Increased excretion of urinary total 17-OHCS is not always the result of increased hydrocortisone secretion by the adrenal cortex. Steroids with a 17.20 diol, or 21-deoxyketol type of side chain, give rise to 17-ketosteroids in this procedure (Appleby and Norymberski, 1955). Normally they are present in only small amount, but in adrenal cortical carcinoma and congenital adrenal hyperplasia they may be greatly increased. The high urinary total 17-OHCS excretion does not then reflect an increase of hydrocortisone production, but the clinical condition is usually clear and does not suggest Cushing's syndrome.

Summary

Some of the problems in the laboratory diagnosis of chronic adrenal insufficiency and Cushing's syndrome are discussed. A major difficulty has been the lack of any convenient method for estimating hydrocortisone and its metabolites in the urine.

A method based on the Norymberski procedure for measuring total 17-hydroxycorticosteroids is described. The steroid outputs of normal subjects were 7.6 to 23.6 mg. per 24 hours in men, and 4.6 to 17.8 mg. per 24 hours in women. In 100 estimations on urines from adrenalectomized patients the steroid output showed good correlation with the dose of cortisone acetate.

The effect of injections of corticotrophin gel on total urinary 17-hydroxycorticosteroid excretion was compared with that on the 17-ketosteroids. It is concluded that corticotrophin tests for adrenal cortical insufficiency are more sensitive if total 17-hydroxycorticosteroids are estimated.

The total 17-hydroxycorticosteroids were measured in 15 cases of Cushing's syndrome and three of virilizing adrenal cortical carcinoma. Estimation of the total urinary 17-hydroxycorticosteroids was of diagnostic value in Cushing's syndrome and should make it unnecessary to undertake numerous time-consuming investigations in patients suspected of having this condition.

APPENDIX

Method for Estimation of Urinary Total 17-Hydroxycorticosteroids (Total 17-OHCS)

A 24-hour urine collection is made without preservative; if the total volume is less than two litres, it is made up to two litres with distilled water.

20 ml. of urine is placed in a 50-ml. ground-glass stoppered test-tube and 100 mg. sodium borohydride added. Excess frothing may be stopped by adding a few drops of ether. The tube is allowed to stand overnight at room temperature, and next morning 20 ml. glacial acetic acid (A.R.) and 4.5 g. sodium bismuthate (A.R.) are added in that order. The tube is stoppered and shaken in the dark for 30 minutes in a Kahn shaker. The stopper is removed and the tube centrifuged at 2,000 r.p.m. for five minutes; the supernatant is poured into another tube and again centrifuged. 25 ml. of the fluid is then pipetted into a 250-ml. round-bottomed flask and the following added in order: 15 drops freshly prepared 5% solution sodium metabisulphite, 25 ml. distilled water, 7.5 ml. conc. hydrochloric acid (A.R.), 25 ml. benzene (A.R.), and a few chips of porous pot. The contents of the flask are boiled under reflux for 30 minutes and then cooled. The aqueous layer is removed in a separating funnel and shaken with two further 25-ml. amounts of benzene. The three lots of benzene are pooled, washed twice with 15 ml. of normal sodium hydroxide, once with 15 ml. N/2 hydrochloric acid, and three times with 15 ml. distilled water, using a 100-ml. stoppered separating funnel shaken by hand. The washed benzene extract is transferred to a 100-ml. round-bottomed flask, evaporated to dryness under reduced pressure in a water bath, and placed in a desiccator for 12

hours. The residue is dissolved in 1 ml. ethanol (R.R. quality, Distillers Co. Ltd.), and 0.2 ml. (representing 2.5 ml. of urine) taken for the Zimmerman reaction, which is performed by the M.R.C. method (1951) using the colour correction recommended. Results are expressed as mg. dehydroepiandrosterone per 24 hours.

If the diluted urine contains more than 0.5% reducing substance, this must be removed at the beginning. 25 ml. of urine is placed in an incubator at 37° C. with about 0.75 g. baker's yeast. The concentration of reducing substance will be less than 0.5% after 6 to 24 hours; the urine is then centrifuged and an aliquot of 20 ml. taken for the estimation.

We wish to thank our colleagues at the Middlesex and other hospitals for urine specimens from cases of Cushing's syndrome. We are indebted to the Clinical Research Committee of the Middlesex Hospital for the provision of laboratory facilities and for a personal research grant to J.D.N.N. The charts were prepared by Mr. V. K. Asta.

