ON FRAGILITAS OSSIIUM AND ITS ASSOCIATION WITH BLUE SCLEROTICS AND OTOSCLEROSIS.

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The purpose of this paper is to give a description of two families with hereditary fragility of the bones associated with grey-blue sclerotics, and in the first family with otosclerosis also; a summary of the literature of these peculiarities in relation to fragilitas ossium is presented, together with a general discussion of the whole subject, case reports of the congenital type, and a bibliography.

HISTORY OF THE CURRIE FAMILY.

In December 1915 John B. (No. 37 in the diagram of the Currie family) was brought to the Royal Hospital for Sick Children, Edinburgh. While talking with the mother it was noticed that her sclerotics, as well as those of the child, were of a deep grey-blue. On inquiry a history of fractures and blue sclerotics through four generations was obtained. The great-grandfather, William Currie, was the earliest individual about whom information could be ascertained. The history was taken subsequently from each adult living in Scotland in order to ensure accuracy.

GENERATION I.

(No. 1).—William C. was reported to have been a short, slender man, much crippled. He sprained his ankles easily as a boy, but no fractures were known to have occurred until his 16th year, when he broke his thigh. During the next few years he had many fractures. He had deformed elbows and claw fingers. He always wore a belt about his hips because of pain in his back. The shape of the head is remembered by all who saw him; they describe other members of the family as having, or not having, "a head like Grandfather C." A soft spot was present as long as he lived. The frontal and occipital regions were prominent. (A daguerreotype was seen.) The sclerotics were deep blue. He had moderate deafness.

(No. 2).—A sister of William C. had fractures and deep blue sclerotics. She lived in Cumberland, and no trace of her or her descendants has been found.

GENERATION II.—Children of William C.

(No. 3).—Mary C. A. Several fractures of legs in youth and at least one fracture of an arm when over 30 years of age. She was said by her daughters and sisters to have had eyes and head like
William C., even having a soft spot on the top of her head throughout life. She was very deaf.

(No. 4).—Joan C. L. A large woman with sloping forehead, white sclerotics, no fractures, and normal hearing. (Photograph seen.)

(No. 5).—Annie C. W. A tall, slender woman with several fractures of the legs, but not crippled; deep blue sclerotics. Not deaf. She died at 23 years. (Photograph seen.)

(No. 6).—Elizabeth C. S. Age 49. Medium height; a woman of slender frame, somewhat crippled. She has sprained her ankles and dislocated her fingers easily since childhood. She had her first fracture, a broken leg, when 3 to 4 years of age. She has had her thighs and legs broken many times. The left leg is shortened, and a radiograph of the hip shows a fracture of the neck of the femur with resulting coxa vara. She has had fractures about both elbows, with displacement, and has claw hands apparently secondary to the deformity at the elbow. She broke her arm at 38, and had her most recent fracture, that of one leg, at 46. Her head shows a full frontal region and a prominent occipital bone; there is no supra-aural enlargement. She has very deep grey-blue sclerotics, and she has been growing deaf since adolescence.

(No. 7).—Mrs. C. H. Medium height. Fractures from early girlhood up to recently of thighs, legs, and arms; she says she has lost count of the number. She has also had many sprains. She has the characteristic full forehead and prominent occipital bone. There is some depression in the region of the posterior fontanelle. She has deep blue sclerotics, and has been somewhat deaf since girlhood.

(No. 8).—Marg. C. P. In Canada, and address unknown. Reported by sisters to have white sclerotics and no fractures.

**Generation III.**—**Grandchildren of William C.**

(Children of No. 3—Mary C. A.).—Nos. 9, 10, and 11 died in early infancy with no history of fractures. There were also two still-born children of whom no description can be obtained.

(No. 12).—Mrs. Joan A. B. Age 39. (See photograph with infant, also radiograph of hand (Figs. 4 and 5)). She is a short woman, with a large head, a full forehead, and a prominent occipital bone. She dislocates her thumbs easily and has sprained her ankles many times. She has had several fractures of the arms, and at present shows a deformity of both forearms near the wrists. She has the typical blue sclerotics, though the colour is not so intense as in some members of the family. She has been growing deaf for twenty years.

(No. 13).—Mrs. A. T. A well-built healthy woman with no peculiarity about the shape of head, no fractures, and white sclerotics. Hearing normal.
(No. 14).—Eliz. C. A. Age 35 years. Height 5 ft. Slender. Both legs have been broken. Her ankles are so easily sprained that she keeps them bandaged constantly. She wears a belt for sacro-iliac joint disease. Her head is very like her sister’s, No. 12. She has blue sclerotics, and has been growing deaf since 16 years of age.

(Children of No. 4—Joan C. L.)—(Nos. 15 to 21 inclusive).—This family shows none of the characteristics of fragilitas ossium. One individual, a man of 29, has had a fracture of the arm, but from violence.

(Children of No. 5—Annie C. W.)—(No. 22).—Mrs. Christina W. S. is a stout, short woman with slender bones. She had broken her thigh twice before 3 years of age, and has had several fractures since then about the ankles. Her fingers dislocate easily. She walks with a decided limp, and from palpation one would judge that she had had a fracture of the neck of the femur. She has some deformity and callus of both forearms. The eyes show the darkest sclerotics of any of the family I have seen. She has somewhat defective hearing.

(Child of No. 6—Eliz. C. S.)—(No. 23).—Died in infancy. Deep blue sclerotics but no fractures. The mother does not know whether or not the skull was soft.

(Children of No. 7—Mrs. C. H)—(Nos. 24 to 30 inclusive).—These seven have had no fractures, and their eyes are normal.

(No. 31).—A boy of 10 years. Short and rather thick-set. He has the full forehead, but more prominence of the parietal and temporal than of the occipital region. He has had two fractures of the arms, one of them recent. His sclerotics are moderately blue.

(No. 32).—A girl of 8 years. Fragile, under-sized, with the typical head. Fontanelle closed, but depressions of both anterior and posterior fontanelles as well as palpable lambdoidal sutures have persisted; no supra-aural bulging. She has already fractured her thighs twice, and has had what was either a sprain or a fracture near the ankle. The sclerotics are a very deep blue.

Generation IV.—Great-grandchildren of William C.

(Children of No. 12—Joan A. B.).—Of six children three died in infancy without fractures. Two of these three had blue sclerotics.

(No. 35).—A boy of 6 years. Height 39½ ins. He has the typically shaped head (Fig. 1). The fontanelle is closed. He is a healthy child, has had no fractures, and shows no signs of rickets. The sclerotics are blue, of moderate intensity.

(No. 37).—A fairly healthy boy of 3 years. (Fig. 2). He has had one fracture of the right arm, caused by falling off a chair when 1½ years of age. He has the same type of head as his brother. The fontanelle is closed. There is no enlargement of the costo-chondral junctions, though the chest is somewhat deformed. No enlargement
Figs. 1 and 2.—David and John B. (Nos. 35 and 37). The younger had an injury at the elbow, with resulting flexion deformity.

Fig. 3.—Elbow of Eliz. C. S. (No. 6). Injuries about the elbow with flexion deformity are common in this family.
Fig. 4.—The Hand of Mrs. Joan A. B. (No. 12). Notice the deformity at the wrist and the rarefied appearance of the bones.

Fig. 5.—Mrs. Joan A. B. (No. 12) with her Child (No. 38). Notice the shape of the head in the child and the deformity of the forearm in the mother.
of the ends of the long bones, or other signs of rickets. The sclerotics are a deeper blue than those of No. 35.

(No. 38).—An infant which died of pneumonia at 11 months, while the family was being studied. The circumference of the head was 18½ ins.; the occipital protuberance was marked (Fig. 5); the anterior, posterior, and lateral fontanelles open, not bulging, and the sutures, especially the lambdoidal, palpable; there was no craniotabes. No enlargement of the costo-chondral junctions. He was cutting teeth, sitting up alone, and trying to stand. No fractures. Moderately grey-blue sclerotics. No complete necropsy was permitted, but one eye was removed for examination. (See discussion of blue sclerotics.)

Children of Nos. 13, 15, and 16, like their parents, have had no fractures and do not show blue sclerotics.

(Child of No. 14—Eliz. A.)—(No. 43).—A fragile little girl of 12 years. Height 53½ ins.; circumference of head 20¼ ins. She has had two fractures of the clavicle, of which the radiograph shows practically nothing now. She sprains her ankles so easily that they are kept bandaged like her mother's. Her head and eyes are very like her mother's (No. 14).

(Children of No. 22—Christina W. S.)—(No. 53).—A healthy boy with no fractures and white sclerotics. However, he is able to dislocate his fingers and toes at will.

(No. 54).—Died in early infancy. Had deep blue sclerotics.

(No. 55).—An infant 4 months old when seen. The head showed a full frontal region. Anterior, lateral, and posterior fontanelles were open widely and all sutures palpable. There were crepitant spots over the occiput. The baby was breast-fed, good-natured, and apparently healthy.

Discussion of Currie Family.

Several subjects are suggested by a study of the preceding family history. There is a hereditary tendency (1) to fractures and dislocations; (2) to a peculiar type of head; (3) to grey-blue sclerotics; and (4) to deafness.

