When both the serum P.B.¹³¹I and the thyroid uptake of ¹³¹I are raised, as in two of our cases, distinction from thyrotoxicosis may be achieved by the thyroxine suppression test.

The raised serum P.B.¹³¹I may be due in part to the presence of an abnormal iodinated protein in the blood and in part to the unusually rapid production and discharge of hormone from a gland with a low iodine pool.

The observation of the effect of potassium perchlorate, which discharges an appreciable amount of the thyroid ¹³¹I content in cases of Hashimoto's thyroiditis, is a useful additional diagnostic aid.

Part of this work was carried out during the tenure of an appointment by one of us (I. P. C. M.) in the Department of Medicine, Gardiner Institute, Western Infirmary, Glasgow, and we thank Professor E. J. Wayne for permission to publish the results obtained in patients who were under his care. We also thank Dr. E. G. Oastler for his helpful advice and criticism. Part of the expenses of the investigation were met by the Rankin Fund of Glasgow University. This research programme has been supported by a grant to one of us (E. M. McG.) from the Scottish Hospital Endowments Research Trust.

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The International Atomic Energy Agency has decided to undertake the measurement and analysis of samples of air, water, soil, and food to help in determining the degree of radioactivity in man's environment. This work, which will be done in the Agency's laboratory, now being built near Vienna, will be undertaken at the request of member states and of international organizations which have relations with the Agency and in collaboration with the United Nations Scientific Committee on the Effects of Atomic Radiation. Arrangements will also be made in the laboratory for a limited amount of training of scientists from interested member states in the relevant techniques. Collection of samples and their analysis would indicate the amount of radioactivity, and help in taking measures to reduce the radiation hazards of peaceful atomic energy work. Several member governments have asked the Agency how it can assist them in the collection of samples and in subsequent analysis and measurements. The Agency's assistance may also take the form of provision of experts and equipment to interested member states for carrying out measurements on the spot and helping national programmes of work in this field. It is expected that, apart from direct and specific assistance, the Agency's work will help in establishing international standards of sampling, measurement, and analysis. (International Atomic Energy Agency. PR 60/9.)

RENAL AGENESIS AND SEVERE URINARY TRACT DYSPLASIA*

A REVIEW OF 50 CASES, WITH PARTICULAR REFERENCE TO THE ASSOCIATED ANOMALIES

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Babies born with renal agenesis, and other forms of severe urinary tract dysplasia, show certain characteristic clinical and pathological features. In 50 cases encountered by us the abnormalities of the urinary tract were as follows: bilateral renal agenesis in 28, severe bilateral cystic dysplasia in 17, and congenital urethral atresia in 5 cases. The fact that intrauterine foetal micturition could not have been present was a feature common to all the cases.

Clinical Features

Quantity of Liquor Amnii

In the 50 cases reviewed the following clinical observations on liquor volume had been recorded: deficiency or absence of liquor specifically recorded in 7, notes suggestive of liquor deficiency in 28, relevant information not recorded in 14 cases, liquor present in 1 case.

The one case in which liquor was definitely present was of particular interest, the foetus being an iniencephalic with bilateral renal agenesis. The possible significance of the iniencephaly in relation to the fact that liquor was not only present but in excess is discussed later.

The following features were regarded as "suggestive" of oligohydramnios: (1) The finding at examinations in late pregnancy of a uterus smaller than expected from the duration of amenorrhoea. (2) Failure to record rupture of the membranes or escape of liquor at any time before or during labour. The space on the case sheet for the insertion of the time of rupture of the membranes was frequently left blank; in the hourly or half-hourly labour records the membranes were often stated to be intact within 10 or 15 minutes of the time of delivery, but there was no record of their having ruptured, or having been ruptured, between this time and the delivery.

To test the reliability of these criteria a series of 100 case records of patients who were delivered of normal babies was sampled. By the above criteria, only 3 out of the 100 suggested a deficiency of liquor. The finding of these features in 28 of the 50 cases of renal dysplasia is therefore extremely significant.

Nevertheless, the most convincing cases are the first small group in which a specific record was made of the liquor deficiency. In three of these a provisional diagnosis of renal agenesis was made at antenatal examination, and the virtual absence of liquor confirmed by particular observation during labour and delivery.