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MATERNAL AGE AND FOETAL OXYGENATION

BY

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In previous papers (Walker and Turnbull, 1953; Walker, 1954) it was shown that the margin of safety in the supply of oxygen to the foetus gradually diminishes in the later weeks of pregnancy, and especially when pregnancy is prolonged beyond the expected date of delivery. These findings have recently been confirmed by MacKay (1957). It was also shown (Walker and Turnbull, 1953; Turnbull and Walker, 1956) that the oxygen supply to the foetus may be reduced if pregnancy is complicated by pre-eclampsia or threatened abortion.

The purpose of the present investigation was to determine whether, in primigravidae, the margin of safety in foetal oxygenation decreases with age; this might be a factor in the well-known fact that the stillbirth rate rises with age, especially in primiparae.

Before the results of the investigation were available the staff of the Aberdeen Maternity Hospital agreed to adopt a new policy of treatment based upon the assumption that foetal oxygenation is, in fact, frequently reduced to dangerous levels in elderly primigravidae who do not go into labour before the end of the 41st week. The procedure and its results are briefly discussed.

Methods

One hundred primigravidae were studied. In all, pregnancy was clinically normal. Spontaneous delivery occurred in 73 cases, caesarean section was performed in 8, and "low" forceps delivery in 19. There were no stillbirths or neonatal deaths in the series. Spinal analgesia was used for caesarean section and pudendal block for low forceps delivery. Most spontaneous deliveries were conducted without gaseous analgesia, but in a few cases "gas and air" was given from a Minnitt machine.

Immediately after delivery a segment of umbilical cord was clamped at both ends, and samples of arterial and venous blood were withdrawn anaerobically. The oxygen content of the blood was measured by the method of Van Slyke and Neill (1924), employing the modified procedure of Orcutt and Waters (1937) in the cases where the mother had been given nitrous oxide.

The haemoglobin concentration of the blood was estimated in an M.R.C. grey-wedge photometer (100% = 14.8 g.). All oxygen and haemoglobin measurements were performed at least in duplicate.

Results

The results have been divided into three groups according to the age of the women: (1) up to 24 years, (2) 25-29 years, and (3) 30 years and over.

Fig. 1 shows the average oxygen saturation in the umbilical vein from the 38th week onwards in the three age groups. The percentage saturation is highest in those under

FIG. 1.—Average oxygen saturation of blood in the umbilical vein at various stages of pregnancy, by maternal age.

25 and lowest in those over 30. In each age group the percentage saturation falls at a similar rate as the pregnancy is prolonged beyond 39 weeks, so that the lines on the graph are almost parallel. The oxygen levels for arterial blood show similar trends, the average difference in arterio-venous saturation being about 27%.

It is clear that the saturation tends to decrease with age and gestation time. The two effects can be estimated simultaneously as follows: Regression of O_2 saturation on age and gestation is

$$O_2 = 212.0 - 0.76A - 3.62G$$

where A is age last birthday and G is the n th gestation week. Standard errors of regression coefficients are $S.E.b_A = 0.205$, $S.E.b_G = 0.765$. The data for individual patients in any given age group and gestation period varied widely around the means shown in Fig. 1. The analysis of variance (Table I) shows that the effects of age and gestation are statistically highly significant.

In the course of the statistical analysis such factors as the length of labour, both first and second stages, and the weight of the baby were taken into consideration, but none of these was found to have an influence upon the oxygen saturation levels.

TABLE I.—Analysis of Variance

	d.f.	C.SoS.O ₂	Mean Sq.	F.	Significance
Attributable to gestation ..	1	1,736.59	1,736.59	16.03	Highly significant
Extra attributable to age ..	1	1,492.95	1,492.95	13.79	..
Attributable to age and gestation	2	3,229.54	1,614.77	14.91	..
Unaccountable	97	10,503.37	108.28		
Total ..	99	13,732.91	138.72		

Discussion

These findings confirm our suspicion that the margin of safety in foetal oxygenation is diminished in the older primigravida. They also show that placental efficiency, judged by the oxygen saturation of the umbilical venous blood, declines after the 38th and 39th weeks of pregnancy. In primigravidae of 30 years or more the oxygen saturation of venous blood is on an average little more than 30% at the end of the 42nd week of pregnancy. Since the average oxygen saturation of blood in the umbilical arteries is about 27% less than in the vein it would not be surprising if the foetus of the elderly primigravida sometimes showed clinical evidence of distress, such as the passage of meconium or irregularity of the heart-beat.

