plexus, and almost always lacking any firm connective tissue stroma.

The masses have no capsule but are separated from the adjacent structures by loose connective tissue in such manner that the individual groups of cells appear, microscopically, as true, sharply defined, islands.

The individual cells are large, having two or three times the circumference of the parathyroid cells in the same individual. They are described as having the appearance of epithelial cells, being round or polygonal in form, with very definite margins to the protoplasm, and having a very large, centrally placed, round epithelioid nucleus, with a delicate nuclear membrane, a scanty chromatin network and several nucleoli. In many cells the nucleus is smaller, homogeneous, and

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1. Pende, N.: Ueber eine neue Druse mit innerer Sekretion (*Glandula insularis cervicalis*), *Arch. f. mikroskop. Anat.*, 1914, lxxxvi, No. 1, p. 193; also *Riforma med.*, 1913, No. 22.

deeply-staining. The cytoplasm consists of numerous small granules so thickly placed that the protoplasm often appears to be stained homogeneously.

In a small number of cells there are seen scattered, larger, drop-like granules which stain well with eosin and other acid stains, but poorly with basic stains. In many cells the protoplasm has a vacuolated appearance. Such cells are met infrequently in the newly born, but their number increases rapidly with increasing age, and especially, says the author, under pathologic conditions. By the end of the first year there is visible a more or less large mass of vacuoles in practically all the cells. These vacuolated cells show then a small pyknotic, eccentrically-placed nucleus of variable size. The after fate of these cells, and the evolution of the islands generally, has not yet been studied; further investigation is in progress.

By applying Ciaccio's method of staining for lipoids, Pende has found that most of the granules are lipoidal in nature. As vacuolization proceeds, true fat globules appear in the place of these lipoid granules with increasing frequency. No pigment granules or other metaplastic structures such as glycogen granules are seen. The chromaffin reaction is negative.

No glandular lumina, cysts, follicles, or enclosed colloidal spaces are present. For this reason Pende thinks that the bodies are not remains of the so-called *post-branchial bodies* on the one hand, nor rudimentary portions of the adjacent glands of epithelial origin, the thyroid, parathyroid and thymus, on the other. The structure of the islands is quite different from that of the last mentioned glands.

The author's statement that these new glands of internal secretion remind one in detail of the appearance of the suprarenal glands, is noteworthy. There are many points about the above description of the new gland that may be applied to the appearance of embryonic fat, and masses of this, it will be recalled, are often met about the poles of the kidneys in the newly born, and in their resemblance to the suprarenal glands, have not infrequently caused confusion.

Prof. Pende is First Assistant in the Institute of Medical Pathology at Palermo. The result of his further studies, which are now in progress, will be awaited with much interest. Excellent plates accompany the present report. A brief, earlier report was made in the *Riforma medica*, 1913, No. 22.

During the past year two studies have been made bearing on the nutrition of infants. Benestad² has subjected the problem of initial loss of weight in the newly born to further analysis. Carlson and his

2. Benestad, G.: Wo liegt die Ursache zur physiologischen Gewichtsabnahme neugeborener Kinder? *Jahrb. f. Kinderh.*, 1914, lxxx, No. 1, p. 21.

collaborators have utilized the reappearance of gastric contraction-waves in the infant to determine the proper interval of feeding.

The initial loss of weight in the newly born has long been known. Scientific attention was directed to it about a century ago by Chaussier, and the fact now finds appropriate statement in all textbooks of pediatrics. The loss begins promptly after separation of the child from the mother and continues until, on the average, one fifteenth to one seventeenth of the original body weight is lost. The recovery from the loss begins usually about the third or fourth day after birth. During the next week the infant recovers its original weight, i. e., by the end of the tenth day.

This phenomenon is not peculiar to the human species. It occurs in some other animals, e. g., guinea-pigs (Edlefsen). It does not occur, or is a very infrequent phenomenon in dogs, cats and rabbits (Kehrer).

As shown by L. Faye, in 1874, the loss consists largely in water, by means of the insensible perspiration, the respiratory loss, the very considerable water content of the meconium, and the scanty urine.

During the first two or three days Nature does little to supply this loss. The child receives only a small amount of colostrum (100 c.c.) to oppose a relatively large loss of fluid.

Some years ago it was reported that this initial loss could be prevented by supplying the child with food during the interval elapsing before the maternal supply appeared, and recently Bailey and Murlin³ have recommended feeding newly born infants, in addition to the breast secretion, a formula of about the same composition as colostrum.