1. Fractures and Dislocations.—The liability to fractures in this family belongs distinctly to the type described by Lobstein in 1833 as "idiopathic osteopsathyrosis." The earliest member of whom we have a history, William C. (No. 1), is reported to have had no fractures until 16 years of age, and the earliest occurrence of a fracture was in his great-grandchild (No. 37) at 1½ years of age. That the liability to fractures continues well on into middle life in some members of this family is illustrated by Elizabeth C. S. (No. 6), who is now 49 years of age. Her first fracture was in her 4th year, and her most recent at 46—a fracture of the leg.
above the ankle, produced by stamping her foot in anger. Dislocations are nearly as frequent as fractures. This tendency to dislocations and sprains was not present in any of the patients who had not fractures and blue sclerotics, except in No. 53, who can dislocate his fingers and toes at will, and yet shows none of the other peculiarities of the Currie family. No. 17, a man of 29, has had one fracture, but from violence.

It is of interest to note that in no member of this family has there been the extraordinary degree of fragility described in many of the non-familial cases or in the cases of osteogenesis imperfecta of Vrolik. Arnott’s patient, a girl of 14 years of age, had thirty-one fractures, the first occurring at 3 years of age. Her sister had nine fractures between 8 months and 6 years; there was no hereditary history. In Cortes’ family, where there was hereditary transmission, no fractures were mentioned in infancy, and thirteen fractures was the largest number in any individual. Pauli described three generations, and noted that no fracture occurred before the 8th year, and no large number in any person. Axhausen reported a child who was normal until the 3rd year, and then suffered from twelve fractures within a year. A brother had twenty fractures, the mother four, and an aunt several.

The fractures in family fragilitas ossium usually occur after birth and even after infancy. That there is no absolute rule is illustrated by Willard’s family of three generations, one individual in which had the first fracture at birth, another at 1 week, a third at 3 weeks, and a fourth at 4 weeks. This family is also exceptional in that, though the onset of fractures was early, the maximum number of them was nine for any one person. In Pritchard’s family, one infant had a fracture on the 2nd day of life, a second on the following day, and a third 3 weeks later. Such examples are exceptional. I have seen no record of family fragilitas ossium in which an infant was born with a large number of broken bones, like Chaussier’s case of the osteogenesis imperfecta of Vrolik, an infant with one hundred and thirteen fractures, who died soon after birth.

In the Currie family the stature varies. The individuals affected speak of themselves as small-boned in contrast to their relations who have no fractures. Of those examined, all are below average height except Eliz. C. S. (No. 6) and Mrs. C. H. (No. 7). A photograph of Annie C. W. (No. 5) would indicate that she was above the average height. The children measured from 1 to 2 ins. less than the average for their ages (comparison was made
with the tables in Holt's *Diseases of Infancy and Childhood*), also about the same amount less than their cousins who have not fragile bones.

2. **The Peculiar Type of Head.**—The photographs of Joan A. B. (No. 12) and her three children illustrate the shape of head seen in all members of this family who have fragility of the bones and blue sclerotics. It will be observed that the frontal and occipital bones are unusually prominent, yet there is none of the squareness of the typical rickety head. The suture boundaries of the occipital bone can be made out by palpation in the majority of the cases. If the history is to be trusted, two individuals had patent fontanelles throughout life. There is, in this family, no supra-aural bulging such as has been emphasised by Cameron in osteogenesis imperfecta congenita. It may be well to state that members of the Currie family without fragility of the bones have sloping foreheads and no prominence of the occipital bones.

The head of the infant (No. 38, Fig. 5) at 11 months measured 18½ ins. The lateral and posterior, as well as anterior, fontanelles were open, but there was no craniotabes. The head of No. 55, a breast-fed healthy infant of 4 months, showed all fontanelles open, and slight gaping of all the main sutures. Crepitant spots were present over the occiput.

In none of the Currie family is the antero-posterior axis of the eyeball rotated downward as in hydrocephalus and as in the family of Thomas W. (see below). Schultze reports a girl of 13 years who had her first fracture at 9 months, and twenty-three fractures in all. Her photograph shows a head shaped very much like that in our family, except that the ears are bent outward by supra-aural bony prominence. In Hartmann's third case the occipital protuberance is marked and forehead full as in our cases.

The explanation of the shape of the head is probably that in infancy certain portions of the skulls of these individuals are less perfectly ossified than others, and unusual prominence of these parts results. In other words, one may say that in hereditary fragilitas ossium there may be present osteogenesis imperfecta of the skull.

3. **Grey-Blue Sclerotics.**—The diagram (p. 246) shows the incidence of blue sclerotics in this family. It will be noted that fractures have occurred in all the persons who had blue sclerotics, and who survived infancy, with the exception of No. 35, a boy of 6 years. Individuals who did not show a tendency to fractures had ordinary sclerotics. The degree of fragility seems to correspond
with the darkness of the grey-blue colour of the sclerotic. That no such rule holds universally is evident from the limited number of fractures reported in the literature of hereditary blue sclerotics, also from the fact that the sclerotics of Alastair R., a non-hereditary case of extreme fragility of the bones (see below), were of a less deep blue than those of most of the individuals in the Currie family. Doris O. (see below) did not show the typical grey-blue sclerotics at all. That the grey-blue sclerotics are not confined to the family type of fragilitas only is evident from its presence in Alastair K., also in the cases of Herrman, Ostheimer, Cones, and E. A. Park (personal communication).

CHART 1.—THE CURRIE FAMILY.

That grey-blue sclerotics may occur in individuals with no tendency to fractures is illustrated by the following case which Dr. Arthur Sinclair, Ophthalmologist to the Royal Hospital for Sick Children, Edinburgh, kindly referred to me:—

CASE WITH BLUE SCLEROTICS WITHOUT FRAGILITY.

Mrs. L., age 36. No children. No history of fractures or blue sclerotics in the family. (Mrs. L., her sister, and sister's children examined.)

Personal History.—She was breast-fed, walked at 1 year, and her development seems to have been normal. She had acute rheumatism at 15 years, and several attacks since; the heart was involved in the
first attack. She had one fracture, but from violence—falling down steps. The blue sclerotics were present at birth.

**Examination.**—Height 4 ft. 11 in.

*Head* shows a full square frontal region. The general shape of similar to the head in the Currie family, but the prominence of the occipital bone is absent.

*Eyes.*—Deep grey-blue sclerotics. The colour is uniform. Glasses for the correction of hypermetropia are worn.

*Extremities* show no deformities which could be attributed to fragility of the bones.

It is evident that, apart from a slight resemblance in the shape of the head and a fracture from violence, there is nothing to correlate the blueness of the sclerotics in this case with that which occurs in certain cases of fragilitas ossium. The colour is, however, the same grey-blue which was present in the Currie family.

Dr. Arthur Sinclair kindly examined the fundi and tested the refraction in Nos. 6, 14, 37, and 43. He found no abnormality of the fundus in any of them. A varying degree of hypermetropia was present in each case, in No. 6 (age 49) combined with presbyopia. He also tested the ocular tension with Schiotz's tonometer in No. 6 and No. 14, and found it to be normal—that is, 20 mm. of mercury.

In the literature, hypermetropia, with or without astigmatism, has been noted in all cases the refraction of which was examined. The presence of embryotoxon is emphasised by Stephenson and noted by others. We found this in several of our cases, but its frequency in normal eyes causes us to attach no importance to it. The irides in our cases were of varying degrees of lead-grey. Stephenson, however, states that the colour of irides varies as well as the hair and complexion.

**The Literature of Blue Sclerotics.**—The incidence of blue sclerotics with fragility of bones was described first by Eddowes in 1900. Twenty years before, while in general practice, he had had as a patient a small boy with ten fractures who showed the deepest blue sclerotics he had ever seen. Hence when a girl with deep blue sclerotics came to him for examination of the eyes, he asked her if she had broken any bones, and received the history that both she and her father (who had eyes like herself) had had numerous fractures.

Peters, in 1908, reported three generations of blue sclerotics and in 1913 he made an additional note of fragility of the bones in these cases; only six fractures in three individuals, however.

Stephenson and Harman, in 1910, published accounts of the
same family of blue sclerotics, altogether fifty-five individuals in five generations, thirty-one of whom showed typical sclerotics. Neither mentioned fragility of the bones, but in 1915 Stephenson showed, at the London Ophthalmological Society, a mother and two daughters belonging to this family with fractures.

Rolleston, in 1911, reported four instances of blue sclerotics in three generations, but mentions fractures only in the third generation, a child of 9 months. In 1914 he stated that this child had had two additional fractures.

Burrows, 1911, described a family of twenty-nine individuals (four generations), thirteen with blue sclerotics, and nine of the thirteen with brittle bones.

Adair-Dighton, 1912, gave accounts of thirteen individuals in four generations; nine of these individuals had blue sclerotics, and six of the nine, fractures. The total number of fractures was only twelve.

Coues, in 1912, recorded the history of a boy of 9 years who had had nine fractures since 2 years of age. He mentioned the “slaty-blue” sclerotics, and stated that he had heard of a family on Cape Cod with similar sclerotics and fragility of bones.

Conlon, 1913, reported twenty-seven persons in five generations; eighteen of these had blue sclerotics, and, of the eighteen, those who had reached puberty had sustained fractures.

In Poynton’s case, 1913, a girl of 11 years, there was no family history of either fractures or blue sclerotics. This child had had repeated fractures since early infancy, and showed, as noted by Rolleston, the typical blue sclerotics.