*Based on a communication to the Pathological Society of Great Britain and Ireland, July, 1958.

Radiological Appearances

Antenatal radiological examination in cases of renal dysplasia usually shows signs indicative of oligohydramnios. The foetal spine appears to be collapsed on an antero-posterior picture, and is confined to the

FIG. 1.—Antero-posterior antenatal radiograph at 35 weeks. Note the extreme flexion of the foetal spine, simulating the collapse which occurs with intrauterine foetal death. There was clinical oligohydramnios, and this baby was subsequently shown to have renal agenesis.

projected outline of the pelvic brim (Fig. 1). Although the foetus is usually alive its radiographic appearance is identical with that which Tager (1952) claimed was diagnostic of foetal death *in utero*. Spalding's sign is, however, not present. Antenatal radiological films were available in seven of the cases studied: four showed extreme flexion of the foetal spine, while the remaining three showed cramped positioning of the foetal limbs with the soft-tissue outline of the uterus closely applied to the foetus.

Presentation at Delivery

The presentation of the foetus at the time of delivery was recorded as follows: breech presentation, 30 cases; vertex presentation, 19 cases; presentation unknown (caesarean section), 1 case. Thus 60% of the babies were delivered by the breech. This extremely high incidence of breech presentation cannot be explained on the grounds of prematurity, because 36 out of the 50 babies in this series were delivered after the 34th week of pregnancy.

Neonatal Survival

All of the 33 babies born alive died early in the neonatal period. The average duration of life was 3 hours 9 minutes and the longest period of survival was 36 hours. The clinical picture in these cases was always one of respiratory distress, and the cause of death appeared to be asphyxia rather than anuria. Blood chemical examinations carried out at necropsy in 6 cases showed no significant abnormality.

Intrauterine Foetal Growth

Babies born with absent or non-functioning kidneys tend to have dry skins, but the skin is also often loose and wrinkled, giving in some cases an appearance of "premature senility" (Fig. 2). In general, the babies are small for the maturity, and appear as if they had failed to gain weight or even to have lost weight.

This clinical impression was confirmed by examining the birth weights of the 50 babies grouped according to maturity at the time of delivery. In Fig. 3 are shown the average weights of the babies in this series compared with those of normal babies of similar maturity. It will be seen that up to

34 weeks the abnormal babies are of approximately the expected birth weight, yet after 34 weeks they apparently failed to gain weight. The heaviest birth weight was only 5 lb. 1 oz. (2.3 kg.).

This is unlikely to be a chance finding, as 32 of the babies were delivered after 34 weeks; nor is it likely to be simply a measure of the absent organs, because (1) the weight of the kidneys is trivial compared with

FIG. 2.—Facies of a baby with renal agenesis. Note the low-set ears, the marked epicanthic folds, the small flattened nose, and the receding chin.

FIG. 3.—The average birth weights of babies with renal dysplasia, grouped according to maturity (stippled columns), compared with the normal average birth weight of babies of comparable maturity (obliquely hatched columns). It will be seen that the babies without kidneys fail to grow to the expected weight beyond 34 weeks' gestation.

the overall body weight; (2) 22 of the cases were of cystic dysplasia in which there would tend to be an *increased* kidney weight; and (3) it is only in *late* pregnancy that the foetal weight is less than expected.

Pathological Features

Face

The distinctive facial characteristics found in association with renal agenesis have become widely recognized through the writings of Potter (1946a, 1946b, 1952). The main features she described were abnormally large low-set auricles, prominent epicanthic folds with increased space between the eyes, slight flattening of the tip of the nose, and a conspicuous crease below the lower lip with recession of the chin. Although Potter originally described these features as associated with renal agenesis, she subsequently noted that such features could also be found with severe forms of renal dysplasia.

These features are all variable, however, and no single one is constantly present. In 10 (20%) of the present series of cases the facial changes were not definite enough to make the diagnosis prior to necropsy. Those which lacked the typical facial appearances were distributed as follows: renal agenesis, 4 cases; severe cystic dysplasia, 5 cases; urethral atresia, 1 case.

Hands

During the course of this study, one of us (A. D. B.) noted a peculiar appearance of the hands. They were broad, clumsy, and "spade-like"; not infrequently there was redundant skin on the dorsum, while the fingers were relatively short in relation to the width of the palm (Fig. 4).