If this initial loss of weight is a normal and inevitable phenomenon it must be accepted as such. Clearly the meconium is an accumulation formed in the intestines during the course of development. It may be regarded as waste material, and no more a true part of the newly born infant than the vernix caseosa. If so, the average weight of this substance might properly be deducted from the average birth weight—about 200 gm.—which, together with the urine voided, would be about one-half the total loss. The older texts taught that the colostrum was laxative in its action on the infant and was Nature's provision for freeing the organism of the meconium. It is not inconceivable that some other part of the initial loss of water may represent a necessary riddance. If the initial loss is necessary or inevitable the pediatricist must be tolerant of it and he may solace himself with the thought that the true loss of weight is not really so great as it seems.

3. Bailey and Murlin: *Proc. Soc. Exper. Biol. and Med.*, 1914, xi, 109.

If, however, the phenomena of the early days of lactation, the production of colostrum and the delayed appearance of milk constitute another imperfect adaptation on the part of Nature, then clearly the attending pediatricist may hope to render the adaptation more perfect. He may supplement the existing provision for supplying fluid to replace that which is being lost. He may feed the child in the interval that elapses before the natural supply of food becomes available.

Benestad has reviewed these points. He finds that the extent of the loss of weight depends, (1) on the degree of development of the infant, (2) on the actual weight at birth, and (3) on the milk supply of the mother. Another factor that is less frequently operative seems to be great loss of blood in the mother (presumably through subsequently diminished milk flow). The severity of the birth process does not in itself appear to be a factor.

The studies of numerous workers (Winkel, Gregor, etc.) have shown that premature infants lose proportionately more weight than full-term infants. This is true even when the latter are small infants at birth (3,000 gm.). The percentage of the birth weight lost decreases with the maturity of the infant. This, the author thinks, is due to the greater deficiency of the digestive apparatus in the mature child.

Newer studies have shown that the more important enzymes are present in the digestive tract of viable premature infants. Formerly it was believed that many enzymes were not present until some weeks after birth. Langstein and Soldin have found erepsin as early as the thirtieth week. The demonstration of the mere presence of these enzymes does not prove, however, that they are present in quantities sufficient for the digestion of the volume of food received by a young infant from its mother.

The failure of all efforts to prevent the initial loss of weight, says Benestad, or even appreciably to diminish it, by supplying newly-born infants with milk from wetnurses, whose children are but a few days older than the patient, seems to indicate a functional inability to utilize the milk during the first days of life, even in a mature infant. Forcing food at this time may even delay the normal recovery of the birth weight (Altherr).

An initial loss of weight is not present, or is very transitory, in most mammals that have been studied. The period of infancy also is shorter in all other animals than the human species. It would be but in accord with this if it were found that the digestive functions were more complete at birth in young animals than they are in the human young. Bahrddt and Langstein's studies show that the calf possesses the power to reduce albumin to amino-acids, even in the first days of

life. Simon's studies led him to the conclusion that in the human infant the breaking down of the albumin molecules stopped at the polypeptid stage, instead of proceeding to the amino-acids and ammonia. These polypeptids formed 10 per cent. of the total nitrogen output in the urine of the first few days, or double the percentage found in the adult. The percentage gradually diminishes and reaches normal by the end of the first week, the proportion of amino-acids and ammonia rising. It would seem that the human infant in contrast with the young of other mammals (for example the calf) is unprepared during the first days of life completely to digest albumin. Similar comparative studies have not been carried out on premature infants. They are, presumably, still less prepared to digest albumin. During intra-uterine life the organism is supplied by the products of maternal digestion—serumalbumin, sugar, and human fat. A shorter or longer period is required for adjustment to the conditions of extra-uterine life in which the organism must itself break down the higher compounds and elaborate them anew. Some days are, as a rule, necessary; the period is longer, or the process less rapid, in the case of premature infants. This period of defective digestion may be accompanied by a period of defective assimilation; the two can scarcely be separated.

Where infants are of the same degree of maturity the average initial loss varies with the birth weight. Infants weighing 3,000 gm. lose, on the average, 175 ounces (5.36 per cent.) during the first three days, while those weighing 4,000 gm. lose, on the average, 252 gm. (5.91 per cent.). As is seen, the difference in percentage loss is not great. It has not been shown on what this small difference depends.

Finally, the initial loss of weight depends on the milk supply of the mother. The most suitable food for the young infant is colostrum. Its fat and its serumalbumin are closely related to those to which the infant has been accustomed in its intra-uterine life, and if not fully broken down in the immature digestive processes are perhaps less liable to prove toxic. No other food can wholly replace it. With improvement in the digestive processes an increasing supply of mother's milk becomes necessary. In the meantime, says the author, artificial feeding increases and prolongs the initial loss of weight.

