the dermatitis following the sanocrysin treatment a daily intravenous injection for three or four days of 5 c.cm. of this 10 per cent. solution will often give relief.

In the early days of the treatment serum was given before sanocrysin in order to ward off the complications. I have never found this of any value, and think its use has now been abandoned by most physicians.

RESULTS OF TREATMENT.

It must be remembered that in all my cases the patients were having rest in bed, with pneumothorax or some other form of treatment. It is not possible, therefore, to give statistics which would be of any value in coming to a conclusion as to the direct results of sanocrysin. Moreover, the treatment has not been employed for a sufficient length of time to enable one to judge anything beyond its immediate results. It is possible, however, to form some idea of these by noting what changes take place when sanocrysin is given while the rest of the treatment remains unchanged. Chart 3 shows a chronic fibro-caseous case with pyrexia.

On March 7th daily injections of ether benzyl-cinnamique were given for a fortnight, and after five days' interval a second course was given. It will be seen that the treatment had no apparent effect on the temperature; the condition of the patient and the quantity of sputum remained unchanged. On April 12th sanocrysin was started; the chart shows that in a few days the temperature began to settle. The sputum became less, and after a reaction on May 15th, following 1 gram of sanocrysin, it dried up altogether. It is useless to draw conclusions from one case, but in this patient the improvement followed so dramatically when sanocrysin was given that it is at least suggestive.

In 28 cases where patients had chronic fibro-caseous tuberculosis and were slowly losing ground in spite of hospital or sanatorium treatment I added sanocrysin to the treatment, and in 15 of these cases tubercle bacilli disappeared from the sputum in six weeks or less.

In this chronic type of pulmonary tuberculosis patients have periods of comparative good health alternating with others when the disease progresses; in other words, they have a series of relapses. Sanocrysin does not seem to prevent these relapses, but it does seem, in many cases, to check a relapse and bring about a period of arrest. Many of my patients relapsed, and in some the relapse was controlled by a second course of sanocrysin. I have not seen any benefit in chronic fibroid afebrile cases, but a course of sanocrysin may cut short an acute exacerbation arising in them.

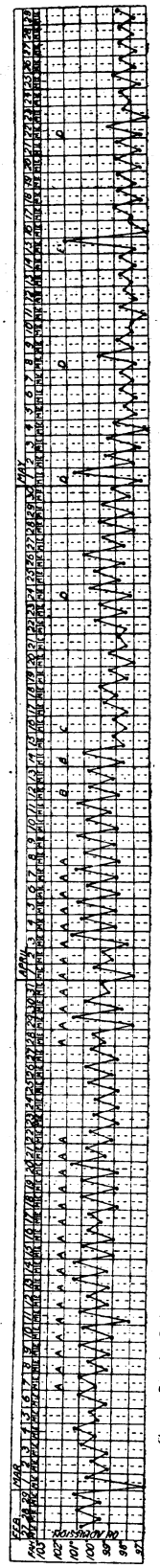

CHART 3.—A=Intramuscular injection E.B.C., 0.25 c.cm. B=Sanocrysin, 0.1 gram. C=Sanocrysin, 0.25 gram. D=Sanocrysin, 0.5 gram. E=Sanocrysin, 1 gram.

Cases of very active bilateral disease sometimes do very well if treated by pneumothorax and sanocrysin. I had 6 such cases in my first series, and 5 of them improved, 4 losing the tubercle bacilli. In acute conditions sanocrysin alone does not yield very striking results. Although sanocrysin is not a specific against tuberculosis, and is most certainly not a cure, it may be regarded as a useful addition to other methods of treatment.

DIABETES MELLITUS AND HEREDITY.