Subsequent to recognition, this appearance of the hands was found to be present in 35 out of 38 consecutive cases, and it has proved to be a most valuable adjunct to the facial appearances in making a diagnosis.

Feet

The occurrence of some form of talipes was extremely frequent. Four foetuses were severely macerated and seven had gross defects involving the caudal region, such as spina bifida or sirenomelia. Excluding these, talipes in some form, either unilateral or bilateral, was present in 28 out of 39 cases—an incidence of 72%.

Lungs

Pulmonary hypoplasia is an almost constant finding in association with renal agenesis or severe cystic dysplasia. In our series it was present in all cases.

Amnion

The association of amnion nodosum with renal agenesis or severe dysplasia has been recorded elsewhere (Scott and Bain, 1958). This condition affects particularly that portion of the amnion which covers the placenta. The lesions take the form of small grey-yellow nodules of 1–2 mm. diameter which may coalesce to form plaques of larger dimensions. On cursory examination they may simulate miliary tubercles. They are found to lie on the foetal surface of the amnion and can be detached from the membrane without disrupting its continuity.

Histologically (Fig. 5) the nodules consist of masses of keratinized squames embedded in an acidophil matrix. The cuboidal cells of the amniotic epithelium are absent in the region of the nodules. There is no evidence of any squamous metaplastic change.

Since these nodules were first observed by one of us (J. S. S.) we have had the opportunity of examining 10 placentae belonging to the present series of cases. All but one of these showed amnion nodosum, the exception being the iniencephalic foetus with renal agenesis. In this, the only instance out of the whole series in which liquor amnii was definitely present, amnion nodosum was absent and there were none of the facial features associated with urinary tract dysplasia nor was there any abnormality of the hands or feet.

FIG. 4.—Photograph of the large, clumsy, spade-like hands of a baby with renal agenesis.

FIG. 5.—Photomicrograph of an amnion nodosum lesion showing keratinized squames embedded in an acidophil matrix. Note the break in continuity of the amniotic cells and the absence of squamous metaplasia. (H. and E. $\times 110$.)

Discussion

The findings in this study substantially confirm Potter's observations on the facial appearances found when the foetus is incapable of micturition. These features, however, are not always present or are not always sufficiently well developed to enable a diagnosis to be made prior to necropsy.

In this series, additional features were observed in a high percentage of cases. These included broad spade-like hands and a nodular condition of the placental amnion—"amnion nodosum." Even when the facial

appearances are normal or doubtfully abnormal, attention to the changes in the hands and amnion makes diagnosis possible. Other points which can be used in corroboration include the presence of talipes, the fact that the baby is considerably under-weight, and antenatal or intranatal evidence of a deficiency of liquor amnii.

What might be termed the "ante-post-mortem" diagnosis of severe renal dysplasia is a matter of greater concern to the obstetrician than Nash (1951) suggests. The majority of these babies present by the breech, and the recognition of the signs indicative of gross renal abnormality in a baby dead or dying after breech delivery saves the obstetrician unnecessary remorse.

The question arises regarding the manner in which these congenital malformations, affecting tissues and organs with no apparent embryological, anatomical, or functional connexion, come to be linked. It would seem that at least two factors are concerned.

1. *Intrinsic: Maldevelopment of the Tissues of the Early Embryo.*—The association of maldevelopment of the urinary tract and displacement of the auricular appendages seems likely to be the result of genetic linkage or an injury to the embryo at a stage when these particular organs are undergoing differentiation. No matter whether these faults are genetic or acquired, it is almost certain that the mechanism concerned is similar to that which determines the association of gonadal dysgenesis with webbing of the neck found in Turner's syndrome.

2. *Extrinsic: Liquor Deficiency.*—Although some fundamental error in development, such as is postulated above, must be held responsible for certain defects, others are undoubtedly the result merely of the oligohydramnios associated with failure of the foetus to void urine. They are caused by the pressure exerted by the uterus and membranes firmly applied on the foetus and preventing its free movement. This not only explains certain deformities but also accounts for some of the special clinical features of pregnancy and labour in these cases.