Williamson⁴ has recently repeated and extended the early work of Leichtenstern (1878) on the hemoglobin content of the blood of the newly born. He examined over 900 patients ranging in age from 1 day to 76 years, and over. He employed the spectrophotometric method and the principle of extinction coefficient as developed by

4. Williamson, C. S.: Influence of Age and Sex on Hemoglobin. A Spectrophotometric Analysis of Nine Hundred and Nineteen Cases (Preliminary Report), *Jour. Am. Med. Assn.*, 1915, 1xv, 302.

Vierordt and Hüfner. Details regarding the method and the author's application of it may be found in the original publication. Only that part of the work that relates to infants and young children will be discussed here.

The infants and children examined were as follows:

TABLE SHOWING NUMBER OF CHILDREN EXAMINED AND THEIR AGES

Age	Number of Cases		
	Male	Female	Total
1 day	16	15	31
2- 3 days	15	16	31
4- 8 days	15	18	33
9-13 days	15	15	30
2 weeks-2 months	15	15	30
3- 5 months	16	16	32
6-11 months	18	15	33
1 year	18	16	34
2 years.....	16	17	33
3 years.....	15	16	31
4 years.....	16	15	31
5 years.....	17	18	35
6-10 years.....	18	15	33
11-15 years.....	17	20	37

The material for the study was selected with care, effort being made to include only strictly normal, healthy individuals. The great majority of the babies were breast fed and all were thriving and gaining weight in a normal manner. A considerable proportion of the older children were school children and were studied early in the fall just after the closing of the summer vacation, and when their physical condition was presumably at its best.

The course of the hemoglobin percentage may be seen in the accompanying Chart 1.

After birth the percentage of hemoglobin begins to diminish at once, and after two weeks the decline is very rapid. By the fifth month the average value is very nearly down to the minimum (about 10/17 the value at birth) and far below the average value at 16 to 20 years (adult value). There is seen a very slight further decline at about 1 year, and thereafter a steady increase until the normal value is reached at 15 to 16 years. Thereafter there are but slight variations, with, toward old age, a slow decline.

The rapid decline in the amount of hemoglobin during the first five months is a highly characteristic feature of the age curve, says the author.

Chart 1.—Curve showing influence of age and sex on hemoglobin percentage. Shaded areas indicate males; diagonal lines, females.

In selecting the material an effort was made to have the two sexes equally represented in each age period. A comparison of the hemoglobin values obtained shows that up to the fifteenth year the hemoglobin content of the blood is almost precisely the same for the two sexes. After the fifteenth year sex differences make themselves plainly evident; the values for the women are, in every instance, considerably lower than those for the men; with age the difference grows less.

The practical conclusions that may be drawn from Williamson's work are:

1. Instruments which are graduated in percentages of a supposed average normal individual can not be utilized for making determinations in children of different ages without correction.

2. During the first two weeks the normal hemoglobin content of the infant is about 36 per cent. greater than that of the normal adult. Between the second and third months it just equals that of the normal adult and from the fourth month to the fourth year it is normally only about 80 per cent. of that of the adult (slightly less during the second and the third year.) The percentage rises gradually thereafter. No correction for sex is necessary.

3. Pediatricists should accustom themselves to allowing for the natural variations in hemoglobin at different ages.

The author gives the following example to illustrate the errors that may arise from disregarding these facts:

Let us say that a mother who is 22 and a father who is 24, and two children, a boy of 1 year and a girl of 2 years, respectively, all being averaged as normal individuals, have their blood examined with any of the instruments which are graduated on the basis of an average normal adult. An inspection of the table with reduction to percentages, will make it evident that the values will be, father 100 per cent., mother 87 per cent., boy 1 year, 74 per cent., girl 2 years, 74 per cent. It thus appears that the mother is anemic to the extent of 13 per cent., and that both children are markedly anemic, to the extent of 26 per cent. The fact is that the mother and both children have the amounts of hemoglobin which they should have for the respective ages and sex. The anemia is merely apparent, and due to the fact that the hemoglobinometer was not calibrated to read in absolute terms, and that the physician did not take the age and sex variations into consideration.

Several papers upon congenital icterus have appeared during the current year. The most extensive and significant paper upon the subject is that from Arvo Ylppö⁵ of Langstein's clinic. Ylppö reviewed the various theories of congenital icterus and our knowledge of the occurrence of biliary pigments in the blood, stools and urine, and restated certain methods that have been employed in the past in

5. Ylppö, A.: Icterus neonatorum (incl. I. n. gravis) und Gallenfarbstoffsekretion beim Foetus und Neugeborenen, *Ztschr. f. Kinderh., Orig.*, 1913, xi.

attempts to determine their presence quantitatively. He introduced the spectrophotometric method of determining the presence of biliary pigments quantitatively, and described the technic that he found applicable in the case of blood, urine and stools. He pointed out certain limitations of the method, but retained it as the most accurate method yet found. With it he investigated the secretion of biliary pigments in the fetus and the newlyborn, and the relation of the secretion to icterus neonatorum and icterus neonatorum gravis. He first took up the excretion of biliary pigments in the stools and urine.