BY

P. J. CAMMIDGE, M.D.

THE possibility of heredity playing a part in the etiology of diabetes appears to have been originally suggested by Rondolet, a physician of Montpellier in the sixteenth century,[1] but nearly two hundred years elapsed before the idea was definitely formulated by Johann Peter Frank, who has also the distinction of having differentiated diabetes mellitus from diabetes insipidus. Most subsequent writers on diabetes mellitus accepted Frank's view, and many published statistics showing the proportion of their cases in which a family history of the disease had been traced: Frerichs, for example, stated that such a history had been met with in 9.8 per cent.; Seegen gave a higher figure, 14 per cent.; and Naunyn found a still higher proportion, 17 per cent.—to quote only a few. Writing on this subject, Naunyn[2] declared that the more carefully the family history was inquired into the more often was evidence of heredity discovered; and this would seem to be the experience of more recent authors, for, with the exception of John,[3] who found only 9.7 per cent. of his cases gave a family history of the disease, they have generally quoted figures in the neighbourhood of 25 per cent., while Hoogslag[4] has reported as high a proportion as 43 per cent. Statistics and general experience alike, therefore, agree in indicating that diabetes mellitus, or a condition predisposing to its development, tends to run in families and is hereditary; but as modern work on genetics has demonstrated that purely statistical methods and general impressions cannot be relied upon when an attempt is being made to establish the inheritability of a character, other evidence must be obtained before a reliable conclusion can be reached.

Our present exact knowledge of heredity in plants and animals has been gained almost exclusively by experimental selective breeding and analysis, but this method is obviously not applicable to man. The alternative usually adopted is to collect all the available data regarding the family histories of a number of individuals exhibiting the character under investigation, arrange them in the form of pedigrees, and compare the results with standard cases resulting from experimental work. In this way it has been found possible to demonstrate Mendelian inheritance in a number of deformities and diseases affecting man, such as brachydactyly, tylosis, night-blindness, haemophilia, etc. Most of these conditions are rare and present striking features by which they can be readily recognized, so that the collection of the necessary information is not difficult once a family suffering from the abnormality has been encountered; but with diabetes it is not so easy, for, in spite of the disease being comparatively common, it is unusual to meet with patients who are sufficiently acquainted with the intimate history of their family to make it possible to construct even a tolerably accurate pedigree of its incidence among their immediate relatives, and still less among distant connexions. On going through my records I find that 224 out of a consecutive series of 800 cases (28 per cent.) gave an ancestral or family history of diabetes. In the majority the known facts are too incomplete for any reliable deductions to be drawn, but some patients have given pedigrees resembling so closely in essential particulars those obtained in experimental breeding that it seems worth while taking representative examples and considering how far they support the view that diabetes mellitus, or a condition predisposing to its development, is transmitted as a Mendelian character.

Before doing so it will be helpful if I describe briefly the results of some of the breeding experiments with animals Mr. Howard and I commenced several years ago with the object of throwing fresh light on the still obscure etiology of diabetes. Working with mice[5] we found that if those having a naturally high fasting blood sugar (116–120 mg. per cent.) were mated together they always produced offspring with similar high blood sugars, but that when mice with high blood sugars were crossed with others

having normal blood sugars (about 85 mg. per cent.) all the progeny possessed normal blood sugars. These findings indicate that a high blood sugar is recessive to a normal blood sugar in the Mendelian sense. Confirmatory evidence was obtained by mating the progeny of these crossings with each other. It was then found that if the mice with high blood sugars were mated with the seeming normal mice they did not produce all normal animals, as might have been expected from the previous experiment, but equal numbers of normal and high blood sugar animals (Fig. 1, A), while when the animals with normal blood

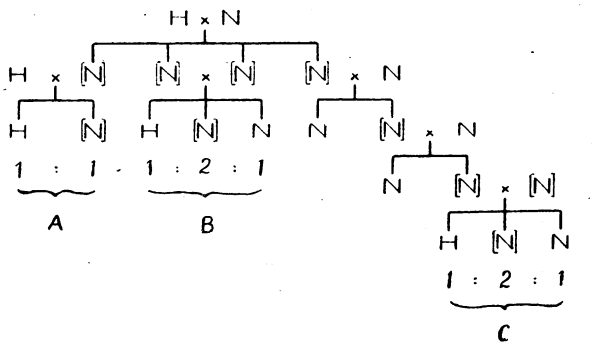

FIG. 1.—Experimental breeding of mice. H=High blood sugar. N=Normal blood sugar. [N]=Heterozygous normal (hybrid carrier).

