in the arteriovenous glucose difference (Moorhouse and Kark, 1956; Purnell *et al.*, 1956).

In a previous study we were unable to demonstrate by the rat-diaphragm technique any increase in the insulin-like activity of the serum in diabetic patients on tolbutamide treatment (Weaver *et al.*, 1958). However, should the hypoglycaemic properties of sulphonylureas be due entirely to a depression of hepatic glycogenolysis, such an effect is probably manifest only if it is associated with some peripheral utilization of glucose, and hence the dependence on insulin.

The finding that males are less likely to respond than females might be expected from the results of Wrenshall and Hamilton (1957) on the levels of insulin extractable at post-mortem examination from the pancreas of diabetic subjects. Their study showed that, at an equivalent age and duration of diabetes, males had a lower content of pancreatic insulin. The greater incidence of failure in patients over 80 years may be related to the observation of Joslin *et al.* (1952) that diabetes at this age resembles more the juvenile than the average adult onset type. Changes in weight in relation to the degree of diabetic control (as judged by the blood-sugar levels) have been relatively unimportant during the period of study, except that some control of the diet is necessary to prevent these patients gaining weight rapidly. Neither the duration of previous diabetes nor the duration of previous insulin treatment seemed to be of any importance in determining the type of response in the female. The duration of previous diabetes may be of some importance in the male.

As regards the severity of the diabetes, the findings of Dunlop (1957) that a patient with a fasting blood sugar greater than 300 mg./100 ml. is unlikely to respond seems to be an important differential criteria. The presence of ketones in the urine even in "trace" quantities, lessened (or almost excluded) the chance of a successful response. An acute test for selecting responsive patients is of limited value only. The previous dose of insulin seems to be important, and the chance of failure increases greatly when the total daily dose is more than 30 units. On the other hand, the duration of insulin treatment does not seem to influence the result. In patients already on insulin treatment the best criteria for the selection of suitable cases for the trial of oral treatment are a history of an original mild onset of the diabetes, original fasting blood-glucose values less than 300 mg./100 ml., and absence of ketones from the urine. The patient's progress on treatment with insulin should have been relatively uncomplicated, particularly in regard to an absence of sudden fluctuations in the degree of diabetic control. During prolonged treatment the difficulties encountered are few, toxic effects are slight, and secondary failure is rare. During acute infections, the patient should be watched carefully for signs of ketosis.

The most significant observation in this study is that prolonged treatment with tolbutamide does not appear to lead to a deterioration in the diabetes. The intravenous glucose-tolerance tests performed at the onset and after prolonged treatment indicate that this drug has not adversely affected the disposal rate of sugar in these patients. The possibility of eventual " β -cell exhaustion" has been mentioned in earlier reports, but these results on the assimilation rate of intravenously administered glucose appear to exclude this, at least in terms of treatment for up to one year.

Summary

The results of oral therapy with tolbutamide in 291 diabetic patients treated for periods up to 2½ years have been studied.

The findings with regard to the type of patient suitable for this treatment are largely in agreement with the previous studies of other workers.

A difference not previously reported in responsiveness of males and females was noted.

Studies on the assimilation of glucose administered intravenously indicated that the ability to utilize carbohydrate had not been adversely influenced by prolonged tolbutamide treatment.

We thank Dr. J. A. Smyth, who was physician in charge of the metabolic unit during the period of this study.

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XANTHINURIA

BY

C. J. DICKINSON, B.M., B.Sc., M.R.C.P.

Medical Registrar, Medical Unit, Middlesex Hospital

AND

JEAN M. SMELLIE, B.M., M.R.C.P., D.C.H.

First Assistant, Paediatric Unit, University College Hospital

In 1954 Dent and Philpot published an account of a patient with "xanthinuria." The only symptoms were urinary, and proved to be due to xanthine stones in the urinary tract. Chromatography of the urine showed a constant biochemical abnormality, in that xanthine and not uric acid was the predominant purine present, no other purines being found in detectable amounts. No purines at all could be demonstrated in the plasma by the chromatographic methods used, but these were not sensitive enough to detect concentrations of less than 1 mg./100 ml. Chemical analysis by the non-specific method of Folin and Trimble (1924) seemed to show that small amounts of uric acid were present both in plasma and in urine.