His material consisted of 6 full-term infants that showed various degrees of icterus, 2 full-term infants that were not icteric, and 2 premature infants. All were examined throughout the first thirteen days of life and two full-term infants were examined between the eighth and twelfth week. One of the premature infants was reexamined in the sixth week.

The infants were placed in metabolism beds directly after delayed tying of the cord, and were kept there for thirteen days, being removed only for nursing. The meconium, the stools and the urine were collected separately and examined. A distinction between meconium and breast stool was made with the eye, or where this proved difficult, was established by the presence or absence, microscopically, of lanugo hairs. The infants were rated in four grades according to the amount of icterus present.

It was found that the weight of the meconium (dried, and in some instances freed from fat) obtained, varied from 0 to 23.23 gm., depending on the amount lost at birth, and that the biliary pigment contained in it averaged 22.5 mg. (0 to 63.43 mg.). The amount of biliary pigment obtained did not vary closely with the amount of meconium recovered.

In a later portion of his report the author established to his satisfaction that the placenta is an effective barrier against the passage of biliary pigments from the blood of the fetus to that of the mother. The amount of biliary pigments excreted during intra-uterine life may thus be estimated from the amount found in the meconium. This total Ylppö placed at about 33 mg.

He drew the following conclusion from his study of the excretion of bile pigments, stools and urine:

Up to the last month of intra-uterine life the formation of bile pigments is minimum. During the last month a striking increase may be demonstrated. During the whole fetal period there is in any case only about 33 mg. of biliary pigment excreted.

The increase in the formation of bile pigment which is recognizable in the last month of fetal life is definitely accelerated with the begin-

ning of extra-uterine life. From about the sixth day of life on, an especially rapid increase in the formation of bile pigment can be seen.

In the first thirteen days a total of about 140 mg. of bile pigment is excreted; of this, 0.5 to 1.6 per cent. (according to the intensity of the icterus) is excreted in the urine of icteric infants, and only minimal amounts, at most 0.1 per cent., is excreted in the urine of nonicteric infants. The total amount excreted shows no noteworthy difference between the icteric and the nonicteric children, and there is not a larger amount excreted in corresponding intervals in icteric infants.

There is no correspondence between the intensity of the icterus and the total amount of bile pigment that is excreted.

With these findings, the foundation, he says, falls from under all those haenatohepatogenous theories which refer icterus neonatorum to an absolutely large destruction of red blood cells in the icteric infant.

Ylppö then turned to the examination of the biliary pigment content of the blood. The circulating blood of normal adults contains a minute amount of bilirubin as Gilbert and Heracher have shown. Hammersten had shown that this is true also for the horse. Gilbert, Lereboullet and Stevens found that the amount is increased in the blood from the umbilical cord and from newly-born infants, as did Biffi and Galli.

Ylppö examined sixty-one children in this regard, including eighteen premature infants and two fetuses. The blood of some of these was examined from five to eight times, just after tying the umbilical cord and then at intervals during the course of the next few weeks. In some instances that of the mother was examined before, during and after childbirth. The findings are summarized thus:

The content of the fetal blood in biliary pigment is increased in comparison with that of healthy adults.

At the time of birth there is found a still more marked increase, which cannot be brought into relation with the conditions of birth (length, severity, etc.).

Those infants which have an especially high content of biliary pigments in the blood of the umbilical cord all become jaundiced, while those which have a strikingly small amount of pigment in the blood do not, as a rule, have jaundice.

After birth the content of biliary pigment in the blood rises in each child. This increase lasts three or ten days and varies in the rapidity with which it increases.

Children in whom the biliary pigment content of the blood exceeds a certain definite (but not sharply defined) *level for cutaneous jaundice*, become jaundiced.

The intensity of the cutaneous icterus shows a correspondence with the content of the blood in biliary pigment.

Infants in whom the amount of bile pigment in the blood ceases to increase by about the third day, and in whom the total content remains under the level for cutaneous icterus, do not become jaundiced.

Premature infants generally show the very high content of biliary pigment in their blood. This continues to increase ordinarily for six to ten days in them, and the amount of pigment in the blood remains above the level for cutaneous icterus for a week or more.

The result of Ylppö's clinical studies are summarized in the following sentences:

All viable premature infants (under 2,500 gm.) show icterus neonatorum: A great majority of them show a very intense icterus that lasts several weeks (forty-two of them were studied).