Cockayne showed a patient in 1914, from a family of twelve, in four generations, of which six had blue sclerotics, and all but the patient, an infant, had had fractures. No fractures had occurred in any of the family who had not blue sclerotics.

Ostheimer’s case, 1914, had blue sclerotics and nine fractures between 1½ and 4 years of age. No family history of blue sclerotics or fragility.*

* At the meeting of the Royal Society of Medicine, Section for the Study of Diseases in Children, 23rd February 1917, Dr. T. R. Whipham showed a boy of 9 years who has had at least six fractures since 5 weeks old. Deformity of the legs was extreme. The head showed the increased bitemporal diameter and frontal prominence. The sclerotics were grey-blue but of less than the average intensity.

In 1914 Wrede showed a girl of 16 years who had had sixteen fractures since 4 years of age, and who showed the typical grey-blue sclerotics. No definite history of heredity stated.
Herrman's case, 1915, of blue sclerotics, fractured the right tibia at 20 months; then, six weeks later, while still in bed, the right femur. No family history.

The report of Salvetti's case, 1915, was not accessible.

In 1915 Hofmann reported, with brief notes, three cases:—
1. A boy with blue sclerotics had four fractures between 6 and 14 years of age. No family history given.
2. A man of 24 years of age had a fracture at 1 year and again at 24 years of age. His mother also had blue sclerotics, but no further history of fractures was given.
3. A man, aged 31, had a fracture in the first year of life and two fractures since. His brother had had ten fractures. Both showed blue sclerotics.

Dr. E. A. Park, Baltimore, in a personal communication, states that blue sclerotics are present in a case of multiple fractures which he has seen but has not published.

In going through the literature of osteogenesis imperfecta and fragilitas ossium I have not found any description of cases with blue sclerotics except those summarised above. Arnott, in 1833, spoke of the presence of "bluish-grey irides" in his cases of family fragility, but he failed to mention the sclerotics.

Etiology of the Blue Sclerotics.—The etiology of the blueness has not been determined. All writers agree that it is due to increased transmission of the colour of the choroidal pigment, not to any inherent colouring of the sclerotics. Eddowes suggested that "the transparency of the sclerotics indicated a want of quantity or quality of the fibrous tissues forming the framework of the various organs of the body, and probably explained the want of spring or toughness in the bones of these individuals." Stephenson agrees with this statement. Peters thinks there is probably an actual thinning of the sclerotics. Conlon considers an increase in transparency the more likely hypothesis, suggesting that if there were thinning of the sclera one would expect to find cases of buphthalmos in these families, or at least some evidence of axial myopia. Fridenberg, who examined the eyes in Herrman's patient, also thinks that the assumption of thinning of the sclerotic as a cause of increased colour transmission is disproved by the absence of any record of a case in which distension of the globe, as in infantile glaucoma or hydrophthalmos, was present; also, there is no mention of the presence of coloboma or posterior staphyloma. He suggests that the blue sclerotic and the lead-grey iris as well are due to a transparency dependent upon the absence of lime salts in the connective tissue elements of the sclera and iris.
Histological Examination of Blue Sclerotics.—Buchanan made a histological examination of a blue sclerotic in 1908. He found the cornea three-fifths and the sclera one-third the usual thickness. There was a decrease in the number, but no change in the size, of the sclerotic fibres. However, there is no history of fractures in this case, and one has no reason to assume that it belongs to the fragilitas—blue sclerotic group.

An infant of 11 months (No. 38 in diagram; see Fig. 5) died while the family was under investigation, and permission was obtained for the removal of one eye. Mr. Richard Muir of the Pathological Department of Edinburgh University made microscopic sections of this. These were examined by Dr. J. V. Paterson, Ophthalmologist to the Royal Infirmary, Edinburgh, who stated that the sclerotic was of normal thickness, and the size and number of fibres normal for a child of that age. Since this infant had the typical blue sclerotic the more probable theory of its etiology is that of increased translucency rather than decrease in thickness.

In regard to the frequency with which grey-blue sclerotics are associated with fragility of the bones, one cannot judge until more observations have been made. Their significance and true etiology have yet to be determined. When opportunity occurs, a quantitative chemical examination of the blue sclerotic should be made and the results compared with the normal.

4. Progressive Deafness.—Seven individuals of the Currie family have had deafness starting in early adult life and growing steadily worse. None of them has become completely deaf. No member of the family without fragilitas ossium and blue sclerotics has had any deafness. In the literature one finds two references to deafness—Dent's case, a man of 29 years, who had been growing deaf for three years; and the case of Adair-Dighton, in which nerve deafness started three months after childbirth. It is absent in the family of Thomas W., reported below.

Dr. John S. Fraser* of the Otological Department of the Royal Infirmary, Edinburgh, examined three persons with deafness and one without deafness or fragility.

1. Mrs. Eliz. S. (No. 6 in diagram).—Age 49 years. Deafness started in her teens, but has grown much worse in the past eight years. No history of otorrhoea. She has noises in her ears "like machinery." She hears better in a noise. Examination showed nose and pharynx

* Dr. Fraser expects to publish detailed notes of these cases in the Journal of Laryngol., Rhinol., and Otol.
normal. Bone-conduction over the mastoid was better than air-conduction. The watch was not heard by either air- or bone-conduction. Dr. Fraser’s diagnosis was otosclerosis, with nerve deafness in addition.

2. Mrs. Joan B. (No. 12).—Age 39. Deafness for twenty years, most noticeable during her pregnancies. She hears best in a noise. She has whistling noises in her ears. Examination showed otosclerosis of an advanced degree.

3. Miss Eliz. A. (No. 14).—Age 35. Deafness started at 16 years of age and has gradually grown worse. No otorrhoea. She is much troubled with buzzing in the ears. Of late she has had dizzy spells. She is a mill-worker, and hears best in the noise of the mill. Examination showed otosclerosis as the cause of deafness.

4. Mrs. T. (No. 13), who has neither fragilitas ossium nor blue sclerotics, was examined and showed no defect in hearing.

Deafness associated with hereditary fragility of the bones has not been described previously. Is the deposition of calcium salts in the middle ear related to the abnormal osteogenetic processes? This possibility raises the question of excessive deposition of calcium salts in other structures of the body, as the arterial systems. In the Currie family there is no history of cerebral hemorrhage, and the arteries of individuals examined showed no excessive sclerosis. It is most desirable that future reports of cases of fragility should make note of the presence or absence of these points.

FAMILY OF THOMAS W.

In October 1916 Winifred W. was brought to the Casualty Department of the Paddington Green Children’s Hospital, London, for a fracture of the right leg. She had been treated there for a fracture of the left leg eight months previously. She showed grey-blue sclerotics. I obtained the following family history:

GENERATION I.—(No. 1).—Thomas W. writes that he has had no fractures, but that he is considered “loose-jointed.” He states that the “whites of his eyes are blue like his son’s.” He does not remember his parents’ eyes.

GENERATION II.—(No. 2).—Thomas W., Jr., age 39 years, has had occasional fractures on slight provocation all his life. The first was of the right thigh at 4 years of age. He remembers details of a Colles’ fracture of the right wrist, fractures of the ribs on three occasions (once on slipping from a chair, once from hitting against a desk at school, and once on slipping on the fender of the fireplace). He also fractured several fingers by grabbing the bridle of a horse. His last injury was a Pott’s fracture one year ago. He has sprained his ankles
many times, and says that these cause him more trouble than his fractures. He has passed for foreign service in the Army, but says he has to drop out in all route marches because his ankles turn.

He is 5 ft. 2½ ins. in height. The head shows no frontal prominence. The bitemporal diameter is increased so that the upper pole of the ear is turned outwards and downwards by the temporal enlargement. The occipital bone stands out in profile. In the region of the posterior fontanelle is a depression, which is continued anteriorly and laterally along the suture lines. The sclerotics show the typical greyish-blue of moderate intensity. The presence of embryotoxon is very noticeable. There is marked hypotonicity of all joints. Callus of the Pott’s fracture is still palpable.

CHART 2.—FAMILY OF THOMAS W.

(No. 3).—Mrs. M., sister of Thomas W., Jr., has blue sclerotics, and looks like him, but has had no fractures.

GENERATION III.—(Children of Thomas W.) (No. 4).—Emily W., age 10 years, a breast-fed infant, had her first fracture at 1½ years, soon after learning to walk. She fell and broke her right thigh and right arm. In the next six months she had two more fractures of the right arm, each in a new spot. An injury to the right elbow soon followed, then fractures of both legs. At 4 years she began to walk again, and had no more fractures until 7 years of age, when she broke her left arm. She is very loose-jointed, somewhat crippled, and unable to lead an active life. Her parents say that she has the darkest blue sclerotics of any in the family. Her photograph shows a head similar to her younger sisters’. She has been treated at the Great Ormond Street Hospital for one of her fractures, and for over a year has been in a convalescent home at Margate.

(No. 5).—Thomas J. W., age 8, does not resemble his father at all. He has had no fractures, there is nothing unusual about the shape of his head, and his sclerotics are not blue.

(No. 6).—Myra W., age 6, is a short, thick-set little girl. Her head
show temporal enlargement, so that the ears are turned slightly outward, but there is little frontal or occipital prominence. The jaw is slightly underhung. The thorax is short and thick-set. The abdomen is full and the muscles relaxed. There is no enlargement of the costochondral junctions, nor of the ends of the long bones. When the patient stands there is hyperextension of the knees and all joint ligaments show hypotonicity. She has had no fractures, but has sprained each ankle once. She has moderately deep grey-blue sclerotics.