Dent and Philpot proposed two possible explanations for their results. The enzyme xanthine oxidase normally catalyses the oxidation of xanthine to uric acid; and this enzyme could have been absent or defective. Alternatively, the disorder could be explained by a very high selective renal excretion of xanthine—

so rapid that most of the circulating xanthine would be removed before it could be converted into uric acid. They were unable to narrow this down further in the absence of quantitative data from their patient's plasma.

Twenty-three case reports of xanthine stones had appeared in the literature at the time of Dent and Philpot's investigation, and three have been published since (Ichikawa, 1954; Jordan, 1955; Boissonat, 1957). None of these has thrown further light on the cause of the condition. Since new highly specific enzymatic methods for estimating xanthine and uric acid are now available, we have applied them to a further study of Dent and Philpot's original patient. The results suggest that there is a specific defect in xanthine oxidase, and at the same time a specific defect in the renal handling of xanthine.

We have included in this report a fuller clinical description of the patient, including her progress from 1954 to the present date (December, 1958).

Case Report : First Investigation

A schoolgirl, born January 9, 1949, was the first child of healthy unrelated parents. Her birth weight was 4.0 kg. (8 lb. 15 oz.). She was breast-fed for three months, and mixed feeding was introduced at four months. Progress and development were normal until 14 months, when she got measles. After this she developed increasing frequency of micturition; and, though forward in speech and walking, did not attain reliable day control of micturition until 2½ years, becoming dry at night at 3 years. Between the age of 24 and 27 months she several times passed dark urine, which on routine testing on two occasions contained no protein or red cells, and in which the deposit was presumed to be urates. Thereafter she remained well until 4½ years.

In July, 1953, at the age of 4½, she was admitted to University College Hospital, under the care of Dr. B. E. Schlesinger, for investigation of two weeks' dysuria and of frank haematuria for one day. Examination showed an intelligent girl of average weight and height. Her blood pressure was 135/80, but no other clinical abnormality was found.

Investigations included routine examination of urine, which contained a trace of protein, very numerous red cells, and occasional pus cells. It was sterile on culture. Blood urea was 18 mg./100 ml., haemoglobin 14.6 g./100 ml., and erythrocyte sedimentation rate 7 mm. in one hour (Wintrobe). Intravenous pyelogram (I.V.P.) showed poorer dye concentration and a mild degree of clubbing of calices in the left kidney, with slight reduction in left renal substance (Fig. 1). The left ureter was not seen. The appearances were suggestive of chronic left pyelonephritis. The possibility of obstruction by a radiotranslucent stone of metabolic origin was suggested by Mr. D. R. Davies, but chromatography of the urine excluded cystinuria (C. E. Dent).

After some 20 days of intermittent macroscopic haematuria and some abdominal pain she passed a smooth oval stone, recovered on routine sieving of the urine. After passage of the stone no further haematuria occurred, routine examination of the urine was normal, and a further I.V.P. showed no significant change. Left retrograde pyelography confirmed the mild degree of generalized clubbing of the calices and reduction in the width of the renal cortex.

The stone was smooth, pale brown, and approximately 1.5 by 1 by 0.5 cm. in size, and weighed 0.9 g. On burning, it left negligible ash, and, while the murexide test failed to give the colour reactions of pure xanthine, analysis by chromatography showed the stone to be almost entirely composed of xanthine. (Further details are given by Dent and Philpot.) Radiological density of the stone was shown to be less than that of cystine; indeed, when immersed in water or when placed on the patient's abdomen it was completely invisible on the x-ray films.

Subsequent chromatography of the urine showed xanthine to be the main purine excreted, no uric acid being detected. There were only traces, if any, of other purines. From a large bulk of urine xanthine was isolated, purified, and identified by classical chemical methods. There was no amino-aciduria or glycosuria.

As there was no further haematuria or abdominal pain, and as the frequency of micturition had subsided, the child was discharged and recommended to drink plenty of fluid. No other treatment was advised.

Follow-up.—Since her discharge from hospital in 1953 there has been no recurrence of symptoms. Growth and development have been normal, and intelligence is assessed at a high average (110–120, Stanford-Binet). Blood-pressure readings have varied between 120/65 and 140/80. The urine

FIG. 1.—I.V.P., 1953; taken before passage of a xanthine stone. Appearance of left kidney suggests chronic pyelonephritis.

FIG. 2.—I.V.P., 1958, showing clubbing of calices of left kidney, with increase in size of right kidney.

has persistently contained large amounts of xanthine, but no uric acid; but it has shown no other abnormality on routine testing. Repeated I.V.P.s (two yearly) have shown increasing size of the right kidney and persistent clubbing of calices in the left kidney, which is now much smaller than the right (Fig. 2).