Eighty-two per cent. of the 355 full-term infants examined showed jaundice. They differed clinically from infants that did not show jaundice, only in so far as those in whom the jaundice was very outspoken, showed secondary symptoms, characteristic of cholemia (drowsiness, itching, etc.).

Three distinct forms of icterus neonatorum were distinguished: Icterus neonatorum simplex; icterus neonatorum prolongatus (duration over two weeks); icterus neonatorum gravis. Their unity was shown through the presence of all possible transitional forms and they are therefore to be looked on as being only various types of a single disease, icterus neonatorum.

This disease, icterus neonatorum, shows great independence in its course and is not influenced by secondary infections or trauma.

Data is then given to support the theory that there is in puppies an increase in the amount of circulating biliary pigments similar to that which appears in the human infant, but that it takes place in utero, and has almost or quite passed away at the time of birth. In the puppy the excess of pigment is laid down in granules in the placenta. In the human infant the phenomenon appears nearer the time of birth. A few granules of pigment may be deposited in the placenta (never any appreciable amount); the bulk of the pigment circulates in the blood until it is withdrawn by the liver or passes out in the urine (a small portion at most), and if present in more than a certain fixed percentage causes cutaneous icterus.

Only the horse and man show bilirubin in the blood normally, and only the young of these two mammals show icterus neonatorum.

The injection of bile pigment into the blood-stream of animals shows that in newly-born puppies and in adult dogs the liver quickly

removes the circulating pigment and passes it out as bile, minimum amounts only (much larger in the newly born) passing off in the urine. Administration of bile pigments by mouth yields no evidence, we are told, of the absorption of unreduced bile pigment from the intestine. Only man and the horse, says Ylppö, show bilirubin in their blood under normal conditions, and in these two animals only can it accumulate in the blood in the absence of injury to the functions of the liver.

As has been seen, Ylppö does not believe that infection plays any important rôle in the etiology of congenital icterus. When he began his work he thought infection played an important part. For this reason, he was especially watchful for any evidence pointing to a relation between infection and icterus in the cases studied by him. He found, on the contrary, that icterus neonatorum ran its course quite independently of infections, whether enteral or parenteral. (The infections whose influence was observed by him were aspiration pneumonia, tetanus neonatorum, umbilical sepsis, intestinal infection, and syphilis.) The fact that icterus neonatorum begins while the child is yet in utero would in itself weaken any theory of an infectious origin for it.

The fact that the percentage of circulating biliary pigment has already begun to increase before the time of birth, shows that the change is not dependent alone on postnatal circulatory changes, if it is dependent on them at all.

In the fact that the incompletely broken down albumin radicals are allowed to pass from the portal system of the newly born, through the liver, into the general circulation whence they are excreted in the urine, Ylppö sees further proof of functional immaturity of the liver in the human fetus at birth. As regards the maturity of their livers, the human young, he says, like the young of the horse, are born prematurely. And premature infants are, as regards the liver, doubly immature.

The mature liver when normally functioning secretes the bile into the bile capillaries. The fetal liver secretes its bile into the blood stream where it enters a closed circuit, very little of it being excreted in the urine in utero and little (in man) being laid down in the placenta. The excess is laid down in the liver itself. There is little excess, for little is produced.

Near the time of birth the liver normally begins to excrete bile into the bile capillaries. The more mature the liver is at the time of the birth of the infant, the more completely will it do this and the more perfectly will it keep the content of the blood in biliary pigments below the level at which icterus is produced. The less mature it is the less effectively will it do this and icterus neonatorum will appear in pro-

gressively severer grades. In the premature infant the liver is so immature that jaundice always results. In any case the depth of the jaundice (i. e., the content of the blood in biliary pigments) and the persistence of the jaundice are indicative of the length of time that passes after birth before the liver comes to the normal or necessary degree of functional maturity.

Such is Ylppö's theory of the etiology of congenital icterus. He portrays it schematically in the accompanying diagram (Fig. 2).

Chart 2.—Diagram of secretion of biliary pigment in icteric and nonicteric infants. Line A-A, pigment formed=100 per unit of time; line B-B, percentage in nonicteric infant; C-C, level for icterus of the skin; dash line, percentage of pigment passing into the blood in icteric infant; solid line percentage in nonicteric infant.

In this diagram it is shown that there is a slow increase in the production of bile pigments per unit of time during the last days of intra-uterine life, and that this rate increases rapidly and continuously after birth. The older the child is, the more bile does the liver secrete, as is shown by the author's analyses. There is no rapid production of biliary pigment at or shortly after birth followed by a subsequent decline in production, as has often been assumed. It is inferred that any change noted in the count of the red cells of the blood or in the hemoglobin content of the blood at or near the time of birth is merely a concomitant phenomenon.