(No. 7).—Winifred W., age $3\frac{3}{4}$ years, had her first fracture—the left leg—at $2\frac{1}{2}$ years; it recovered rapidly. No other fractures occurred until the present, an oblique fracture of the right tibia—October 1916—caused by slipping and falling. (In January 1917 she fractured her right femur just above the knee.)

She was a breast-fed infant, first tooth at 7 months, and walked at 16 months, but crawled for six months previously. She is generally healthy, except that she takes cold readily. She has had no severe illness.

Examination.—A short, thick-set child of rather apathetic disposition. Height, 31$\frac{3}{4}$ ins.

Head.—Circumference, 20$\frac{1}{4}$ ins. Temporal and frontal regions are full. The head is too broad for its length. The ears are bent slightly outward by the temporal enlargement. The lambdoidal suture is palpable as a ridge, yet the occipital bone is not prominent. The axis of the eyes is tilted slightly downward. The sclerotics are a moderately intense grey-blue. The jaw is slightly underhung, and almost no neck is present.

Thorax.—Short and thick-set. No rosary. The lower ribs flare outward somewhat.

Abdomen.—Large, relaxed. Abdominal muscles show poor tone. There is a small umbilical hernia. The liver is 1 in. below the costal margin; the spleen not palpable.

Respiratory and circulatory systems normal. Glands not enlarged.

Reflexes normal.

Extremities.—No enlargement of the ends of the long bones. No disproportion between the arm and forearm, thigh and leg. No palpable callus of the right leg. The muscular tone is poor all over the body, and hyperextension of the joints is possible.

Digestive System.—Teeth in excellent condition. Tongue clean. Tonsils small, and pillars and pharynx not injected.

Urine examined, negative. Von Pirquet, negative. Wassermann, negative.

Radiographic plates show no marked changes in the structure of the bones. There is now, after eight months, no trace of the fracture of the left leg.
The recent fracture of the right tibia was united firmly with a moderate amount of callus in two weeks.

(No. 8).—Child of Mrs. M., died at 1\(\frac{1}{2}\) years, soon after a fracture of one leg. This infant had blue sclerotics like her mother.

**Discussion of Family of Thomas W.**

Although the family of Thomas W. is another example of Lobstein's osteopatathyrosis, the physique of its members resembles that of Alastair R. and Doris O. (see below) more than that of the Currie family. In fact, Winifred W., when shown with Doris O. at a medical meeting, was regarded as her sister, yet Doris O. had fractures at birth, and would naturally be classed as osteogenesis imperfecta congenita. In general, the characteristics of the head in this family are a frontal and supra-aural prominence, a slight tilting downward of the axis of the eye, ears bent outward and downward, and a slightly underhung jaw. The shape of the head and palpable sutures are probably due to the same cause as in the Currie family, but are more pronounced. The grey-blue of the sclerotic is less intense than in most individuals of the Currie family. There is no history of deafness. Of especial interest is the presence of blue sclerotics and hypotonicity of joints in the grandfather, and the presence of blue sclerotics only in his daughter, yet their children had fractures.

**History of Alastair R.**

**Case I.**

Alastair R., age 4\(\frac{3}{4}\) years, was attending the Surgical Out-Patient Department of the Royal Hospital for Sick Children, Edinburgh, for treatment of a fracture while the Currie family were being studied.

There was no history of fractures nor blue sclerotics in parents, grandparents, or brothers and sisters. The father is a soldier. The patient is the fifth of seven children. One of these died of pneumonia, otherwise they have been fairly healthy. The mother worked hard, doing washings up to a short time before the birth of the patient.

He was a full-time baby, the labour was easy, with delivery by a midwife. At birth he was a large, healthy-looking baby, the "finest of the seven." He was breast-fed until 6 months, then given cow's milk. At 8 to 9 months milk pudding and eggs were started, also extra cream. He was always fed better than the other children. He had his first tooth under 6 months, was creeping under 1 year, but he has never walked. He talked at 11 to 12 months. The history of illnesses has been quite negative except for an attack of diphtheria.
Special Condition—History of Fractures.—1. At birth the mother says the thighs were much swollen and bent, and that in the left there was a sharp angle. When a few days old they were put in cardboard splints by the military doctor, and a skiagram was taken.

2. At 4 to 5 months patient broke his right thigh while being nursed by his grandmother. This was set at the Connaught Military Hospital.

3. A few months later the right thigh was broken again while his father was playing with him.

The mother noted that he often cried out in infancy when picked up. When about 1 year old he was shown to students at a London hospital, because of a soft spot on the right side of his head.

4. When $1\frac{1}{2}$ years old he was admitted to Dr. Melville Dunlop’s ward in the Royal Hospital for Sick Children, Edinburgh, with a fracture of the thigh. This was treated by suspension, and he was sent home in a Thomas’ splint, to be worn during the day only.

5. Fracture of right thigh soon after leaving hospital.

6. Two months later another fracture of thigh. At this time the Thomas’ splints were changed to double Hamilton, in which he has been day and night since.

7. When $2\frac{9}{12}$ years of age, while in splints, he broke his leg, trying to turn over. He was admitted to the surgical ward under Mr. Stiles, with fracture of right femur. The house surgeon made the note at that time that the other bones were “very rickety.”

8. Two weeks later while in extension in the ward he fractured the left femur. There was little displacement and no swelling.

9. Five weeks later, after extension was removed, he fractured his right tibia.

10. When 3 years of age—February and March 1915—he was in the surgical ward again with a fracture.

11. When nearly 4 years—November 1915—he cried out at night, and though in splints there was a fracture of the left femur, for which he was under observation when first seen by the writer.

Examination.—A somewhat pale, well-nourished, short, thick-set child of normal intelligence. Height, 32\frac{1}{3} ins.; weight, 27 lbs. 13 ozs.

Head.—Circumference, 21\frac{1}{4} ins. The fontanelles are closed, but there are depressions still at the regions of the anterior and lateral fontanelles. The occipital bone is slightly raised beyond the level of the rest of the skull, and its margins are easily outlined. The frontal region is full, but not square like a rickety head. There are no supraural bony prominences. On the right temporo-parietal region is a depression in the bone 1\frac{1}{2} by \frac{3}{4} in.

Eyes.—The iris is a deep bluish-grey. There is a slight embryotoxon. The sclerotics are a uniform grey-blue of moderate intensity.

Neck.—Is short, and jaw somewhat underhung.
Spine.—Shows lower dorsal curvature of the weak-back type. The patient sits up if placed in upright position, but seems unable to pull himself up.

Thorax.—Short and broad. An angle and easily movable joint is present at the junction of the manubrium and xiphoid process. There is no enlargement of the costo-chondral junctions.

Abdomen.—No distension and natural looking. Neither liver nor spleen are palpable.

Circulation and respiratory systems show nothing abnormal.

Nervous System.—Deep tendon reflexes are somewhat exaggerated, and slight facial irritability is present.

Digestive System.—No abnormality. Teeth good.

Glands.—No groups even palpable.

Extremities.—There is little, if any, disproportion between the length of distal and proximal long bones. There is no enlargement of the ends of the long bones. There is deformity and callus of former fracture just above right wrist. (The mother does not recall any fracture in this place.) The thighs and lower third of the tibiae show marked anterior bowing. The feet lie in complete extension, with toes in same plane as the tibiae. Hyperflexion, however, is not possible, actively or passively. Lateral movements of the feet are greater than normal. Nearly all joints show hypotension. He is a dead weight to handle, the shoulders slip through one’s hands, and legs hang limp from body. He uses his arms somewhat, but can raise his feet only 6 to 8 ins.

Urine.—Clear, acid. No excess of phosphates. Sugar, albumen, indican, negative. Sediment, negative.

Blood.—Hb, 80 per cent.; R. B. C., 5,952,000; W. B. C., 10,100; P. M. N., 60 per cent.; P. M. E., 1 per cent.; S. M. N., 29 per cent.; L. M. N., 10 per cent.

Von Pirquet, negative. Wassermann, slightly positive.

Ophthalmoscopic examination by Dr. A. H. Sinclair showed nothing abnormal.

Treatment.—This patient has been under treatment with emulsion of cod-liver oil and phosphorus most of his life. He was in the Royal Infirmary, Edinburgh, for six weeks—in February and March 1916. After discharge, the mother, at my advice, left off the double Hamilton splints. Two weeks later, while reaching for something, he broke his right tibia. In the early summer he had another fracture of left leg. In August, he was still without splints, crawling about the floor. There was noticeable improvement in his muscle tone.

Summary.—Case I.—Alastair R. is an example of non-familial fragility of the bone associated with blue sclerotics. The onset was at birth or previously, yet the skull does not show signs of any extreme grade of imperfect osteogenesis. The long bones are
Fig. 6.—Alastair R., Case I. Notice that there is no marked bilateral enlargement of the head, also the short, thick-set body with no disproportionate shortening of the long bones.