sugars were crossed with each other the offspring proved to have high and normal blood sugars in the proportion of one to three (Fig. 1, B). Both these results are in agreement with Mendelian expectation in the particular circumstances of the experiments, and demonstrated that the mice with normal blood sugars resulting from the mating of the original mice having high blood sugars with normal mice were what is known as heterozygous normals or hybrid carriers. Animals of this description, although apparently normal, transmit the abnormality to their offspring, with consequences which vary according to the way they mate, as the experiments quoted show.

A third variation, which from a practical point of view is of extreme importance, must also be considered. It was found that if our hybrid carriers were mated with normal animals from another stock, all the progeny had normal blood sugars; these again, when crossed with normal partners, only produced normal offspring, and so on for several generations; when, however, two related animals resulting from such crossings were mated with each other, or with mice from another stock having a similar ancestral blood sugar history, mice with high blood sugars appeared among their progeny in the proportion of one to three (Fig. 1, C). By further selective breeding it was then proved that two out of the three apparent normals were in reality hybrid carriers, and that only one was actually normal and incapable of transmitting the abnormality to its descendants. It is consequently certain that in mice—and subsequent experiments have indicated in other animals also—a natural high fasting blood sugar is recessive to a normal blood sugar in the same way as albinism is recessive to colour. In addition to the fact that this is the first experimental proof of the transmission of a chemical abnormality in accordance with Mendel's theory, these results are of interest as demonstrating how such an abnormality can lie dormant in apparently normal animals, maybe for many generations, to appear again in their descendants under appropriate conditions of mating.

Since the abnormality of carbohydrate metabolism giving rise to a high fasting blood sugar in animals is undoubtedly a recessive character, it is not unlikely that similar defects in the chemistry of the body in human beings may be transmitted in the same way, and that some forms at least of hyperglycaemia and glycosuria, or the conditions predisposing to their development, may consequently run in families like a high fasting blood sugar in mice. The relationships in a pedigree indicating that such is the case are briefly as follows.

1. If both parents are affected all the offspring will be similarly affected.

2. If one parent is affected and the other is not, all the offspring will appear to be normal, but all will be hybrid carriers (heterozygous normals) and transmit the disability to their descendants.

3. If one parent is affected and the other is a hybrid carrier, half the children, on the average, will be affected and half will be hybrid carriers.

4. When two hybrid carriers mate, one-quarter of the offspring, on the average, will be affected and three-quarters will be apparent normals, although two out of the three will be hybrid carriers and only the third will be actually normal.

5. Since a hybrid carrier is merely a bearer of the affection and does not suffer from it, an affected individual need not have an affected parent, or even an affected grandparent or great-grandparent, although evidence of the presence of the affection in the family can usually be found among collaterals.

Owing to the single births, limited families, and monogamous habits of the human species, clear-cut evidence of heredity comparable in every respect with that furnished by the experimental breeding of animals cannot be expected, but careful investigation should reveal hereditary relationships in human pedigrees corresponding sufficiently closely in essential particulars to the experimental findings to make it evident that they are governed by the same principles if diabetes, or some forms of it, are transmitted as a recessive character.

Clinical methods for estimating the sugar content of the blood are of such recent origin that it is rarely possible to trace back hyperglycaemia for more than a generation, so that reliance has to be placed upon the occurrence of glycosuria and the symptoms of diabetes in working out human pedigrees. On comparing such pedigrees with our mouse results it is evident that there is a close correspondence in many instances, although, as we shall see later, not in all.