Family Tree.—The family tree was provided by Dent and Philpot. All members of the family, including one sibling, excrete uric acid, not xanthine. The parents were not related.

Present Investigation

The patient (now aged 9) reattended in February, 1958, for the present investigation. Clinical examination showed nothing abnormal; blood pressure was 120/75. The body proportions showed a slight decrease of upper/lower segment ratio. Her weight was 31.6 kg. (5 st.) (50–75 percentile), height 145 cm. (4 ft. 9 in.) (90–97 percentile), and armspan 140 cm. (4 ft. 7 in.).

Methods

The patient was asked to take a low-purine diet (milk, eggs, cheese, bread-and-butter) for 36 hours before admission. No food was given for 14 hours before the clearance period, but a high urinary flow was maintained by regular drinks of water. 652 ml. of urine was passed between 8.14 a.m. and 11.23 a.m. (approximately 3.5 ml./min.), during which time the bladder was emptied in the normal manner four times. Blood samples were taken into heparinized syringes, and the plasma was separated within 10 minutes. This is essential, to avoid the rise in hypoxanthine and xanthine concentrations which occurs soon after blood is withdrawn (Jørgensen, 1957). Plasma and urine were stored at -15°C . and analysed three days later for oxypurines. No detectable loss occurs in storage under these conditions.

Uric acid was estimated by the method of Praetorius and Poulsen (1953). After the initial optical extinction of the solution has been measured at 292 m μ , uricase is added and further readings are taken at short intervals of time. These readings lie on a straight line, which can be projected back to zero time to give the true initial optical extinction of the solution. When no further change occurs, a second reading is taken of the final extinction. The difference between the readings is proportional to the concentration of uric acid originally present. Readings were taken with a Unicam SP 500 ultra-violet spectrophotometer. Plasma proteins need not be precipitated, using this method, and errors due to the precipitation of albumin-bound uric acid are thereby avoided (Morris, 1958). Xanthine and hypoxanthine were estimated together by the method of Jørgensen and Poulsen (1955). Specificity in this method is obtained by converting these purines into uric acid by means of xanthine oxidase, and then estimating the uric acid so formed with uricase, as described above. The original uric acid is first removed by prior treatment with uricase, which is then itself inactivated with strong alkali. Purified uricase "Leo" was used; xanthine oxidase was a gift from the Chester Beatty Institute of Cancer Research. The accuracy of this method of analysis at normal low plasma concentrations (1–3 $\mu\text{g./ml.}$) is not much greater than $\pm 10\%$, because of the large number of steps involved. At the higher concentrations found in this patient repeated estimations agreed to within $\pm 6\%$ of the mean.

Estimation of proportions of xanthine and hypoxanthine present in plasma was made by an extension of the technique described by Bergmann *et al.* (1958). The purines are prepared as mercury complexes in a strongly acid solution. Mercury is removed with hydrogen sulphide, and the basic purines are adsorbed on a resin column and eluted with ammonia. The eluate is chromatographed in one dimension in 95% ethanol–water–acetic acid (85:10:5). Spots are identified, with standard solutions for comparison, under an ultra-violet lamp giving a short wave-length. The spots are cut out and eluted with a glycyl-glycine buffer at pH 8.2, containing xanthine oxidase. After incubation at 37°C ., the uric acid formed is titrated with uricase (at pH 9.3) as already described. Recovery of purines was incomplete (about 85%); but the method has the advantage that quantities of hypoxanthine and xanthine less than 1 $\mu\text{g.}$ can be detected and identified with certainty. Urinary purines were separated similarly, using direct chromatography with 100 $\mu\text{l.}$ of undiluted urine. De-salting helped to clarify the spots on the paper, but had no influence on the R_f values of xanthine and hypoxanthine in this urine.

Plasma and urine creatinine concentrations were measured as total chromogen (Bonsnes and Taussky, 1945), and plasma and urine urea by the method of Peters and Van Slyke (1932).

Results

The results obtained in the clearance period are shown in the accompanying Table. We have also indicated, where appropriate, the approximate normal range of values obtained by the methods used under similar (clearance) conditions. It is obvious that two abnormalities are present.