Fig. 7.—Pelvis of Alastair R., Case I. Observe the poor shadow cast by the bone, the slenderness, bending, and scars of many fractures of the long bones, also the coxa vara and shape of pelvis.
most affected, with at least fourteen fractures without violence. The trunk is short and thick-set, and extremities are not disproportionately short. The skiagrams show slender bowed bones, with little callus at points of fractures. All the bones are much rarefied.

**History of Doris O.**

**Case II.**

Doris O., age 4 years, has been under the observation of Dr. Leonard Guthrie * at the Out-patient Department of the Paddington Green Children’s Hospital for the past five months.

*Family History.*—Negative. Patient is the only child. Full-time, breast-fed infant. First tooth at 9 months. Talked early. No illnesses, and considered generally healthy.

*Special Condition.*—At birth the legs were twisted at right angles to the body. The nurse attempted to straighten them, but because they continued crooked, at the fifth week they were put in splints by the doctor. Thereafter splints were kept on day and night. No fractures were noted by the mother until the 18th month, when the child cried on being bathed, and the thigh was found broken. At 2 years an unsuccessful attempt was made to teach the child to stand. At 3½ years the right arm was broken. Five months ago, under the direction of Mr. Lees, Assistant-Surgeon of the Paddington Green Children’s Hospital, the child began to stand, and later to walk, supported under the arms by a harness. She is walking short distances without aid now, but shows marked hypotonicity of the knees and ankles.

*Examination.*—A short, thick-set, well-nourished child of normal intelligence. Height, 30½ ins.

*Head.*—Large. Circumference, 20½ ins. Not square like a rickety head. The bitemporal diameter is very noticeably increased; this supra-aural enlargement bending the ears slightly outward and downward. The occipital bone is also prominent. The fontanelles are closed. The axis of the eyes is not tilted downward. The jaw is slightly underhung. The sclerotics show a slight blue tinge, but not more than one frequently sees in normal children.

*Thorax.*—Bilateral diameter increased, giving a short, thick-set body. There is some enlargement of the costo-chondral junctions, and Harrison’s groove is present.

*Abdomen.*—Large, relaxed; muscle tone poor. Liver 1 in. below costal margin. Spleen not palpable.

*Heart* and *lungs* negative.

*Glands.*—No general enlargement. Thyroid gland is palpable.

I am indebted to Dr. Guthrie for the privilege of taking the history and examining this patient.
Extremities.—Some enlargement of ends of long bones. Marked angular deformity of the right arm. Anterior bowing of tibiae. In this child the proximal bones of the extremities are disproportionately short to the distal bones. Skiagrams show marked bowing of the extremities, scars of many fractures, with little remaining callus, and a structure of bone similar to Alastair R., except that the long bones are shorter and thicker than his.

Summary.—Doris O., Case II., like Alastair R., Case I., is an instance of fragility of the bones, with fractures at birth or previously in a child surviving infancy. She differs from Case I., in the somewhat shorter, thicker long bones, the disproportion between their proximal and distal portions, and in the much more marked abnormality in the shape of the head.

**History of Peter McN.**

**Case III.**

Father and mother are healthy. No miscarriages. There were nine children. The first child was a 7-months infant, and died at 3 weeks of age. The patient was the second child. One of the seven remaining children died of whooping-cough, the others are healthy. No fractures in the family.

Normal birth, and a strong baby, though two weeks premature. Breast-fed three weeks, then cow’s milk.

He had his first tooth at 2½ months. He was reported to have had his full first set at 9 months. He walked at 2 years. The “opening of his head” did not close until he was over 18 months old.

Except for breaking bones he has been a healthy child. He has always been very thin.

Special Condition.—Fractures—(1) Left femur at 3 years, by falling down two steps of a staircase. (2) Left clavicle at 3½ years, by falling from a small barrow. (3) Right femur broken and knee dislocated at 4 years. (4) Right clavicle at 5 years, by falling down steps. (5) Right femur at 9 years, by a slight fall.

There was no history of sprains or dislocations except the right knee. This knee is fixed in partial flexion, also the elbows. At the wrists an unusual degree of passive lateral movement is permitted and crepitation is elicited. There was no pain nor tenderness. The stature is normal, and there is no disproportion between the lengths of proximal and distal long bones. The joints appear enlarged, but the absence of pain and tenderness is against any arthritis. (Bruck and Anschütz

* This boy was under Mr Caird’s treatment at the Royal Infirmary, Edinburgh. Permission was obtained from him by Prof. Lorrain Smith for me to see this patient.
Fig. 8.—Doris O., Case II. Notice the short, thick humerus in contrast to the long, slender ulna and radius.

Fig. 9.—Doris O., Case II. Notice the short, thick humerus in contrast to the long, slender ulna and radius.
both describe a joint disease, associated with fragility of the bones. In Bruck’s case the joints went on to ankylosis, while there was distinct improvement in the fragility. In Anschütz a synovial arthritis was present. In these cases one regards the joint involvement as coincident.)

The head of Peter McN. resembles that of the Currie family rather than Alastair R. or Doris O. There is a full but not square frontal region. The bitemporal diameter is not increased. The occipital bone is prominent, irregularly bossed, and the sutures about it are palpable as depressions. The eyes do not show typical blue sclerotics. There is no depression of the bridge of the nose, and nothing about the boy’s appearance to suggest congenital syphilis.

**Summary.**—Peter McN. illustrates an isolated case of bone fragility starting after infancy. Like the family cases reported above, a certain amount of violence is needed to produce the fractures. His sclerotics are not the typical blue. The shape of his head is very similar to that of the Currie family, and the supposition is that there was a degree of osteogenesis imperfecta in his earlier development. There is no dwarfing.

**General Discussion.**

**Terminology.**—Although Lobstein used the term Osteopasathyrosis to denote the idiopathic as well as other types of bone fragility, and Vrolik, in 1849, described the prenatal idiopathic type under the term Osteogenesis Imperfecta, “Fœtal Rickets” was formerly the usual designation of a group of conditions including Osteogenesis Imperfecta, Achondroplasia, and Cretinism. In 1878 Parrot described Achondroplasia, and 1892 Kaufmann definitely separated this condition from the group under the name of Chondrodystrophy foetalis. Cretinism is now also a clinical entity, and even in 1861 was separated clinically from Osteogenesis Imperfecta by Heckel. As early as 1889 Stillling, in a careful report of a case of prenatal Osteogenesis Imperfecta, suggested that so loose a term as “Fœtal Rickets” was superfluous. Other names occur: Kundrat speaks of Osteoporosis congenita, Hochsinger of Osteopsathyrosis foetalis, Bamberg and Huldschinsky of Osteopsathyrosis congenita, Marchand of Congenital Osteomalacia, Klebs of Periosteal Dysplasia, Looser of Osteogenesis, congenita and tarda. Fragilitas Ossium is one of the terms most frequently used.

What is the most suitable name depends partly on whether it is considered that there are two distinct conditions—one prenatal,
affecting the skull and causing a large number of fractures in all bones; the other postnatal, and affecting chiefly the long bones—or whether we accept the pathological identification of the two types, and regard them as degrees of intensity of the same pathological process.

**Etiology of Bone Fragility.**—In regard to the etiology of bone fragility the only factor we know is heredity, and this occurs, according to Ostheimer, in only 9.8 per cent. of cases, though there is a history of affected brothers or sisters in as many as 29.6 per cent. The inheritance, when present, is direct transmission—what Bateson calls “knight’s move,” namely, the characteristic of fragility is a dominant one. Davenport thinks the condition of blue sclerotics is also a dominant one, but he is not certain that the two are linked. The line of transmission is not through females to males, as Greenish and, later, Harman suggest.

Syphilis is not a factor. The thyroid gland was examined and no pathological lesion found by Stillig, John, Ballantyne, Michel, Dieterle, and Sumita. Occasional reference is found to overwork or poor physical condition of the mothers, but more often both parents were healthy. Ostheimer considers that there is some fault in the metabolism of the mother. Zesas emphasises the lack of some internal secretion. Klose also suggests that the endocrin glands are concerned, quoting Cushing’s finding, that the posterior lobe of the pituitary gland has an influence on the metabolism of calcium and magnesium. Von Recklinghausen’s suggestion, which Sumita revised, that there is a fundamental malformation or a “vitium primae formationis” of the bone-forming cells, is a satisfactory expression of our ignorance.

**Clinical Picture and Gross Pathology.**—In Osteogenesis Imperfecta of prenatal onset the typical description is that of an undersized, frequently premature, infant, either still-born or dying soon after birth. The extremities are short and thick-set; the diaphyses irregular, with rings of callus, and circumference increases in proportion to the size of the epiphyses. The head is a crepitant bag with only a mosaic of small plates for a bony covering.