That liquor amnii is usually deficient in pregnancies in which intrauterine foetal micturition cannot occur has been disputed in the past (Browne and Browne, 1955). Nevertheless, those papers in which critical attention has been paid to this problem and which have covered a substantial number of cases, seem to have established that oligohydramnios is the general rule in these circumstances. Bardram (1930), in a review of 20 years' material in Copenhagen, found oligohydramnios in 10 out of 13 cases of renal agenesis or severe cystic dysplasia in which renal function was apparently absent. Bates (1933) noted lack of liquor in 6 out of 7 cases of renal agenesis; in the seventh no information was available. One of these 6 cases was delivered by elective caesarean section, and the absence of liquor was thus definitely confirmed. Bates also referred to 7 cases of extreme renal hypoplasia, in all of which liquor deficiency was noted. His total figures thus present a picture of 14 cases of agenesis or severe hypoplasia with oligohydramnios recorded in 13 and no information in the fourteenth.

Potter (1952) stated that in 30 cases in which necropsy revealed renal agenesis in the foetus, liquor amnii had not been seen at the time of delivery by any obstetrician. She further commented: "Membranes are commonly thought to be intact during the course of labour because a history of rupture is lacking, but when no fluid is found at delivery the conclusion is ordinarily reached that the membranes ruptured previously with loss of fluid despite the absence of such history." This seems to have been the sequence of events in some of the cases recorded with allegedly normal liquor volume.

Hinman (1940) and Plentl and Gray (1957) stated that normal amounts of liquor "may be found" or "are frequently found" in association with a congenital foetal abnormality incompatible with micturition. They did not, however, adduce any evidence to support these statements. Perhaps the most important case recorded is that by Selby and Parmelee (1956), who saw a baby without kidneys, born with the amnion intact. No liquor was present. Recently, Weber and Israel (1958) reported two cases of renal agenesis and one of renal hypoplasia all associated with oligohydramnios.

Nevertheless, there are several cases, and the one reported here, in which liquor was without doubt present. In our own case the renal anomaly was associated with iniencephaly, the latter defect being likely to make the foetus unable to swallow. This appears to be the mechanism which leads to hydramnios in cases of anencephaly (Scott and Wilson, 1957) and will presumably also operate in cases of iniencephaly.

The mechanism of production and disposal of liquor amnii in normal pregnancy, together with the findings in cases of oligohydramnios and polyhydramnios, are reviewed elsewhere (Jeffcoate and Scott, 1959). These findings lead to the general conclusion that, if the

FIG. 6.—Case of renal agenesis associated with oligohydramnios and amnion nodosum. Note the position of the legs and the glazing of the skin over the external malleoli, suggestive of pressure.

mechanisms for disposal of liquor are operating normally, absence of foetal urination will be associated with oligohydramnios. In cases in which there is some interference with the normal channels of disposal, liquor which has arisen from non-renal sources may accumulate.

The effect of a deficiency of liquor shows in the radiological signs, mentioned previously and described by Kent, Rubin, and Dann (1957). The high incidence of breech presentation is almost certainly a consequence of the lack of liquor, which prevents the foetus turning in the normal way to adapt itself to the uterine shape in late pregnancy. Amnion nodosum seems to be specifically related to oligohydramnios. The only one of our cases in which this was searched for and not found was that in which liquor was present. In addition, we have observed amnion nodosum on three occasions in association with oligohydramnios not due to renal dysplasia. It appears that when the liquor

is deficient the foetal prominences rub and abrade the surface of the amnion; desquamating foetal epidermal cells then become adherent to these denuded areas, forming the nodules.

Talipes is probably another effect of oligohydramnios; indeed, in several of our cases there were skin marks suggestive of pressure on the external malleoli (Fig. 6). These findings confirm the views of Browne (1936, 1955) on the importance of intrauterine pressure in the production of deformities such as talipes. It seems possible that the flattened hands associated with renal abnormalities are also due to pressure secondary to the liquor deficiency.

The explanation of pulmonary hypoplasia is more doubtful, but this condition could be the result of oligohydramnios rather than of a genetic taint. Compression of the thoracic cage or absence of the normal volume of liquor circulating into the developing lungs might be responsible. If, however, the pulmonary abnormality is primary, it has to be recognized that it might in part be the cause of the oligohydramnios. This possibility has to be entertained because Whitehead, Windle, and Becker (1942), Macafee (1950), and Morison (1952) have suggested that the lungs contribute to the volume of liquor.