Take, for example, the case of a woman suffering from diabetes who stated that two of her brothers were similarly affected, but another brother and two sisters had been repeatedly examined for sugar with negative results (Fig. 2). In this family the affected and unaffected were equal in number, a condition arising in mice, as we have seen, when an affected individual mates with a hybrid carrier (Fig. 1, A). Further inquiry revealed that the woman's father was a diabetic, and, although her mother was normal, her mother's sister suffered from the disease, consequently the mother was almost certainly a hybrid carrier.

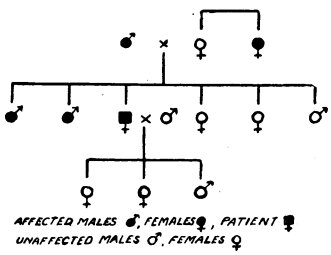

FIG. 2.*

That the disease, or a condition predisposing to it, behaved as a recessive character in this instance is also indicated from the fact that all the three children resulting from the marriage of the patient with a normal husband were found to be normal. Similar family histories are not very uncommon among diabetics, although it is unusual for the figures to correspond so exactly to Mendelian expectation.

The experimental breeding of mice with high blood sugars showed that, when two hybrid carriers were mated, affected and unaffected offspring appeared, on the average, in the proportion of one to three (Fig. 1, B).

This proportion was found in a family of which another patient (Fig. 3) was a member, his sister and two brothers all being normal. The patient's father, who was an only son, was apparently normal, as was also his paternal grandmother, but his paternal grandfather was a diabetic, consequently his father was probably a hybrid carrier. On the maternal side the mother herself, the grandmother, and the grandfather were all apparently normal, yet, as a sister of the mother had died of diabetes, there seems little doubt that the mother, as well as the father, of the patient was a hybrid carrier.

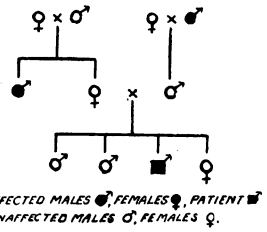

FIG. 3.

In both the preceding examples it was not necessary to go far back in the family history of the patient to discover

* The explanation of the signs used in this figure applies also to the later figures

evidence of the transmission of the disease as a Mendelian recessive character. An interesting pedigree showing how in human beings, as well as in animals, the affection may lie hidden for several generations in hybrid carriers (Fig. 1, C) was given to me by a biologist interested in genetics who brought his only child, a daughter, suffering from diabetes (Fig. 4). The father was free from sugar himself, and no case of diabetes or glycosuria had been known among his direct ancestors for at least two generations previously, but, as his father's brother and his grandfather's brother had both died of diabetes, it seemed certain that he, his father, and his grandfather were all hybrid carriers. The mother of the patient was free from sugar, but she had a sister undergoing treatment for diabetes, consequently it may be inferred that the mother was likewise a hybrid carrier. Since there were no other children of the marriage, it is not certain that the Mendelian expectation of one affected to three apparent normals would have been fulfilled, but it is probable that it would, as both parents were apparently hybrid carriers.

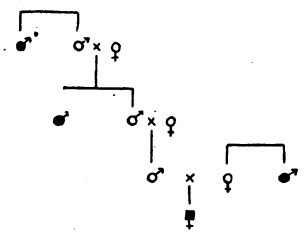

FIG. 4.

The following is one of the most remarkable cases I have met with, from the point of view of heredity.

