THE METABOLISM AND ACIDITY OF THE FOETAL TISSUES AND FLUIDS.*

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IN the course of our studies on the nature of malignant neoplasia we have obtained and have published^{1-4, 11} evidence in support of our original hypothesis, and in particular of that part of it which assumed that the chorionic epithelium of the placenta is a malignant tissue.

In this paper we present further observations along the same lines, which, moreover, are of considerable obstetrical interest, both from physiological and pathological points of view.

It will be useful first briefly to consider current views concerning the carbohydrate supply of the foetus.

Current Views of the Carbohydrate Supply of the Foetus.

A large number of observers have investigated what is called the glycogenic function of the placenta since Claude Bernard⁵ in 1859 first demonstrated glycogen in the pregnant uterus of the rabbit; and it appears that considerable confusion has been caused by the inclusion of the maternal decidua basalis in the term "placenta." The placenta should be regarded as an entirely foetal structure, and the maternal decidua as auxiliary only to the functions of the placenta proper. This is further emphasized by the observations of Driessen,¹² who showed that glycogen is stored in the premenstrual endometrium (in which a decidual reaction occurs), as in the decidua of pregnancy.

Chipman,¹⁰ and Lochhead and Cramer,¹⁵ a little later, showed conclusively that glycogen is found only in the maternal decidua and never in the foetal—that is, the true—placenta.

According to Chipman, whose investigations were micro-chemical in nature, the quantity of glycogen is greatest in the deepest part of the decidua—that is, the part adjacent to the uterine musculature—and the maximum is reached about the sixteenth day of pregnancy (approximately half-term) in the rabbit. Subsequently, there is gradual diminution until full-term, when only a mere trace is to be detected. Chipman observed an inverse relationship in regard to the quantity of glycogen in the foetal liver, so the accumulation of glycogen in the decidua in the first half of gestation came to be called "the glycogenic function of the 'placenta.'" Lochhead and Cramer, employing chemical methods, obtained results similar to those of Chipman, and stated that the maximum glycogen content in the decidua is reached on the eighteenth day of pregnancy in the rabbit, when the glycogen in this tissue amounts to 5.5 per cent. of the total (? dry) weight. These authors believe that the glycogen stored in the decidua is absorbed by the placenta in the form of simpler carbohydrates produced by enzymes.

It is clear, then, that carbohydrates are presented to the chorionic epithelium of the placenta in two forms: (a) glucose contained in the maternal blood that fills the sinuses surrounding the villi; (b) glucose derived from glycogen contained in the decidua.

Slemons,²⁴ whose investigations were concerned with a quantitative estimate of the glucose in the foetal and maternal circulations of the human subject, stated that the glucose contents of the maternal and foetal bloods at full-

term are practically the same: out of 24 cases examined, in 5 they were identical, and the mean glucose value for the maternal blood was 0.132 per cent., and for the foetal 0.115 per cent. Slemons concluded that this finding indicates that glucose is diffused entirely from the maternal to the foetal circulation. While glucose certainly must so diffuse, it is likely that the chorion also derives some glucose from the glycogen of the decidua, although, of course, this mechanism could not operate at the end of pregnancy, when the glycogen has disappeared from the decidua.

The Carbohydrate Metabolism of Malignant Neoplasms.

To Otto Warburg²⁵ of Berlin is due the credit of demonstrating fully the importance of glycolysis in the metabolism of malignant neoplasms. Warburg has shown—and his findings have been confirmed by ourselves and others—that this is a process which differentiates between malignant and non-malignant tissues, and, further, between malignant neoplasms, benign neoplasms, and normal tissues.

When the processes which supply energy to the cell are considered, glycolysis is found to yield more energy, with the exception of oxidation reactions, than any other process—for examples, proteolysis and lipolysis. Meyerhof²⁰ has shown that in muscle there is an equilibrium:

The forward reaction, glycolysis, proceeds freely, but the reverse reaction requires a supply of energy, and, therefore, proceeds only when respiration is taking place simultaneously.

The net amount of glycolysis depends on the amount of respiration taking place—one molecule of oxygen respired furnishing enough energy to bring about the resynthesis to carbohydrate of approximately two molecules of lactic acid.

If the respiration is high in comparison with the glycolytic power, there will be little net glycolysis. If the converse obtain, then appreciable glycolysis will take place under aerobic, as well as under anaerobic, conditions.

Malignant neoplasms, unlike the somatic tissues from which they arise, can glycolyse even under aerobic conditions. This is due to the glycolytic power being large in comparison with the function of respiration. In normal tissues the respiration, which does not differ greatly from that of malignant tissues, is sufficient to cause the resynthesis of the limited products of glycolysis, which can be observed under anaerobic conditions. Warburg's findings may be summarized thus:

(A) Glycolysis can occur to a considerable extent only in growing tissues.

(B) Glycolysis occurs to a considerable extent under aerobic conditions only in malignant tissue, with the exception of retina, erythrocytes, and leucocytes. Benign tumours show some aerobic glycolysis, but in a more limited degree.

The Carbohydrate Metabolism of the Placenta.

The active elements in so far as the function of the placenta is concerned consist of the various parts of the chorionic epithelium—Langhans' layer and the syncytium. It is to be noted in the human subject that the epithelium, especially the syncytium, is, relatively to the size of the ovum, of far greater extent in the early stages of gestation than in the later, when, except for a thin layer of syncytium, it tends to disappear. In the human subject, therefore, account must be taken of the duration of pregnancy at the time when experimental investigations are conducted. In some animals, such as the rabbit, the trophoblastic cells persist throughout the whole of pregnancy.