In primigravidae booked for hospital confinement the incidence of "unexplained" perinatal deaths in mature infants (birth weight $5\frac{1}{2}$ lb. (2.5 kg.) or over) in the years 1938-52 increased steadily from 2.3 per 1,000 in the age group 15-19 to 19.0 in those aged 35 or more; a similar, though less marked, rise occurred in multiparae (Baird, Walker, and Thomson, 1954). At necropsy the appearances characteristic of anoxia were found in 70% of the "unexplained" deaths (Walker, 1954). In about 40% of all "unexplained" deaths the pregnancy had lasted 42 weeks or more, compared with 20% of all pregnancies, so that both age and gestation time influence their occurrence. Deaths from birth trauma and the stress of labour also increase steadily with the mother's age, and again in about 40% of them the pregnancy has reached the 42nd week or more. These findings suggested the possibility that in many cases the baby of an elderly primigravida undelivered at or soon after term had little reserve of oxygen at the onset of labour; if dystocia then occurred the reserve would be further diminished.

In this clinic, induction of labour in the 42nd week began to be practised in occasional "normal" cases from 1948

TABLE II.—Caesarean Section Rates in Primigravidae, 1938-56, All Aberdeen (Percentages)

Age:	15-19	20-24	25-29	30-34	35+	Total	No. of Cases	Caesarean Sections
1938-42	—	0.6	1.2	1.6	4.0	1.1	4,878	55
1943-5	0.5	0.3	1.6	1.7	6.0	1.4	2,996	41
1946-7	—	0.6	1.5	2.6	8.3	1.6	3,004	49
1948-50	0.3	1.0	3.0	5.3	20.9	2.7	3,325	91
1951-2	—	1.4	2.0	7.5	28.6	2.8	1,863	53
1953-4	2.3	2.2	5.5	11.5	28.8	4.7	2,014	94
1955-6	0.8	2.2	5.6	10.1	33.3	4.1	2,112	87

onwards. During the years 1953-6 it was adopted as a routine procedure in primigravidae aged 25 years or more. It was hoped in this way to anticipate and thus avoid some of the "unexplained" intrauterine deaths occurring before the onset of labour, and to start labour while the baby's oxygen supply was still good and thus decrease the incidence of foetal distress during labour and the need for caesarean section. Induction was not practised routinely in primigravidae under 25 years of age, partly because of the large numbers involved and partly because at that age the incidence of both "unexplained" and traumatic deaths is relatively low. Table II gives the incidence of caesarean section by age in primigravidae since 1938 for the City of Aberdeen. It shows that a rise in the caesarean section

rate began in the years 1943-5 in the age group 35+ and gradually spread to the younger age groups.

Fig. 2 shows that the great increase in the caesarean section rate in the years 1948-52 was accompanied by some decrease in the perinatal mortality, but in women over 35, where the caesarean section rate rose from 8 to 28%, the fall in perinatal mortality was relatively slight. The policy of routine induction of labour in the years 1953-6 led not to the hoped-for decrease in the caesarean section rate but to a slight increase; it was, however, accompanied by such a

FIG. 2.—Perinatal mortality rates (stillbirths plus first-week deaths per 1,000 births and stillbirths) in Aberdeen Maternity Hospital booked primigravidae, by age, in 1938-47, 1948-52, and 1953-6.

FIG. 3.—Comparison of stillbirth rates in primiparae, by age, in Scotland and in the City of Aberdeen.

striking fall in the perinatal mortality in women aged 30 or more that the age gradient disappeared.

Between the periods 1948-52 and 1953-6 the caesarean section rate in primigravidae rose from 2.7 to 4.3%. In the latter period only a few more caesarean sections were done for dystocia but many more for foetal distress in women over 25, since routine rupture of the membranes often revealed that the liquor was already heavily stained with meconium—a valuable sign of foetal distress. Induction of labour, therefore, made delivery by caesarean section possible in those cases where formerly intrauterine death occurred before the onset of labour or suddenly and unexpectedly early in labour. The fact that the perinatal mortality has fallen more in the years 1953-6 than in 1948-52 suggests that the policy of induction plus caesarean section in the last four years has proved more effective than that of increased use of caesarean section alone in the years 1948-52.