A. Hirsch,⁶ of von Pirquet's clinic, reported a less extensive study of icterus neonatorum. She employed less accurate methods than Ylppö, but reached similar conclusions.

A more recent publication is that by Fridtzo Bang⁷ of Copenhagen. Bang used the Gmelin-Gilbert-Sunde method of estimating bile pigments in the blood and reached results that are substantially in accord with those of Ylppö. His publication is chiefly of interest in its criticism of Ylppö's deductions.

Bang holds that Ylppö has not demonstrated in a conclusive manner that bile pigment discharged into the intestine may not be reabsorbed in part, and, passing around the liver through the *ductus venosus Arantii*, get into the general circulation.

Ylppö denied that there is any *sudden* increase in the percentage of bile pigment in the blood at or immediately after birth. Bang believes that there is such, and offers diagrams to prove it. He finds in this phenomenon proof that some new factor enters into the production of bile pigment at the time of birth. He theorizes as to what it may be.

Ylppö had attributed the accumulation of bile pigment in the blood of the newly born to a defective functioning of the immature liver parenchyma and held this was more marked in premature infants. Bang assumes that the fetal heart and the circulatory mechanism are at fault, and sees the cause of the abnormal biliary secretion in venous stasis.

At birth the pulmonary circulation is suddenly augmented, the placental circulation is interrupted. The heart of the newly-born infant is unable to adapt itself at once to the changed conditions. It needs time to make the adjustment. The regulating mechanism, cutaneous and other, is still imperfect, and stasis results in the liver and elsewhere.

As a result of stasis in the cutaneous capillaries, serum escapes into the tissues and the blood becomes concentrated, the hemoglobin index rises and also the count of red cells. As a result of stasis in the liver, the concentration of bile-pigment in the blood rises. It does this to a slight degree during stasis in adults (figures are given) and in infants the phenomenon should be more marked because the weight of the liver is relatively much greater with respect to the blood volume—56 to 77 instead of 28 to 77. As the heart gradually adapts itself to the changed conditions of circulation, the stasis passes away, and with it

6. Hirsch, A.: Die physiologische Icterusbereitschaft der Neugeborenen, Ztschr. f. Kinderh., Orig., 1913, xv.

7. Bang, F.: Recherches sur l'origine de l'ictère des nouveau-nés, Arch. mens. d'Obst. et de Gynéc., 1915, viii, 296.

the jaundice. The weaker heart of the premature infant requires longer to adapt itself, hence the jaundice persists longer.

The whole discussion is highly theoretical.

How often the healthy baby shall be fed and how much shall be given him at a feeding, are fundamental questions in pediatrics, yet there is no unanimity regarding this. Examination of recent text-books and pediatric writings makes this clear. Great variety of opinion is expressed by leading teachers. The intervals advocated range from two hours for the first month to three, three and a half, and even four hours. Taken as a whole, American writers seem to prefer short intervals, while continental writers incline toward longer intervals. Some advocate shorter intervals in breast feeding, and longer ones in artificial feeding.

The normal healthy human infant, as the young of all animals, nurses when the sensation of hunger becomes strong enough to be uncomfortable, provided food is at hand at the time.⁸ When careful records of nursing babies have been kept, it has been found that not only do the intervals between apparent inclinations to nurse vary greatly, but also the amount of food taken at a nursing varies. In the same child the length of the intervals may vary from 1 hour to 6 hours; the amount of milk taken at a nursing from 1 to 3 ounces, or more widely. Even when the child is placed at the breast at regular intervals he may yet vary the amount of milk taken at each nursing. These variations depend on factors within the child, such as hunger, and on others beyond his control, e. g., the amount of milk in the breasts at the time of suckling, and the comfort of the child while nursing.

The apparently arbitrary regime selected by the pediatricist has been chosen because it works. It is in a great measure empirically chosen. It is the mode of feeding that the individual finds works best in the majority of infants that come under his care. It is generally agreed that the regular feeding at stated intervals is desirable. Opinions differ as to amount of food to be given at a feeding and as to the interval that is most desirable. The two are in a measure, reciprocals of each other.

The total daily amount of food necessary for a healthy infant of a given weight and age has been rather satisfactorily determined by the statistical methods of Camerer and the experimental methods of Heubner. One hundred and ten calories of food pro kilo body weight is needed during the first month. This gives the total amount of food for the day. If, now, a three hour interval is selected, eight feedings

8. Ginsberg, H., Tumpowsky, I., and Carlson, A. J.: The Onset of Hunger in Infants After Feeding. A Contribution to the Physiology of the Stomach, *Jour. Am. Med. Assn.*, 1915, lxiv, 1822.

in twenty-four hours, one-eighth of the total amount may be given at a time. If a four hour interval is selected, six feedings of one-sixth the total amount must be given.