Results Obtained in 3-Hour Renal Clearance (Fasting)

	Urea	Creatinine	Xanthine + Hypoxanthine (Expressed as Xanthine)	Uric Acid
Plasma concentrations, in mg./100 ml.	24	0.75	0.74 (0.1–0.3)	<0.2 (3.0–5.0)
Urine concentrations, in mg./100 ml.	350	16.6	13.3 (0.2–1.0)	<0.1 (5.0–20)
Renal clearances, in ml./min. (uncorrected)	50	76	62	—
Renal clearances, in ml./min. (corrected to 1.73 sq.m. body surface area)	76 (normal)	114 (normal)	94 (≈ 20)	— (≈ 12)
Renal clearances as percentages of creatinine clearance	67%	—	82% ($\approx 15\%$)	— ($\approx 10\%$)

The approximate normal range is indicated, where appropriate, in italics in brackets. These figures represent the expected normal values which would be obtained in a normal subject, under fasting conditions, on a low-purine diet, and with a fast rate of urine flow.

1. *Absence of Uric Acid, and Excess of Xanthine, in Plasma and Urine.*—No uric acid was detected in plasma (diluted 1/5) and none in urine (diluted 1/10). These results were not explicable by the presence of a uricase inhibitor, since uric acid added to plasma and urine was fully recoverable. The concentration of xanthine + hypoxanthine in plasma was moderately increased in the plasma and grossly increased in the urine.

2. *High Renal Clearance of Xanthine.*—The renal clearance of xanthine + hypoxanthine (estimated together) was 82% of the creatinine clearance instead of the normal 10–20%. Ultrafiltration of plasma did not reveal more than minimal protein binding of xanthine and hypoxanthine; but this might suffice to make the clearance of these substances a little greater—that is, virtually the same as the creatinine clearance.

We at first assumed that our methods were measuring mainly xanthine, since Dent and Philpot (1954) had never detected any purine other than xanthine in the urine. To confirm this, we extended the study and performed differential chromatography (as described) on the original specimens, which had been preserved for four months at -15°C . We were surprised to discover that hypoxanthine was present in these specimens in relatively high concentrations. The hypoxanthine/xanthine ratio of the urine was approximately 1:2 and that of the plasma approximately 2:3. Further fresh specimens were therefore obtained from the patient while on a normal and on a low-purine diet. These also revealed hypoxanthine, but in considerably smaller quantities (hypoxanthine/xanthine ratios 1:5 to 1:10).

Professor C. E. Dent kindly carried out chromatograms on some of these urine specimens, using the technique he employed in his previous study (Dent and Philpot, 1954). He made the unexpected discovery of small amounts of uric acid in a concentrated urine specimen passed while the patient was taking a normal diet. We confirmed this, using the specific uricase method. Professor Dent has also found that, if stood in an ordinary refrigerator for only a few days, some of the xanthine originally present in this patient's urine is gradually converted into uric acid and hypoxanthine. The uric acid in fresh specimens is found only when the patient is on a normal purine-containing diet, and is therefore presumably of dietary origin. However, even in fresh specimens taken while the patient was on a low-purine diet we find that hypoxanthine is consistently present in concentration about one-tenth that of xanthine. This would be quite compatible with the formation of a pure xanthine stone, because xanthine is less soluble in urine than hypoxanthine.

Discussion

There is a continuous turnover of nucleic acid in the body, contributed mainly by the cells of the blood. The purine compounds adenosine and guanosine are

liberated from nucleotides by the action of phosphatases. Guanosine is then converted to guanine by the action of nucleoside phosphorylase, and guanine is de-aminated by guanase to form xanthine. Little adenine is formed from adenosine, since nucleoside phosphorylase preferentially attacks inosine and guanosine (Wyngaarden *et al.*, 1958). Instead, adenosine is probably first de-aminated to inosine, and the inosine then split to liberate hypoxanthine. Adenase is absent from human tissues (Schmidt, 1955). Finally (in primates) the enzyme xanthine oxidase converts both hypoxanthine and xanthine to uric acid, most of which is excreted in the urine:

It is clear that lack of xanthine oxidase should produce accumulation of hypoxanthine as well as of xanthine, unless there is some other enzyme which will oxidase hypoxanthine. No such enzyme has ever been found in man, though Fellig and Wiley (1958) have recently reported a hypoxanthine dehydrogenase system in chicken liver which is probably different from xanthine oxidase. Attempts have been made to produce xanthine oxidase deficiency in mammals, but so far have failed to influence the pattern of purine excretion (Higgins *et al.*, 1956), possibly because very small amounts of xanthine oxidase will catalyse the transformation of very large amounts of substrate (Bergel *et al.*, 1957). However, Higgins and his co-workers were successful in producing xanthine oxidase deficiency in chicks by a low-molybdenum diet and tungstate administration. This procedure prevents incorporation of molybdenum into xanthine oxidase; and, since molybdenum is essential for normal enzyme activity (Westerfeld *et al.*, 1956), a substantial proportion of the uric acid normally excreted by the chicks was replaced by a mixture of xanthine and hypoxanthine in approximately equal amounts.