**Shape of the Head.**—The shape of the head has been noted since the condition was first described, and the term “hydrocephalic” most frequently applied to it. The erroneous conclusions which may follow such a use of the word hydrocephalic are illustrated by Esser’s suggestion that the etiology of the fractures is of central nervous origin, some trophic disturbance as
syringomyelia and tabes, probably the result of a pachymeningitis, which may be assumed by the frequent presence of hydrocephalus. The softness of the skull accounts, in all probability, for the early death of most of the typical congenital cases. In the infants that survive birth, yet have defective ossification of the skull, the ultimate shape of the head will depend upon what portions yield most readily to pressure. This process is illustrated well by Preiswerk's case, an infant with deformed legs at birth (fractures when seen at fifth day by a doctor) and a head like a crepitant bag. At 2 months the skull was much harder, but deformed, and at 2 years of age there was marked bilateral enlargement, with ears bent outwards and downwards, and a full frontal region. Another similar instance is Bamberg and Huldschinsky's second case. At 2 months of age the skull was soft, and the fontanelle measured 7 by 5.5 cm., yet the head was not especially abnormal in shape. When 2 3/4 years of age, however, there was marked bitemporal enlargement and turning out of the ears. It should be noted, however, that though the head was very similar to Preiswerk's case, the first fracture of the long bones was on the eighth day of life, not before birth. The bitemporal enlargement in Ewald's second case was very striking, and in this instance the fontanelle was open—not bulging—until 4 years of age, though no fracture of long bones occurred until the seventh month. In Scheib's case a similar deformity, with ears turned out, was present at birth, and the skull showed only a moderate degree of defective ossification, suggesting that this deformity is not necessarily of postnatal origin. Harbitz speaks of the cranium of his patient—an infant dying a few minutes after birth—as a sack, yet he adds that there was nothing hydrocephalic nor unusual in the size and shape of the head. The question arises whether or not this child would have developed an abnormally shaped head if it had lived.

The bitemporal enlargement was emphasised by Cameron as characteristic of congenital Osteogenesis Imperfecta. That it is not limited to cases dying in infancy, nor to those having fractures at birth, is illustrated by the cases of Ewald, Nathan, Schabad, Lange, and others. My Case II. shows this characteristic, and it may even be present in family fragility of bones, as illustrated by the family of William W. That it is not an essential feature even of the cases with fractures before birth is shown by Lovett and Nichol's patient, who had a normally hard skull at birth, without deformities, yet had fractures. In Fowler's case the
entire skull was soft at 4 days of age—the time of the first fracture. When 1 year of age the back of the skull was ossified; at 2 years the anterior fontanelle was \( \frac{3}{4} \) in. across. Simmon's patient, a girl of 13, who had had ten fractures, with the first at birth, still had a depressed, soft posterior fontanelle. Nathan's case showed open sutures and movable cranial bones at 17 years. In my cases of the Currie family there is a history of patent fontanelle throughout life in two individuals.

Enough has been said to indicate that, while a bilateral increase in diameter is of frequent occurrence, no single characteristic in the shape of the head is pathognomonic in the diagnosis of Osteogenesis Imperfecta congenita, also that the so-called typical head of the congenital type is found in certain cases with fractures of postnatal onset, and even in hereditary Fragilitas Ossium. On the other hand, it is reasonable to expect the greatest cranial defects in infants with intra-uterine fractures. The cases cited indicate that in certain instances there is a selective process, so that some portions of the bony frame escape while others are markedly involved.

An increase in the size of the head is frequently mentioned. In my opinion the apparent size and the actual increase in occipito-frontal circumference is due usually to an abnormal arrangement of diameters, but the total volume of the head is the same. Preiswerk mentions huge callus formation on the skull in his case. This is a possible explanation of increase in size, if present. Except in Dillenburger's case of associated pachymeningitis, there is no history of bulging fontanelles nor other signs of hydrocephalus.

An underhung jaw was mentioned by Cameron. This showed in several photographs from the literature, and was slightly present in our cases,—Alastair R., No. I., and Doris O., No. II., and in Winifred W. of the family of William W.

Blue Sclerotics.—The blue sclerotics, as present in Alastair R., have been noted in non-familial cases by Herrman, Ostheimer, Poynton, Coues, Hofmann, and E. A. Park. (Personal communication.) Their frequency is unknown.

Stature.—The short stature has been mentioned from the earliest descriptions in the literature, especially of the prenatal type. A disproportionate shortness of the proximal to the distal long bones has been also noted occasionally. That short stature must not be assumed an essential characteristic was maintained by Vrolik, Bidder, S. Müller, Sumita, Fuchs, Lovett and Nichols,
Maier attempted to distinguish between the prenatal and postnatal type by the length of the long bones as revealed by radiographic plates. He believed that short, thick bones were characteristic of the former, and long, thin bones of the latter. No such universal rule can be formulated, yet, in general, one may say that the earlier the onset of symptoms of imperfect osteogenesis, the greater will be the effect on the stature. However, short stature is not confined to cases with fractures before birth, as illustrated by Willard’s family and my cases, the Currie family, and family of William W. Also that slender bones and short stature are not incompatible is shown by Case I. above. Griffith’s case, which fractured on the second day of life, was a normal-sized child; also Maier’s patient, a girl of 6 years, with many fractures since 1½ years, was not stunted. Miura’s case was similar though there had been seventeen fractures.

The theories to explain the shortening when present are—

1. That it is due to deformity, the result of many fractures. This supposition does not explain the shortening in cases like Stilling’s, where the skull was like paper, yet only a few fractures of the long bones; nor cases like Fuchs’ and Scharlau’s, in which no fractures were found at necropsy, yet marked shortening and an extreme grade of Osteogenesis Imperfecta were present.

2. Fuchs suggested that the shortening depends on whether or not the endochondral bone-formation is especially affected, that is, there may be a specificity in the region of the osteogenetic processes involved. Should the endochondral ossification be adequate for the normal growth in length, but the subperiosteal be deficient, the bones would not be shortened, but would be very thin. If, however, the endochondral bone-formation were especially defective, with the subperiosteal less so, the length of the diaphyses would be diminished. In the latter case, if circumference of the diaphyses were increased, this might be due either to a diminution in osteoclasts or to excessive, but abnormal, subperiosteal bone-formation.

If one accepts Fuchs’ theory, the observation that the shortening is usually most marked in cases with intra-uterine fractures is explained by the preponderance in the long bones of endochondral to subperiosteal bone in foetal life as compared with adult bone, which is almost entirely of subperiosteal origin. On the other hand, since all osteoblasts are derived from the primordial connective tissue of osteogenetic layer of the periosseum.
(Piersol, and Bailey and Miller), one must explain why the osteoblasts passing centrally into the preliminary cartilage calcination zone should differ in functional capacity from those lying under the periosteum. It would become necessary to define even the stage in their development at which osteoblasts become functionally incapable of laying down normal bone.

3. The supposition of defective cartilaginous proliferation, as in achondroplasia, is not supported by pathological findings.

Fractures.—The earlier the onset of fractures the greater the liability is the general rule. The prenatal cases dying at birth often have an extremely large number, as in Chaussier's case of one hundred and thirteen. Blanchard reported a woman of 27 years with forty-one fractures since 2 months of age. In the family cases the onset is usually after infancy and the number less, yet in Pritchard's family one individual had a fracture the second day of life, and in Willard's family at birth. One member of the Currie family had her first fracture at 4, and her most recent at 46 years. In some instances the liability to fracture decreases with age. Graham's patient had eighteen fractures between 1 ½ and 15 years, then at 30 years had had no more. Possibly the inheritance of only a mild tendency to fracture is dependent upon the fact that badly crippled individuals are not so likely to reproduce themselves.

The absence of pain at the time of fracture is often emphasised. The probable explanation of this is the diminished amount of trauma to the soft tissues.

Union is usually rapid. The amount of callus may be excessive, as in Matsuoka's case of postnatal onset. Many of the prenatal cases showed excessive callus in a ring-like arrangement, as emphasised by Cameron. On the other hand, Lewy's patient with fractures at birth showed no callus, and the line of fractures was barely visible in radiographs. In Cases I. and II. given above there is little callus. In my case, Winnie W., of the family of William W., eight months after the accident the line of fracture could not be detected in the radiograph.

The most frequent location of fractures in individuals surviving birth is in the lower extremities, and in the thighs more than in the legs. In still-born children the ribs often show many fractures. However, there is no universal site of election to fractures. Fractures of the vertebral column and of the pelvic and shoulder girdles have been described in addition to all long bones.
Dislocations.—The tendency to sprains and dislocations was described by Velpeau in 1847, and has been noted frequently since. Hypotonicity of the joint ligaments is mentioned in congenital as well as delayed types. An exceedingly thin fibrous periosteum was described by Axhausen and Dieterle. Muscle atrophy is frequent, but can be explained by disuse. The electrical reaction of degeneration was obtained by Larat, but this was contradicted by Miura, Bookman, and Zesas, who found the reaction that of inactivity atrophy.

Comparison with Osteomalacia.—In regard to the resemblance of some cases of idiopathic fragility of bones to Osteomalacia, Doering’s patient, male, 15 years of age, is of interest. He walked at 10 months and was healthy until 4 years of age, when he began to have fractures, twenty-two in all. The long bones were much bowed, though at the time of the report rigid and brittle. The pelvic ring was compressed, and acetabula were deep in the pelvis. To explain these facts Doering assumed that at some time there must have been present an abnormal softness of the bones. Similarly in Ewald’s patient with twenty-five fractures between 2 and 14 years there was an osteomalacial shape of pelvis. Enderlen’s case is classified as senile Osteomalacia by Looser and others. Rehn’s case is discussed by von Recklinghausen, who is uncertain whether to classify it as Osteomalacia or Osteogenesis Imperfecta. Axhausen thinks that early Osteomalacia is the groundwork of all Idiopathic Osteopsathyrosis. He describes three patients, the first an example of typical hereditary Osteopsathyrosis; the second a fairly typical case of Osteomalacia starting at puberty; and the third (summarised under pathology) seems undoubtedly Osteopsathyrosis, clinically and pathologically. In my cases of the Currie family I obtained no history of difficulty in childbirth, which one would expect in the osteomalacial type of pelvis. No gynaecological examinations were made.