The patient was a girl of 6, who died of diabetic coma after an illness lasting altogether under three weeks (Fig. 5). Two older sisters had died of the same disease, one when she was a year old and the other at the age of 18 months. The only surviving member of the family was a boy of 10, who had never shown any signs of diabetes and whose urine was found to be free from sugar, although it was said he passed traces of reducing material in his urine at intervals when suffering from "bilious attacks," to which he was liable. The urine of the father was found to be sugar-free, but, like his son, he was subject to "bilious attacks," and, as one of his brothers was stated to have died jaundiced, there was apparently a tendency to hepatic disturbances in the family, although no history of diabetes or glycosuria could be discovered. The patient's mother, a woman aged 40, was known to have been passing sugar for about twenty years. One of her sisters had died of diabetes mellitus and two of diabetes insipidus, one at the age of 16 and the other at 20. A brother appeared to be normal, and had two normal children by a normal wife. The maternal grandmother of the patient, who was alive at the age of 70, had suffered from glycosuria for over twenty years, but her husband was said to be normal. In the preceding generation there was no known history of glycosuria, and the great-great-grandmother of the patient was also said to have been normal, although her sister had died of diabetes. It would therefore seem that the disease was transmitted for at least two generations by hybrid carriers and then became manifest in the grandmother, probably owing to her mother having married a hybrid carrier like herself. Two of her daughters, including the mother of the patient, developed the disease, most likely as a consequence of her union with a hybrid carrier, and both showed it at an earlier age than their mother. In the next generation a rapidly fatal form of diabetes developed at a very early age in three out of four of the children, most probably as the result of the mating of a diabetic with a hybrid carrier.

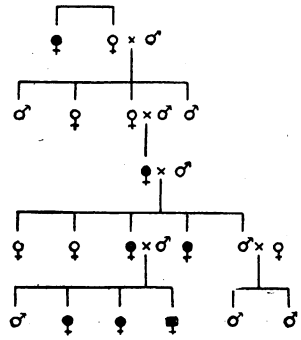

FIG. 5.

The weak point of this pedigree, as of so many others, is that the known history relates almost entirely to one side of the family and the other can only be inferred, but if the assumptions which have been made are admitted it would seem to be a fairly typical example of the transmission of diabetes mellitus as a recessive character. The earlier age of onset and increased severity of the disease with each succeeding generation is noteworthy, although the apparent tendency to hepatic disturbances on the father's side was possibly a contributory factor in the production of the final tragic results.

If the whole available pedigree of the case we have been considering is taken into account it suggests that the diabetic tendency was transmitted as a Mendelian recessive character, but if only the last three generations are considered it might well be that it behaved as a dominant, for with a dominant character (1) all the affected individuals have an affected parent; (2) in families where both affected and unaffected occur their numbers are, on the average, equal; (3) none of the unaffected, although springing from affected parents, have affected descendants. Apparent dominance of this description is not uncommonly encountered in work on human heredity, and may be a source of error if the pedigree is short; there are, however, many cases in which the characters of a true Mendelian dominant are so plainly present that there can be no doubt some forms of glycosuria are transmitted in this way.

Take, for example, two boys, one aged 6 and the other 7, who were brought to me suffering from glycosuria (Fig. 6). Their mother was normal, but their father had been passing sugar from the age of 27, and his brother from the age of 30. The mother of these two brothers, who was still alive aged 70, was said to have developed glycosuria when she was about 50. Now this woman had been married twice, on both occasions to apparently healthy husbands, and from one of these unions the family referred to had originated; by the other husband she had one son and two daughters, all of whom had developed glycosuria about the age of 30.

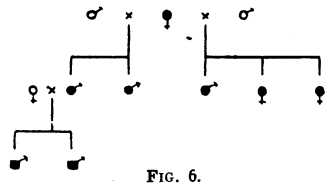

FIG. 6.

Since it is unlikely that both husbands were hybrid carriers, and as, moreover, all the descendants of both marriages suffered from glycosuria, it is evident the disease must have been transmitted as a dominant character in this instance.

I will quote another example of the same type of transmission.

A girl, aged 14, was brought to me suffering from nocturnal enuresis, and was found to be passing sugar in her urine (Fig. 7). Glycosuria had been discovered in her mother and a maternal aunt at the ages of 45 and 40 respectively, and her mother's brother was also said to be diabetic. The mother and the aunt had both married apparently normal husbands, but both had diabetic children—the patient in the one instance and a girl of 18 in the other. The maternal grandmother of these girls was alive and well at the age of 80, and when her urine was examined it was found to be free from sugar; her husband, however, had died of diabetes at the age of 72.