The data in Fig. 2 are for perinatal mortality in Aberdeen Maternity Hospital booked primiparae. Fig. 3 compares the

trends with age of stillbirth rates in primiparae in Scotland, 1948-52 and 1953-5, and in the City of Aberdeen as a whole, 1948-52 and 1953-6. During the earlier period the Aberdeen rates were less than those for Scotland, and in both there is a rise with increasing age after the age group 20-24. In the later period the Scottish figures still show a rise with age, but the Aberdeen rates are considerably modified; in the city there is no rise with age, at least up to the age group 30-34. The relatively high rate in Aberdeen primiparae aged 35 and over is based on three deaths only, and may be due to chance. These statistics suggest that if the policy of routine induction in the Aberdeen Maternity Hospital since 1953 were adopted more widely many deaths from anoxia and birth trauma could be prevented.

These findings are of particular importance to primigravidae in the upper social classes, who tend to be older than the average; consequently the foetus is more exposed to the risks of anoxia and dystocia. Table III shows that the

TABLE III.—Stillbirth Rate in Primiparae by Social Class: Scotland, 1953-5, and Aberdeen City, 1953-6

Social Class:	I and II	III	IV and V	All Classes
Scotland	19.8	25.0	29.3	25.6
Aberdeen	11.2	15.4	24.6	16.8
Aberdeen as a percentage of Scotland	57	62	84	66

stillbirth rate in primiparae in Aberdeen is considerably lower than that of Scotland as a whole, 16.8 compared to 25.6. It is also evident that the difference between the rates is greatest in social classes I and II (professional, managerial, and generally well-to-do classes) and least in classes IV and V (semi-skilled and unskilled working classes). The relatively very low rate in the upper social groups in Aberdeen is thought to be attributable, at least in part, to the policy of routine induction applied to elderly primiparae. The policy has much less effect upon primiparae in the lower social classes, who are mostly young, and in whom deaths due to anoxia and birth trauma are relatively infrequent; in these classes, prevention by obstetrical intervention is much less easy, since about 70% of the perinatal deaths are due to other causes, particularly prematurity, accidental haemorrhage, and certain types of foetal malformation.

Conclusion

It is well to point out that although the results of a policy of routine induction in primigravidae aged 25 and over have been gratifying, the method is essentially inefficient. Even in prolonged pregnancy in elderly primigravidae the oxygen levels in foetal blood vary widely and in many instances are compatible with safety. Routine induction therefore means that many unnecessary operations are undertaken to prevent relatively few deaths. More lives could be saved by routine induction at term, but the proportion of unnecessary operations would then be greatly increased. Again, induction is not entirely free from danger, since infection may be introduced, and, rarely, a foetal blood vessel may be punctured (Mitchell, Anderson, and Russell, 1957). In our hands, however, the gains appear greatly to have outweighed the risks.

There is, at present, no alternative to a policy of routine induction if lives are to be saved. It is not enough to await the spontaneous onset of labour and postpone intervention until signs of foetal distress supervene: before the new policy was introduced about 40% of "unexplained" (anoxic) deaths took place suddenly before the onset of labour, and even when labour was being very carefully supervised foetal death sometimes occurred suddenly with a few or no warning signs. A very high standard of antenatal and intranatal care of the usual type is therefore of limited value in preventing these deaths.

What is needed is a practical method of predicting the onset of foetal distress or of lethal lack of oxygen in the individual case. It would then be possible to differentiate

those cases where induction or immediate caesarean section is indicated from those in which pregnancy may be allowed to proceed with safety.

Summary

The oxygen content of venous and arterial blood from the umbilical vessels was determined after 100 first deliveries. Pregnancy in all the primigravidae had been clinically normal. The average oxygen saturation became less as maternal age and the length of gestation increased, and was sometimes dangerously low, especially in primiparae aged 30 or more delivered after the 41st week of pregnancy.

It is suggested that the relatively high rate of perinatal mortality in elderly primiparae—often clinically unexplained and accompanied by post-mortem evidence of foetal asphyxia—is due in part to inadequate foetal oxygenation after term.