It seems certain that our patient can have little or no xanthine oxidase in her body, for Dent and Philpot (1954) showed that this patient's excretion of xanthine was of the same order of magnitude as that of uric acid in a normal subject. Since mammals can be rendered grossly deficient in xanthine oxidase without producing any change in the pattern of purine excretion, we think it unlikely that the very small quantities of uric acid found in some concentrated specimens of our patient's urine can be derived from endogenous oxidation of xanthine. We believe that this uric acid is probably of dietary origin.

It is remarkable that the predominant urinary purine is xanthine, since theory might predict nearly equal accumulation of xanthine and hypoxanthine. Two explanations at least are possible. First, the adenine nucleotides may be degraded in part by prior conversion to guanine compounds, and enzyme systems are known which will perform these conversions (Bergel *et al.*, 1957). In this case, therefore, the relative proportions of xanthine and hypoxanthine accumulating might fluctuate widely according to the relative amounts of purine derivatives degraded via inosine and via

guanosine. Second, it is possible that the enzyme deficiency in this case is a selective one, and affects only the reaction $\text{xanthine} \rightarrow \text{uric acid}$. A theoretical basis for this is provided by Bergmann and Dikstein (1956), who showed that the attachment of xanthine oxidase to its substrates xanthine and hypoxanthine was different. Therefore a slight imperfection in the protein moiety of the enzyme might prevent one action while leaving the other intact. It is interesting that lethal x-irradiation of dogs produces a great rise in urinary xanthine excretion, with little change in hypoxanthine excretion (Jackson and Entenman, 1957). If this rise is caused by a relative xanthine oxidase deficiency it may be equivalent to the metabolic defect in xanthinuria. We are not able at present to determine the exact status of the reaction $\text{hypoxanthine} \rightleftharpoons \text{xanthine}$, in our patient.

The normal human kidney handles xanthine and hypoxanthine in a way similar to uric acid. Four-fifths or more of the substances present in the glomerular filtrate are reabsorbed by the tubules, presumably by "active transport" processes. These processes can be blocked by drugs, and tubular reabsorption of all these purines can be blocked in man by organic mercurials, which are "xanthinuric" as well as "uricosuric" agents (Dickinson, unpublished observations). It seems reasonably certain that in our patient there is a complete failure of renal tubular reabsorption of xanthine, and probably also of hypoxanthine. This accounts for the fact that the total oxypurine concentration of the plasma was so low—far lower than the plasma concentration of uric acid in a normal subject.

Biochemical Defect in Xanthinuria

We suggest that the most reasonable explanation for the coexistence of two hitherto unknown biochemical defects in a single individual is that both defects reflect an inborn genetic error in the synthesis of a specific protein molecule. This molecule may form part of the enzyme xanthine oxidase, and may also be part of the "permease" or "active transport" mechanism located in the renal tubules, which in normal persons is responsible for reabsorbing xanthine from the tubular lumen. (Xanthine oxidase itself in active form has not so far been demonstrated in the kidney of man: Praetorius and Kirk, 1950.)

This patient seems to be the first likely example of a combined renal and general metabolic defect of the type predicted by Harris (1956), although without further studies of enzyme activity and analysis of trace metals we cannot exclude the possibility of a combined defect analogous to that in Wilson's disease, in which deposition of copper probably explains both the general and the renal tubule disorders.

We can offer no convincing explanation for the case described by Israel (1901) of the simultaneous occurrence of xanthine stones and uric acid crystals in the same patient. No recent examples of this combination have been reported. Pearlman (1950) has described a case of xanthine calculus in which the blood uric acid was quoted as 4.2 mg./100 ml. The method used was not stated, and it is possible that xanthine was in fact being measured.