Clinical Classification.—The classification of infants as Fuchs’, with defective cranial ossification yet no fractures, as instances of Osteogenesis Imperfecta seems to be generally accepted among modern writers. However, after infancy, if the abnormal shape of head, with possibly stunted growth, is the only means of identification we have, diagnosis is impossible. Similarly a case like the one Biggs reports, with twenty-two fractures without known etiology between 20 and 30 years of age, is difficult to classify. Lovett and Nichols say that it is not possible to diagnose a case
as Osteogenesis Imperfecta (they use this term to designate pre- and post-natal onset of fractures) if the first fracture occurred late. In the absence of pathological evidence it is not known how late the first fracture may occur. I agree with this opinion, with the exception of familial and hereditary cases. In these, fractures without violence starting late in one individual must be considered as the same type as those starting earlier in relatives.

Summary.—The classical type of the Osteogenesis Imperfecta of Vrolik is a stunted infant, still-born or dying soon after birth, and showing defective ossification of the skull, and many fractures of the ribs and long bones. If the infant lives, lines of pressure acting on the soft skull produce an abnormally-shaped head. Since a similar type of head is found in certain instances of post-natal onsets of fractures, so-called Idiopathic Fragilitas Ossium or Osteopsathyrosis; in these cases also it is reasonable to suppose that there has been imperfect prenatal osteogenesis. Ossification of the skull may be nearly normal, yet the extremities show many fractures, and the reverse is true. The length of the long bones may or may not be affected, but the earlier the onset of signs of osteogenetic defect, the greater the shortening is likely to be. Hypotonicity of joints with dislocations occur. The number of fractures is, generally speaking, parallel with the earliness of the onset.

Pathological Chemistry.

Few metabolic or chemical studies have been made. Verneuil in three patients and Blanchard and Rehn in their cases found phosphates increased in the urine.

Bookman, 1911, found relatively enormous losses in calcium and increased retention of sulphur, nitrogen, and phosphorus. These were the same results as McCrudden obtained in Osteomalacia, and the history, age, and rapid wasting, with death, make one doubt if this case were Fragilitas Ossium of the idiopathic type. Three years later, however, Bookman reported metabolic results of two six-day periods, on a 10-weeks-old infant with Osteogenesis Imperfecta. Taking the normal for that age from Orgler's work, he found calcium retention below normal in the first period and increased in the second, when calcium lactate had been added to the food.

Swartz and Bass, 1913, report nitrogen, phosphorus, and fat-retention normal, magnesium increased, and calcium slightly
decreased in an infant weighing 7 lbs. 8 ozs., which had many fractures at birth.

Bamberg and Huldschinsky in the same year recorded a variation in calcium metabolism from a loss of 0.019 grms. without treatment to a gain of 0.136 grms. under treatment with emulsion of cod-liver oil. However, as this child subsequently developed rickets, this cannot be taken as an example of benefit of treatment with emulsion in Osteogenesis Imperfecta.

Schabad, 1914, published the results of twelve periods of six days each of metabolic tests extending over 2½ years on a child 7 years of age at the beginning of the study. This child had had twelve fractures. At least one week of rest was allowed between the tests, and the food kept approximately the same throughout the experiments. His conclusion was that there was increased loss of calcium in Osteogenesis Imperfecta. The loss of phosphorus was parallel with that of calcium. The distribution of phosphorus was physiological: that is, urine phosphorus was greater than fecal phosphorus, while in active rickets the opposite condition is noted. He tried therapeusis with (1) Phosphorus with emulsion of cod-liver oil; (2) the same plus calcium acetate; (3) emulsion plus thyroid extract; (4) iodothyrin; (5) arsenic; (6) hypophyseal extract. Of these, phosphorus with cod-liver oil had the most beneficial effect on the retention of calcium. Hypophyseal extract showed a similar result, but the fact that a fracture occurred during its use did not speak in its favour clinically. Clinically, however, emulsion has had little effect on the condition. The use of thyroid extract actually decreased the retention of calcium. This result does not favour thyroid as a therapeutic agent.

**Microscopic Pathology.**

*Cases with Postnatal Onset of Fractures.*—Of the postnatal types of fragility of bone, the only careful histological examinations found in the literature were those of Looser, Doering, Axhausen (Case III.), and Hagenbach.* Axhausen preferred to class his case as juvenile Osteomalacia though the clinical history and radiographic appearance of the bones would indicate that it belonged to our group. He admitted that the microscopic findings tallied almost exactly with those of Looser’s case.

* One does not consider Enderlen’s case, a man of 61 years with six fractures of femora after he was 54 years of age, as belonging to this group. Hawards, in a brief report of examinations of bone removed from his case at osteotomy, found no microscopical changes.
Looser's patient was a 17-year old young man who had had forty-three fractures, forty of them in the legs, since 1½ years of age. A 6-year old brother was also a bone-breaker. An amputation was performed because of the deformity, and a histological examination made. In this instance the length of the bone was normal, but showed either a high degree of atrophy or a decreased growth in circumference. The epiphyseal cartilages were normal, as was also bone formation within them, though decreased in intensity. The bone marrow appeared unchanged, and only in places where there had been mechanical injury, as fractures and infractions, was it fibrous. No fatty changes were noted. His essential finding was an insufficient functioning of all bone-forming cells, both of periosteum and bone marrow. In normal conditions a limited number of osteoblasts produced enough bone; in this condition abundant osteoblasts laid down insufficient bone. Reabsorption by osteoclasts went on as usual. With the decrease in the formation of lamellar bone by osteoblasts there was associated a varying degree of direct calcination of cartilage cells, and their persistence, in contrast to their becoming shrivelled up and disappearing in front of the advancing osteogenetic tissue, as in normal ossification. The bone built thus by metaplasia lacked the strength of lamellar arrangement and was crumbling in character.

Doering's case, a 15-year old boy who had had twenty-two fractures between 4 and 15 years of age, resembled Looser's clinically and pathologically. Examination was made of bone removed at an osteotomy of the left tibia. He emphasised the abnormal shape and size of the osteoblasts. He, however, thought that there was an increased resorption of subperiosteal bone.

Axhausen examined an amputated leg from a boy of 16 years, so deformed he could not walk, who had had many fractures of the lower extremities. The bones were slender, cortex thin and soft. The microscopic findings agreed with Looser.

Hagenbach's case was a somewhat dwarfed woman who died at 45 years of age of hypophyseal tumour. The history is incomplete, but a hospital note made when she was 6 years old stated that she was not walking and was very rickety. She had had many fractures. The microscopic examination of the bones seems to place this case in the same category as Looser's.

Cases with Prenatal Onset of Fractures.—The pathology of the prenatal type of fragility has been much more minutely studied than the postnatal type. The fact that many of this class are
stillborn or die soon after birth furnishes the reason. The first microscopic examination was made by Professor E. Wagner on J. Schmidt's case. Other early examinations were by Bidder, Fisher, Stilling, Buday. More recent careful reports have been made by Scheib, Harbitz, Michel, Hildebrandt, Dieterle, Fuchs, Sumita, Niklas, and others.

Harbitz reported the histology of a 4 to 5 weeks' premature infant dying a few minutes after birth. The bones were short and thick, with many fractures. The head was a mosaic of small thin bones, many of which were broken. The proliferating zone at the epiphyseal-diaphyseal border in the long bones was normal in form, number, and arrangement of cells. The proliferating cartilaginous calcification zone was regular. The primary medullary canal was formed as usual. The great irregularity came in bone formation, both enchondral and periosteal. The bone plates or spicules were few in number, far apart, irregularly arranged, and often in islands without proper union. No lamellar system nor Haversian canals existed. Osteoblasts were present in usual numbers but were abnormal in appearance. Osteoclasts were not increased. Harbitz thought a certain amount of calcification took place directly in the capsules of cartilage cells, metaplasia instead of neoplasia.

Scheib's patient was a full-time infant born with rather short, bowed, and thickened extremities. The head was large, especially in the bitemporal diameter, and the photograph showed the ears bent out and down by supra-aural bossing. All fontanelles were open, but otherwise ossification of the skull was not defective macroscopically. At 2 months the weight was 3300 grms. Death was at 3 months from intercurrent infection. There was no history of fractures while under observation. At necropsy fractures of the long bones and ribs, with much callus, were found. Microscopically the preparatory ossification processes were normal, but the laying down of new bone by osteoblasts was deficient, and resorption of newly-formed bone increased. Bony trabeculae were slender or absent, and in contrast were found large spaces filled with osteoclasts. The marrow was gelatinous and fatty. Similar abnormalities were found in periosteal bone formation. The callus was more strongly formed, mostly of periosteal origin, but showing also metaplastic bone changes from cartilage.

In Lovett and Nichols' case there were fractures of both thighs and both legs at birth, also a healed fracture of right thigh, yet the bones of the skull were normally hard and sutures no wider than usual. The shape of the head was normal. The
legs were short in proportion to trunk. Ten fractures occurred up to the 5th month of life and none thereafter. Death took place at 10th month from acute diarrhoea. They emphasised the presence of normal preliminary bone-forming processes, a deficiency of osteoblasts, and abnormality in the structure of these. Cartilage cells persisted, their capsules did not rupture, and direct calcification took place. True bony trabeculae were deficient; lamellar structure and Haversian canals were lacking. Subperiosteal osteoblasts were in places abundant, but more spindle-shaped than normal. The marrow was myxomatous. Reabsorption by osteoclasts was not excessive.