That some of the facial features, such as the low-set ears, are embryological defects seems certain, but others, such as the flattened nose-tip and the receding chin with its deep fold, may well be the effect of the dry amniotic sac being tightly applied to the foetus.

The failure of the affected foetuses to gain weight in the latter weeks of intrauterine existence remains to be explained. Three possibilities present themselves. (a) It may be that the foetal kidneys are normally important for excretion of the products of foetal metabolism. This is opposed to the generally accepted concept that the placenta is the essential excretory organ for the foetus *in utero*. Moreover, it is rendered unlikely by the fact that babies born devoid of renal function show no gross change in the blood levels of urea and other waste products (Davidson and Ross, 1954). (b) It may be that the imbibed liquor amnii normally nourishes the foetus. This is unlikely if this fluid, as found in late pregnancy, represents mainly foetal urine. (c) The third possibility is that foetal growth is normally dependent on progressive distension of the uterus by amniotic fluid. Adequate distension of the uterus may well be necessary for proper placental development and function.

This last explanation appears the most likely and is in agreement with the conclusions of Harrison and Malpas (1953), who, in regard to early pregnancy, concluded that the function of liquor at that stage of pregnancy is to provide a distension-growth stimulus to the uterus. They showed a definite correlation between the volume of liquor and foetal size. Text-books have for long recorded the association of hydramnios with large babies and oligohydramnios with small babies, but it has always been assumed that the volume of liquor is secondary to the size of the foetus. The opposite cause-and-effect relationship may well obtain.

The fact that the iniencephalic foetus (maturity 30 weeks), which, despite absence of renal function, was surrounded by liquor in large amount, was the only one which failed to show any defects such as talipes, spade-like hands, amnion nodosum, and peculiar facies

is strong supportive evidence for the concept that liquor deficiency is the principal mechanism of production of these features. The birth weight in this case was 2 lb. 5 oz. (1,050 g.), but if allowance is made for the considerable tissue deficiency constituting the iniencephaly the weight of the baby probably corresponded to that expected from the maturity. Further evidence that many of the external features which we have described are the effect of oligohydramnios rather than of a genetic linkage is the fact that these features were found in association with urethral atresia—an anomaly which is embryologically quite distinct from renal agenesis.

Summary

Fifty cases of severe urinary tract dysplasia are reviewed (28 of bilateral renal agenesis and 22 of other anomalies incompatible with micturition). The characteristic clinical and pathological features are described.

During the intrauterine period there often is evidence of deficiency of liquor amnii, suggesting that foetal urine provides a major contribution to liquor volume in late pregnancy. In the only case in which liquor was definitely present the foetus was also iniencephalic. The significance of this is discussed. Characteristic intrauterine radiological appearances are described.

At delivery the foetus presented by the breech in 30 of the cases. The average period of survival of the 33 babies born alive was 3 hours 9 minutes; death being apparently due to asphyxia. A comparison of the birth weights of these babies with the normal average at comparable maturity shows a failure to gain weight after the 34th week *in utero*.

The characteristic facies was present in 40 of the cases, while flattened spade-like hands and a peculiar nodular appearance of the amnion—"amnion nodosum"—were other common features. Pulmonary hypoplasia was a constant finding and is the usual cause of death. Diagnosis of these anomalies during life is usually possible, and may be of some value.

The cause of the associated anomalies is discussed. A genetic factor appears to operate, but many of the features are evidently a consequence of oligohydramnios, which is due to absence of the foetal urinary contribution to the liquor amnii. Oligohydramnios accounts for the amniotic lesions, the talipes, some of the facial features, the high incidence of breech presentation, and the radiological appearances. The impaired foetal growth in late pregnancy is also probably due to liquor deficiency, and suggests that the distensile effect of liquor amnii on the uterus is just as necessary for normal foetal development in late pregnancy as it is in early pregnancy.