If other patients with xanthine stones suffer from a biochemical defect similar to that in our patient, the defect could be identified simply by estimating plasma or urinary uric acid by the specific uricase method,

which is cheap, simple, and accurate. Urinary purine chromatography will confirm the diagnosis, and spectrographic analysis of the stone is also conclusive. It is interesting that Professor Pierre Cartier has discovered by spectrography two examples of xanthine stones amongst an old collection of renal stones (Boissonat, 1957). This emphasizes that xanthine stones can be mistaken for uric acid unless specific analytical methods are used. There is no doubt that many xanthine calculi must be overlooked, though we would certainly not claim that the condition is a common one. It is surprising to find that the metabolic defect in our patient has produced predominantly unilateral renal disease.

Summary

A clinical description is given, with a four-year follow-up, of the patient with xanthinuria described by Dent and Philpot in 1954. No change in metabolism has occurred; but the patient has been studied again, new specific enzymatic methods being used to determine uric acid, xanthine, and hypoxanthine.

Traces of uric acid were found only when the patient was taking a normal purine-containing diet. Xanthine was the predominant oxypurine present both in plasma and in urine. The renal clearance of xanthine was very high, probably indicating complete failure of normal tubular reabsorption. Hypoxanthine was also present, but its concentration was variable and low.

A single biochemical lesion could account for this disorder. We suggest that in this condition there is a minor, inborn, genetically determined abnormality in the protein moiety of the enzyme xanthine oxidase; and we believe that this same protein also plays a part in the renal tubular reabsorption of xanthine.

We wish to thank Professor C. E. Dent and Professor A. Kekwick for helpful criticism and advice, and Dr. B. E. Schlesinger for permission to study this patient. We are also most grateful to Dr. F. V. Flynn for estimations of urea and creatinine, and to Dr. Ivor Smith for advice about chromatographic techniques. One of us (C. J. D.) wishes to thank the Middlesex Hospital Clinical Research Committee for laboratory facilities; and Professor A. Haddow and Dr. R. C. Bray for the generous gift of xanthine oxidase. We are most grateful to the patient and her mother for their co-operation.

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THE CASE FOR CONSERVATISM IN MANAGEMENT OF FOETAL DISTRESS

BY

NORMAN WALKER, M.B., Ch.B., D.Obst.R.C.O.G.

Registrar, Department of Gynaecology and Obstetrics,
University of Natal, Durban

The diagnosis of foetal distress during the course of labour is based primarily upon the recognition of two signs—the presence of meconium in the liquor amnii and alterations in the foetal heart sounds.

Reference to five standard textbooks of obstetrics show general agreement that meconium-staining of the liquor means that the foetus is or has been distressed. Likewise, all agree that foetal bradycardia means distress, but there is some difference of opinion on the exact point beyond which slowing of the heart rate becomes pathological.

Munro Kerr (Chassar Moir, 1956) regards a steady slowing of the heart rate to below 110 beats a minute as certain evidence of foetal distress, and irregularity superimposed on slowing as indicative of impending foetal death: Gibberd (1947) accepts a heart rate of below 110 a minute as meaning foetal distress: Eden and Holland (Brews, 1953) accept 100 a minute as the critical level and regard progressive slowing as an indication for immediate delivery; Claye (1955) states that a drop in heart rate of 25 beats a minute is of serious significance. Greenhill (1951) declares 100 beats a minute to be the critical point, but stresses that on occasion the child may be born alive and well despite persistent intra-partum bradycardia.

Eden and Holland stand alone in regarding foetal tachycardia as a sign of distress, and set the upper limit of normality at 160 beats a minute.

All these authorities agree that the foetus is in grave danger if the heart rate is persistently slow, if it is both slow and irregular, or if bradycardia accompanies the passage of thick meconium in the liquor amnii. All but one agree that such severe foetal distress indicates a need to rescue the foetus immediately either by forceps delivery or by caesarean section, according to the conditions obtaining. Gibberd strikes the more cautious note and states: "It is not often that foetal distress of itself is a good indication for caesarean section, but it may sometimes be possible to save the baby, for instance when the cord is prolapsed, if operation is undertaken without delay." This conservative attitude serves as a reminder that caesarean section is not without risk to the mother, for, as shown in the Report on Confidential Enquiries into Maternal Deaths in England and Wales (Ministry of Health, 1957), the operation carries a mortality rate which is seven times greater than that of vaginal delivery. This risk can be justified only if it is reasonably certain that a foetus showing one or more of these signs of distress is in fact in such danger that it will inevitably succumb.