Since 1953, in Aberdeen, labour has been induced routinely by rupture of the membranes in primigravidae aged 25 or more who are undelivered before the end of the 41st week, and caesarean section has been used more frequently if there are signs of foetal distress, especially meconium in the liquor amnii. Apparently as a result, the excess perinatal mortality in elderly primigravidae has been eliminated. Possible limitations and hazards of the procedure are discussed.

We wish to thank Mr. W. Z. Billewicz for undertaking the statistical analysis.

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RESPIRATORY AND CARDIAC ARREST DURING ANAESTHESIA IN CHILDREN

BY

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Outside the realms of cardiac surgery, cardiac arrest often occurs unexpectedly, sometimes during quite minor operations. During recent years an ever-increasing number of publications have appeared in this country and in America suggesting both increased awareness and increased incidence of the condition. In the United Kingdom nearly three million operations are performed annually with an average anaesthetic death rate of 600 (Milstein, 1956).

Stephenson *et al.* (1953) pointed out that cardiac arrest is by no means rare in children. Out of 212 fatalities, 20% were found to have occurred in children under 10, the highest incidence of any age group reviewed.

Following the occurrence of two deaths on the table in 1951 and 1952, a method of resuscitation was developed by one of us (E.H.R.) which has been employed successfully on eight occasions without a

single failure. We believe it saved the lives of at least five of these children. In the other three instances there is some doubt whether the heart had definitely stopped beating after cessation of respiration, but, as is stressed later, the method can be applied so easily and quickly that we would not wait for confirmatory evidence before resorting to it.

The literature on cardiac arrest has been amply reviewed in recent years (Palomera, 1952; Stephenson *et al.*, 1953; Johnson and Kirby, 1954; Lewis and Stanley-Brown, 1955; Milstein, 1956). Survival rates generally were low (from 10 to 28%). A notable exception was the 66% survival rate reported by Lahey (1953). Prompt action, a prearranged plan, and readily available equipment are considered to have been the reasons for this good survival rate.

Diagnosis and Treatment

Cardiac arrest is presumed to have occurred if it is impossible to feel the peripheral pulses (carotid, radial) or the apex beat. In addition there will be no respiratory movements, no operative bleeding, ashen-grey pallor, dilating pupils. (Looking for capillary refill and recording blood pressure are probably a waste of time.) We agree that a diagnosis can be made with certainty only by electrocardiogram or by opening the chest and inspecting the heart directly.

Resuscitation in cardiac arrest requires restoration of heart action and pulmonary ventilation within a very short time. After three to four minutes permanent damage will occur to the vital brain centres. Thus an effective cerebral circulation must be instituted in this time by artificial means, and maintained until a spontaneous heart-beat returns.

We claim that in young children it is possible in most—if not all—cases to restore heart and lung action by a single, simple, and effective manœuvre which can, if necessary, be carried out single-handed. Of our eight cases only two can be described as "poor risk" cases. The patients' ages varied from 8 weeks to 13 years. In all cases respiratory failure preceded cardiac arrest.

One of us (J.B.) had personal experience of only one of these cases, which occurred after this paper had been prepared. The other seven cases occurred at four different hospitals, each with a different anaesthetist.

Five cases are described in some detail. Of the other three cases, unfortunately, no adequate data were kept, though in none of them could a pulse be felt before resuscitation began. All our cases were preceded by respiratory arrest due to one or more of the following factors: prolonged hypoxia or anoxia; hypercapnoea; overdosage of anaesthetic agents—for example, thiopentone, cyclopropane; and possibly vagal stimulation.

There is no doubt that some degree of anoxia was present in every case, either as part of a general oxygen lack or owing to an inadequate airway. In one case inhalation of a small quantity of blood appears to have been a factor. It was not always possible to be quite certain of the exact stimulus or agent responsible. Most accidents occurred during induction of anaesthesia or at the end of operation.

Description of Method

As soon as it appears reasonably certain that cardiac arrest has occurred (the signs of which have already been described), no time-wasting manœuvres for confirmation of diagnosis are employed. It is then possible to start effective resuscitation in a matter of seconds, as follows:

1. Any blankets, towels, instruments, or other impediments close to the patient having been quickly discarded, the table is lowered to approximately 10 degrees Trendelenburg by the anaesthetist, while the surgeon positions himself at the patient's right side.

2. A nurse is instructed to check the time and call out each minute (as suggested by Bailey, 1941, 1947).