The question at once arises, has the infant's stomach capacity enough to receive the large amounts of liquid that are necessitated by the feedings at long intervals? The answer to this question has been sought in two ways. First, the actual capacity of the infant's stomach has been determined post mortem; and second, attempts have been made during life to give these amounts of food. Studies of the actual capacity (after death) of the infant's stomach have been made by the various authors. The picture given by Holt in the fifth edition of his textbook of diseases of children, life-size illustrations, are readily available. They show that the stomach of an infant during the first month has a capacity of 1 to something over 2 ounces. That is, the capacity is not sufficient to receive the amount of breast milk required for each feeding at four hour intervals. Still less would it seem sufficient to receive the greater amount of fluid that is necessary for giving cow's milk in suitable dilution. Clinically, however, the infant's stomach is usually able during life to receive either amount, and that without unpleasant symptoms. The explanation lies in the fact that five, ten, or more minutes is consumed in taking the fluid, and that the liquid begins to leave the stomach within a few minutes after the first enters. The actual volume capacity of the stomach, post mortem or intra vitam, is thus not necessarily a true guide to the amount of fluid to be given at any one time. Nor is it, as a rule, a sufficient guide to the most desirable interval between feedings. It is certain that many infants do unusually well when nursed (or fed) at intervals of four hours from the first days on.

When the stomach has once been filled more or less completely, it seems desirable not to introduce more food until that previously given has completely passed out. Otherwise symptoms of indigestion are likely to result. It may even be that a somewhat longer delay is desirable. A certain period of rest for the gastric glands may be beneficial.

The roentgenogram studies of Pisek and LeWald⁹ seem to show that "three hours is practically the emptying time of the child's stomach, and often less than that." Czerny and others had earlier concluded that the stomach of the normal infant empties itself in from about one and a half to two hours. Whether the use of bismuth and other substances for Roentgen-ray work has any influence on the rate of emptying is perhaps debatable; many state that it has not. Normally, the time of emptying the stomach seems to depend on the quan-

9. Pisek and LeWald: *The Infant Stomach*, Tr. Am. Ped. Soc., 1913, xxv, 150.

tity of food taken, the rate of gastric secretion, and the vigor of gastric (digestion) peristalsis.

In any case satisfactory determination of the capacity of the stomach for receiving an amount of food, and of the time required for emptying the stomach after receiving the amounts given, is not all that is needed for the selection of the optimum amount of food and the optimum interval. It may be well to allow the stomach a period of rest between feedings. It may also be well to await the appearance of the sensation of hunger before introducing more food. Here again there is difficulty.

Until the last few years there has been no certain objective criterion for the existence of hunger. Such a criterion has now been found, it is thought.

In work published by Cannon and Washburn¹⁰ in 1912 and by Carlson¹¹ in 1913, it seems established that a "subjective sensation of hunger is caused by a certain type of contraction of the fundal end of empty stomach stimulating sensory nerves in the wall of the stomach." These contractions are peculiar to the cardiac and fundal ends of the empty stomach, and are, in normal individuals (adults) at least, "an objective index of hunger." Their presence is determined by introducing into the stomach a small balloon connected with a chloroform manometer. (For technic, see articles here referred to.)

Carlson⁸ and his collaborators have applied this method to determine the time of onset of hunger in infants after previous feeding. The determination of this question may aid in fixing the time that should elapse between the nursings of normal infants.

Their observations were made on thirty normal infants, from twenty-four hours to four weeks old. The frequency with which the infants were being fed and the amounts they received are not stated. They seem to have been breast-fed ("nursing") infants. The balloon was introduced into the stomach half an hour or more after feeding and the tracings published were obtained from infants who were asleep or otherwise quiet. Introduction of the balloon directly after nursing led to vomiting of the balloon and part of the food, and restlessness on the part of the child caused the inhibition of the hunger contractions.

Fifty-five observations were made upon the thirty infants. Tracings made from the chloroform manometer while the inflated balloon was in the fundus showed practically no contractions when the stomach was full. As the stomach gradually emptied itself feeble tonus contractions appeared. These increased in rate and intensity until, about two and a half hours after a nursing, they passed over into typical

10. Cannon, W. B., and Washburn, A. L.: *Am. Jour. Physiol.*, 1912, xxix, 441.

11. Carlson, A. J.: *Am. Jour. Physiol.*, 1913, xxxi, 175.

hunger contractions. In Carlson's series the minimum time elapsing before the appearance of hunger contractions was two hours and the maximum time was three hours. The time of onset of hunger contractions after the previous feeding varied for each infant. The hunger contractions of the empty stomach were seen to be modified tonus waves of the fundus of the digesting stomach.