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Addendum.—Since this paper was prepared we have encountered 10 further cases. In eight, liquor was noted to be deficient or absent, and in all of these amnion nodosum was present. In one case of renal cystic dysplasia associated with hydrocephalus and spina bifida, liquor volume was apparently normal and there was no amnion nodosum. The

remaining case resembled the one in the text, having both renal agenesis and iniencephaly. Again there was hydramnios and a normal amnion.

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RELATIONSHIP OF STRESS TO THE DEVELOPMENT OF SYMPTOMS IN ALOPECIA AREATA AND CHRONIC URTICARIA

BY

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Agreement has not yet been reached on the part played by emotional disturbance in the development of two common disorders, alopecia areata and chronic urticaria. In an attempt to assess the relationship of psychological stress to symptoms, a study was made of patients suffering from these two conditions in the out-patient department of St. John's Hospital for Diseases of the Skin. The effects of adequate psychotherapy on symptoms were also studied. The study depended on the taking of a very long and detailed history of every case (when necessary, over several interviews of an hour each), together with a careful follow-up of patients, each of whom was seen at short, regular intervals over a period varying from 3 to 18 months, during interviews which lasted from 45 to 15 minutes. Most patients were followed up for more than one year.

The time devoted to the patients seemed to be of extreme importance. Many were not able to discuss their difficulties in the first few interviews, but as time went on they were able to talk more freely. From the therapeutic point of view also, the time devoted to each patient was of major importance. In many studies of this kind the psychotherapy offered may consist of brief interviews spaced widely over a varying period. In the present study it was, in certain cases, not possible to give adequate psychotherapy for the condition, the psychological disturbance being too profound.

There were 52 cases of alopecia areata and 27 cases of chronic urticaria. The groups are here treated first separately and then together, as the conclusions relate equally to both groups. Patients were referred for psychiatric assessment in a haphazard manner by various members of the staff of St. John's Hospital. There was no definite selection of cases, but it is possible that physicians remembered to refer patients when some psychological disturbance seemed present. Cases were studied between the beginning of July, 1957, and the end of January, 1959. All the cases were followed up for three months at least, several for more than a year. In both these groups there was not a single patient who did not reveal either a very unhappy or stressful life previous to onset of alopecia or urticaria, or moderately severe neurotic symptoms in life previous to onset of symptoms. Frequently there was a combination of both.

The patients were divided into the following groups.

Group A: Those in whom a long history of stress had occurred before the onset of symptoms. Symptoms might have been precipitated by a sudden fresh stress—major in character.

Group B: Those in whom a long history of stress had occurred before the onset of symptoms. Symptoms might have been precipitated by a sudden fresh stress—minor in character.

Group C: Those in whom a long history of stress had occurred before the onset of symptoms, without a fresh, obvious stressful situation precipitating symptoms.

Group D: Those in whom no very clear history of stress was obtained, but signs of previous psychological disturbance were present—for example, insomnia, fear of crowds, fear of the dark, nervous breakdown, and so on.

Group E: Those in whom symptoms were associated with an obvious depressive illness—that is, severely depressed mood, insomnia, loss of weight, feelings of guilt, inadequacy, refusal to go out, and so on.

Group F: Those in whom the symptoms occurred in conjunction with other so-called psychosomatic illness—for example, asthma.

Group	Alopecia Cases	Urticaria Cases
A: Long history of stress and major crisis ..	6	1
B: " " " " minor " " ..	9	13
C: " " " " but no crisis discovered ..	27	7
D: Psychological disturbance but no stress ..	4	2
E: Depressive illness (but always stress as well) ..	3	2*
F: Other psychosomatic illness ..	3	2

* Plus considerable stress and also crisis.

The groupings of the 52 alopecia cases and the 27 urticaria cases are shown in the Table. The urticaria patients were tested in the laboratory and not found to react to specific allergens.

Alopecia Areata

The following case-histories illustrate the type of case in the various groups.

Group A

Case 1.—The patient, aged 15, was the elder daughter in a family of two girls. Both parents are alive. The mother, a weak psychopathic woman, had had a love affair with another man (who was a minor criminal, often in trouble with the police) while her husband was away in the Forces during the war. Some time before the development of the present crisis the mother's lover turned up again. She found herself greatly attracted to him and would go out to be with him on the pretext of going to visit her mother. This was suspected by the husband and family, and tension gradually increased. One day the mother went out and took