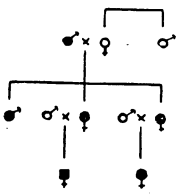

FIG. 7.

Other examples could be cited, but space forbids, and sufficient has been said to show that defects of carbohydrate metabolism giving rise to glycosuria may be transmitted either as a recessive character, like hyperglycaemia in mice, or as a dominant character, like brachydactylia or night-blindness in human beings. In my experience the former type occurs most commonly before the age of 40, while the latter is more frequently met with in elderly people; but as there is a tendency for both to develop earlier in successive generations, the age of the patient alone cannot be relied upon as an indication of the way the defect has been inherited. The dominant variety is almost invariably mild, and may persist for many years, even in young people, without causing serious symptoms or materially affecting the general health. The recessive form, on the other hand, is generally grave from the onset, is more difficult to control by diet, and is inclined to progress, corresponding, in fact, to the "true diabetes" of Naunyn[6] and others. The recessive type tends to be self-exterminative, whereas the dominant variety, owing to its generally later appearance and comparative mildness, interferes little, if at all, with reproduction and length of life. Dominance is consequently the prevailing form of inheritance found when a series of cases of glycosuria of all descriptions is examined, and, as direct transmission from parent to child is more obvious than inheritance through hybrid carriers, it bulks even more prominently in the results of researches on heredity carried out on purely statistical lines. This, no doubt, is the

explanation of the common belief that heredity is a favourable sign in diabetes, which, although true of the more common and obvious dominant variety, is not correct when the condition is inherited as a recessive character.

At present it is not clear whether the inherited factor is itself the determining cause of diabetes, or whether it merely predisposes to the development of the disease by subsequent illness or injury. The occurrence of severe cases without demonstrable cause in early youth and infancy is in favour of the former hypothesis, but the undoubted connexion of diabetes with infections and other recognized causes in some instances indicates that, in later life at least, an exciting agent is often necessary. It is possible that the diabetes of young people may arise from inherited defects of the recessive type, which prevent the development of the organism in a particular direction keeping pace with the increasing demands of the growing body, and, as the inherited factor probably differs in intensity, so the period of life at which the symptoms of diabetes appear also varies. In this way we can account for the severe form met with in infants, the tendency for the disease to develop about the age of puberty, when, as was pointed out by Priscilla White,[7] it is frequently related to excessive height, and the influence of infections, toxaemias, injury, pregnancy, etc., when growth has ceased. The mild and relatively innocuous form transmitted as a dominant character is an entirely different condition, and, as it is comparatively rarely met with before an age when the vigour of the body is naturally beginning to decline, it would seem to depend upon the development of an inherited tendency to abnormally early failure of some function concerned in carbohydrate metabolism, accelerated, as a rule, by acquired faults of assimilation and nutrition. The notoriously benign type of diabetes so common in certain races, particularly Hindus, Japanese, and Jews, is very likely of this variety, and probably depends upon an inherited dominant strain developed by a lifelong adherence to an improperly balanced diet.

Although there can be no doubt that heredity plays a part in the production of the defects of carbohydrate metabolism, giving rise to glycosuria and diabetes in many instances, there is not as yet sufficient evidence to justify the conclusion that an inherited factor is a necessary basis for their development in all cases. Should further research prove that such a basis exists, it would do much to simplify our ideas of the etiology of diabetic conditions by providing a common bond between the various forms, the differences in symptomatology, severity, and age incidence which occur being then accounted for by the character of the inherited factor and the nature of the exciting cause. Prognosis, too, would be more certain, for it would be largely determined by evidence pointing to the hereditary tendency being of the dominant or recessive type, while the fact that the glycosuria associated with the former is mild and easily controlled, whereas the recessive form is generally progressive and more severe, would be of assistance in formulating an appropriate line of treatment. Even in the present state of our knowledge inquiry into the family history of a patient suffering from glycosuria will often supply information which is useful in treatment, and, by the reassuring prognosis it may suggest, go far to dispel the fear of "diabetes" the discovery of sugar in the urine arouses in so many people.