The authors conclude: In the normal individual the presence of vigorous hunger contractions is probably biologic evidence that the stomach is in proper condition to receive fluid. If this is the case, the stomach of a normal infant is ready to receive food from two to three hours after the previous feeding.

From what has already been said, it is clear that, even if the reliability of the method used by Carlson and his associates be granted, many factors must be taken into consideration before pediatricists can accept the above evidence as indicative of the proper feeding interval.¹²

A paper by Smith and LeWald¹³ emphasizes the importance of placing infants in a semi-erect position during and immediately after nursing, and puts the instinctive inclination of mothers to lay colicky babies over their shoulders and fondle them, on a scientific basis. In the stomach of every individual there is a certain amount of gas. It may be derived from swallowed air, from gastric fermentation or from the intestines. In the large majority of cases, swallowed air accounts for the gas in the stomach. The size and anatomic relations of the pharynx are such that it is unable to close down completely on the small quantity of fluid swallowed at each gulp and, as a result, a certain amount of the air that is always present in the pharynx is carried down by the contraction of the muscles in the act of swallowing. When food is semisolid and a bolus is formed, less air proportionately is carried down.

Smith and LeWald introduced their study with a consideration of the anatomic position of the stomach. Roentgenography has shown that the stomach is not vertical in position in infants. The stomachs of infants resemble those of adults in a general way. The important features are these:

The esophagus enters the abdomen by an opening in the diaphragm, almost in the midline, in contact with the aorta and the ventral surface of the bodies of the vertebrae. The cardiac orifice lies just to the left of this position and the cardia is firmly held to the posterior abdominal wall by the esophagus as it pierces the diaphragm. The fundus of the stomach lies in the left para-vertebral groove, that is, in the lateral recess formed by the projection forward of the vertebral column into the abdominal cavity. The fundus reaches a plane considerably dorsal to the cardiac orifice. It is covered in front only

12. One cannot help wondering how far these waves were not simply evidence of increasing effort on the part of the empty stomach to expel the balloon, an indigestible foreign body.

13. Smith, C. H., and LeWald, L. T.: *The Influence of Posture on Digestion in Infancy*, *AM. JOUR. DIS. CHILD.*, 1915, ix, 261.

by the liver and extends to the anterior abdominal wall. The pyloric end of the stomach is pushed forward by the vertebral column, pancreas and duodenum. The pyloric opening is directed backward toward the duodenum, but lies in a plane which is ventral to that of the cardia. The cardiac opening is behind the center of the anteroposterior diameter of the stomach.

As food enters the stomach it gravitates to the lowest part, displacing any gas present to the highest part. If the infant is in a horizontal position the liquid food passes to the posterior portion of the stomach, that is, to the fundus, and any gas present is forced to the anterior part of the fundus and toward the right end of the stomach. They say:

Since the cardiac orifice is situated well back against the vertebral column it follows that it will be covered by the liquid and that the gas cannot escape into the esophagus. It can escape only through the pylorus, if at all. If the amount of food plus gas is enough to distend the stomach, either food or gas must be forced out through the pylorus or regurgitation of food must take place through the esophagus until the tension on the stomach wall is relieved. The horizontal position causes a perfect water-lock to form as far as the gas and the cardiac opening are concerned.

When the child is held upright the liquid gravitates at once to the dependent part of the stomach and displaces the gas to the highest part, that is, to the upper part of the fundus. This makes it possible for the gas to escape by the esophagus, and it often does so at once.

These conditions are well illustrated by roentgenograms. These were obtained from four infants ranging in age from 4 to 7 months, who were given their usual feedings of 4 to 7 ounces of modified milk, to which one-half ounce of bismuth subcarbonate had been added. They showed a progressive accumulation of gas in the stomach during the act of nursing. In two instances this was accompanied by regurgitation or vomiting. In one the accumulation of gas became relatively enormous; the distention of the stomach caused evident distress, and the infant refused to finish the bottle. Changing to an erect position, some minutes afterwards, caused a large eructation of gas, and the child at once stopped crying and went to sleep.

The presence of swallowed air is regarded by Smith and LeWald as objectionable. Extreme distention must be unfavorable to gastric secretion through pressure on the mucosa and blood vessels. The symptoms may often be entirely relieved by assisting the expulsion of the gas by mouth, so that it need not be passed through the intestine. If it does pass through the intestine, it causes colic. A horizontal position in nursing favors the accumulation of gas. Hospital feeding cases are often examples of the bad result of this. Except in the case of feeble infants, the feeding should be taken in five to ten minutes, or at most in fifteen. There are fewer disadvantages in having several holes in the nipple so that the milk runs freely, than in prolonging the nursing.