Unfortunately no careful histological examinations of cases with fractures at birth which lived beyond infancy, as our patients Cases I. and II., have been made. The same is true of instances of defective skulls at birth but postnatal onset of fractures, as Nathan's Case II. This boy, aged 15 years, had had thirty-five fractures between 3 weeks and 15 years, and according to the history a very soft head at birth. His photograph showed the increased bitemporal diameter with ears turned outward and downward, which Cameron emphasised as characteristic of true Osteogenesis Imperfecta. Another instance where a microscopic examination might be instructive, is Ewald's—Case II.—a stunted child of 10 years with large skull, and ears bent out. She had an open fontanelle and palpable sutures until 6 years of age, and had had ten or eleven fractures since 7 months. I have not found any histological examination of a case in which heredity was a factor, though Looser's patient had a brother similarly affected.

In going through the literature the pathological point upon which there was agreement was the presence of an abnormal structure and functioning of the osteoblasts. A deficiency in number was recorded by Michel, John, Stilling, Scholz, Frangenheim, Porak and Duranti, Dieterle and Fuchs. Others, as Looser, Doering, and Harbitz, found the number not decreased, and Buday reported an increase, yet all agreed about functional disturbance. Rarely, as in Scheib's and Dieterle's cases, was there an increase in osteoclasts. Buday, Stilling, Looser, and the majority of others found them normal.

In regard to the marrow, opinion was most divergent. Michel S. Muller, Fuchs, Stilling, Hildebrandt and Frangenheim considered the amount increased, the marrow cavity large with thin shell of cortical bone. Scheib and Bidder found the marrow fatty; Nichols, myxomatous. Buday reported the marrow in places
fibrous, again gelatinous. Dieterle, Ziegler, Harbitz, and Sumita agreed that the original eruption of marrow capillaries into cartilage tissue was normal, but later the marrow became hyperæmic, poorly cellular (Dieterle found the cells abnormal but not decreased), and fibrous. In the neighbourhood of the marrow blood-supply, Buday, Hildebrandt, Michel, and Sumita found homogeneous masses of tissue, which seemed to be eliminated by giant cell resorption. Looser described similar tissue near cartilaginous callus formation in his adult case. Sumita studied the staining properties and discussed this tissue in detail, but was unable to explain its origin. Though frequently there have been reported obvious defects in the marrow, in support of the supposition that the marrow framework is not the underlying defect in causing bone fragility is the fact that in many cases the bones of the skull in which there is no marrow are especially involved.

Metaplasia, or the direct transformation of cartilaginous tissue into bone tissue, is described by Scholtz, Scheib, Harbitz, Dieterle, Sumita, and others. Scheib thought metaplastic ossification partly compensatory for the deficiency in osteoblasts. Dieterle was not certain that metaplasia was an essential lesion, since it was not unreasonable to suppose that such mechanical damage as fractures might upset osteogenetic processes and metaplasia result. This view was strengthened by one finding the most frequent mention of metaplasia in connection with callus formation; on the other hand, metaplasia is not reported in the formation of callus in normal individuals.

All writers agreed that the epiphyseal-diaphyseal border was normal, and most writers spoke of the cartilaginous basis of the long bones as normal. Buday and Fuchs found some narrowing of the cartilaginous proliferating zone.

Pathological Classification.—Looser identified his adult case of bone fragility by the similarity of pathological findings with Osteogenesis Imperfecta Congenita, using the term "Tarda" for the individuals with postnatal onset of fractures. His definition of the condition was a defective enchondral and periosteal bone formation, involving insufficient functioning of the osteoblasts both enchondral and periosteal, while the preliminary calcination of cartilage and the resorption of bone were normal. In contrast to this view, von Recklinghausen insisted that there were two separate conditions, and states the following as essential to the diagnosis of Osteogenesis Imperfecta:—

1. The presence of numerous fractures and infractions.
2. The intra-uterine onset and the continuance of the same into earliest childhood.

3. The existence of structural changes in the bones which would account for the spontaneous character of the fractures.

Thus he would classify as Osteogenesis Imperfecta an infant with fractures at birth, but an infant with fracture on the second day of life and frequently thereafter, as Pritchard's family case and Griffiths' isolated case, he would call Idiopathic Osteopsathyrosis. Such a division is obviously too empirical. I have quoted pathological notes on adults, a premature child dying soon after birth, a full-time infant dying at 3 months, and an infant dying at 10 months. The pathology of the infants with fractures before birth was similar to that of the adults, yet because of the absence of careful pathological reports on the border line cases one must admit that the last word has not been said in regard to the identification of the two groups.

Summary.—Idiopathic Fragilitas Ossium, whether of pre- or post-natal onset of symptoms, shows a deficient functional activity of the osteoblasts whether these have to do with subperiosteal or enchondral ossification. The preliminary ossification processes are normal. In regard to any primary abnormality in the marrow or in the function of the osteoclasts there is no general agreement. Metaplasia is frequent, but is probably compensatory, not primary in character.

Treatment.—There is at present no known rational treatment. Most of the infants and young children have been given emulsion of cod-liver oil and phosphorus. Clinically, as regards fractures there has been no beneficial result. Thyroid extract has been tried frequently. One questions the advisability of the constant application of splints to prevent fracture, because of the extreme atrophy of the bone and muscles which results. As noted above under Mr. Lees' Case II., Doris O. was taken from splints and gradually taught to stand, then walk by the use of a harness supporting her shoulders. She has been under treatment with both emulsion of cod-liver oil and thyroid extract. The use of the latter, according to Schabad, increases the loss of calcium from the body. A difficulty in gauging the effect of any therapeutic agent is the fact that the liability to fractures often decreases spontaneously.
Summary of the Main Facts of the Two Families.

1. In the first family, consisting of fifty-five individuals in four generations, twenty-one had grey-blue sclerotics.

2. Of these twenty-one, only one, a 6-year-old boy, who survived infancy, has had no fractures. The number of fractures in any individual is not excessive, and they require a certain amount of force for their production. Sprains and dislocations are also common. The majority of adults are in good general health, and are able to do ordinary work. The mortality among infants with blue sclerotics is in this family greater than among those not affected.

3. The heads of those individuals in this family who have blue sclerotics and bone fragility show an abnormal prominence of the frontal and occipital bones. In two of them there is a history of patency of the fontanelle throughout life.

4. Of eight adults with blue sclerotics and fractures, seven had varying degrees of deafness, the eighth died at 23 without deafness.

5. In the second family, consisting of eight individuals in three generations, seven have blue sclerotics, and four of these have had fractures, two others have a tendency to sprains. All are able to lead an ordinary life, except one child, who is somewhat crippled and incurs fractures too easily to be able to run and play.

6. In this family the head has the characteristic shape frequently seen in Osteogenesis Imperfecta congenita, namely, increase in the bitemporal diameter, so that the ears are turned outward and downward, slight downward tilting of the axis of the eyes, and an underhung lower jaw.

7. There is no tendency as in the first family to deafness, nor is there any to arterial sclerosis.

8. In both families the stature of the affected individuals is below the average, with the exception of three members of the first family.

Summary of Isolated Cases and General Discussion.

1. Cases I. and II. are fairly typical examples of Osteogenesis Imperfecta of prenatal onset. They both have had numerous fractures without violence since birth, and both show signs of imperfect ossification of the cranial bones. Case III. illustrates fragility of the bones of postnatal onset, but a shape of head which also suggests softness in earlier life of the cranial bones.
2. The terminology is varied. Probably Looser’s terms—Osteogenesis Imperfecta Congenita and Osteogenesis Imperfecta Tarda—are the most satisfactory.

3. The etiology is unknown. The hereditary factor is present in only a limited number of cases.

4. Clinically the condition is characterised by defective cranial ossification and by numerous fractures without violence. The earlier the onset the greater is the liability to fracture. Dislocations also occur. Blue sclerotics may or may not be associated.

5. A limited number of metabolic studies indicates an increased loss of calcium.

6. In both prenatal and postnatal onset of symptoms pathological findings indicate a deficient functional activity of the osteoblasts. In respect to other abnormalities writers disagree.

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CLINICAL RECORDS.

TWO CASES OF CONGENITAL SUPERIOR RADIO-ULNAR SYNOSTOSIS.

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Probably not such an uncommon condition as might be thought, but still of sufficient rarity to merit report, radio-ulnar synostosis takes its place among the congenital deformities. One of the best and concise, as it is one of the most lucid, expositions of the subject is a paper by Wilkie, in which he records three cases that had come under his own observation. Though existence of the condition has been known for more than a century it is natural that in recent years the application of radiography should have resulted in a considerable addition to the number of cases hitherto recorded.

In the two cases which have come under my notice there is a striking similarity in the defect occurring in otherwise vastly different subjects.

CASE I.—A. F. C., a lad of 19, recently consulted me on account of inability to supinate the forearms, a defect which had existed, he said, since birth. His father is well. His mother died at the age of 40 of Bright’s disease. Three brothers and two sisters are well, and, according to patient, present no abnormality. His facies has a some-