The main value of the evidence regarding the occurrence of an hereditary factor in defects of carbohydrate metabolism is, however, its bearing on the question of marriage. The marriage of diabetics is clearly inadvisable, and intermarriage between families where there is even a remote history of the disease is to be discouraged; but as our advice on such matters, although often asked, is rarely taken, the children and grandchildren, even to the third and fourth generation, should be watched and guarded as far as possible from exciting causes likely to develop a latent and inherited defect.

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INJURIES OF THE EAR ARISING FROM FRACTURES OF THE SKULL.*

BY

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IN view of the increasing frequency of motor and street accidents, a discussion on fractures of the base of the skull from the aurist's point of view should be useful.

Patients suffering from this injury are usually sent for an aural examination some weeks after the accident, when deafness exists, or when the question of compensation arises. Inspection of the ears immediately after the accident would be more valuable and would enable the aurist to give a more accurate estimation of the damage. The additional information so obtained might be helpful in the treatment and prognosis.

The majority of the fractures of the base of the skull involve the middle fossa, and this proportion is to be expected when the base of the skull is viewed from below and it is seen that a line of weakness extends through both Glaserian fissures and the Eustachian tubes to the foramina lacera media, with the sphenoidal sinus as a connecting link. The two halves of the skull are more or less cemented together by the union of the basi-occipital and basi-sphenoid, and the fracture of the middle fossa usually follows this weak line wholly or in part. The thin roof of the canal of the tensor tympani and Eustachian tube, and that of the tympanum and mastoid antrum, lie in this line and are almost invariably involved in this fracture. The extent of the injury varies considerably with the violence and site of application of the blow received. Comminution of the thin bone of the tegmen sometimes happens, and spicules of bone are subsequently found in the auditory meatus. It is the middle ear which is practically always damaged in patients who survive, and the capsule of the internal ear or labyrinth is rarely fractured. Only a few fatal cases of great violence show fractures of the internal ear, and J. S. Fraser,[1] in 1916, recorded, with microscopical sections, four instances in which the fractures involved the labyrinth capsule in two and the middle ear only in the remaining two. The two middle-ear cases survived for a variable period and then died of meningitis, but the labyrinth cases were quickly fatal.

The external auditory meatus is often involved in the fracture when the line is through the Glaserian fissure, and the fracture appears to split the meatus longitudinally, dividing it into an upper and a lower half, or, more commonly, a crack in the roof of the meatus is caused. In exceptional cases, where great force has occurred, the fracture has extended across the upper or anterior surface of the petrous bone into the internal auditory meatus. A smashing blow on the mastoid process has been known to fracture off the mastoid from the wedge of the petrous bone with injury to the lateral sinus. Fractures of the posterior fossa commence in the thin bone of the cerebellar fossa, and radiate into the lateral sinus groove of the same side; they then pass, either along the groove for the inferior petrosal sinus, or across the petrous pyramid near the inner edge of the lateral sinus, through the cancellous bone surrounding the mastoid antrum and semicircular canals, and behind and external to the internal auditory meatus. The various lines of fractures of the base of the skull can be seen in the museums of the Royal College of Surgeons and the medical schools; the tendency is for the fractures to take those lines indicated previously.

A moderate blow on the temporal fossa may produce a radiating fracture which cracks the roof of the middle ear, and blood effuses into the tympanum without rupture of the drum. No blood escapes into the auditory meatus, but the typical bluish drum can be seen on examination. Four such cases have been observed, and the only indication was deafness. This lesion would not have been detected without an aural examination, and, moreover,

* Read in the Section of Laryngology and Otology at the Annual Meeting of the British Medical Association, Cardiff, 1928.