The experimental methods of Warburg have been used by several workers in the study of placental and related tissues. Negelein,²² working in Warburg's laboratory, has examined the "aussere Haut" of the fertilization sac in the rat, and later²⁷ the same investigator re-examined the metabolism of this tissue, using rat serum as a medium instead of the horse serum earlier employed. The structure described by Negelein as the outer layer of the fertilization sac has been identified by us from the author's photomicrograph as resembling maternal mucosa; it shows

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no aerobic glucolysis. The "innere Haut" examined by Negelein²² consisted, in our opinion, of the fused amnion and chorion; in this case the aerobic glucolysis was not measured. Thus Negelein does not appear to have studied the invading cells of the trophoblast.

Murphy and Hawkins²¹ worked with rat placenta at mid-term and near full-term, using Ringer's solution, containing glucose, as the medium. They concluded that the metabolism of the placenta resembles that of a frankly malignant tumour. In connexion with the results of Negelein, quoted above, it is interesting to note that the wall of a pregnant uterus and the embryonic membranes were found by Murphy and Hawkins to show the type of behaviour usual to embryonic somatic tissues—that is, little or no aerobic glucolysis was observed. Loeser¹⁷ has studied the glucolytic power of human placenta in Ringer's solution. Two experiments are quoted—one with a young placenta, and the other with the same tissue at full-term. The results of these experiments are recorded below.

Our own investigations were carried out with the type of apparatus used by Warburg, to whom we are much indebted for demonstrating his methods to us. The experimental details are fully described in Warburg's papers. The method used is a manometric one. A slice of the tissue under investigation, thin enough to allow adequate diffusion of the metabolites throughout, is shaken to and fro in a suitable medium, maintained at a temperature of 37.5° C., and the gas exchange is observed. Several slices, each in its own vessel with manometer attached, are required for a complete experiment. The gas space in the apparatus is filled with oxygen or nitrogen containing 5 per cent. CO₂. By this means the medium is maintained at a physiological pH, the pH being determined by the concentration of bicarbonate ions in the liquid and the dissolved carbon dioxide derived from the gas mixture.

The results so far obtained with human placental tissues are given in Table I. In three cases human amniotic fluid was used as the medium, and in the remaining two human serum. The nature of the tissue used was checked by histological examination.

The most important value in connexion with the quantitative expression of the results is the magnitude of U—the corrected aerobic glucolysis which is given by the equation—

$$U = Q \frac{N_2}{M} - 2Q_{O_2}$$

where $Q \frac{N_2}{M}$ is the anaerobic glucolysis of the tissue and

Q_{O_2} the respiration. For the full significance of this relation the publication of Warburg²⁴ should be consulted. It suffices to state that normal and embryonic somatic tissues give zero or negative values for U, benign neoplasms give zero or small positive values, and malignant neoplasms larger positive values.

It may be noted that, calculated on this basis, the results of Murphy and Hawkins on rat placenta give a value $U + 0.3$, and those of Loeser¹⁷ a value $U = -4.2$ for a young human placenta, and $U = +1.0$ for a full-term placenta. In both these cases Ringer's solution was used as the medium.

TABLE I.—Human Placenta containing Chorionic Epithelium.

Age.	Respiration Q_{O_2}	Aerobic Glucolysis Q_{O_2} M.	Anaerobic Glucolysis N_2 $Q \frac{N_2}{M}$	U.
Medium—Human serum.				
Full-term ...	2.3	1.0	5.3	+0.7
Full-term ...	1.8	0.0	3.9	+0.3
Medium—Amniotic fluid.				
Twenty-four weeks ...	0.3	1.8	—	(>1.0)

TABLE I (continued).—Human Placenta containing no Chorionic Epithelium.

Medium—Amniotic fluid.

Age.	Q_{O_2}	Q_{O_2} M.	N_2 $Q \frac{N_2}{M}$	U.
Eighteen weeks ...	4.1	0.2	5.5	-2.7
Twenty-four weeks ...	4.0	0.2	5.5	-2.5

Experiments were also conducted with rabbit placental tissues at and before half-term, using horse serum as the medium, and similar results were obtained; that is to say, placentae containing chorionic epithelium gave positive values of U; on the other hand, placentae containing no chorionic epithelium, and likewise the fused amnion and chorion, gave negative values.

These observations demonstrate the ability of placenta containing chorionic epithelium to split glucose into lactic acid under aerobic conditions; but before a quantitative estimate is made as to the malignant character of the metabolism of the invading trophoblast, it should be pointed out that in the tissue slices used in these experiments the chorionic epithelium was mixed with foetal mesoderm, which shows little or no corrected aerobic glucolysis. Probably, approximately only one-fifth of the volume of tissue examined was composed of the epithelial cells of the chorion. In these circumstances the evidence obtained is in favour of the view that the chorionic epithelium possesses malignant properties in regard to glucolytic behaviour.

The Process of Infiltration.

The chorionic epithelium, like malignant neoplasms, has the power of infiltrating the differentiated tissues with which it is in contact; this process has been the subject of much speculation, and is still a matter for further investigation.

The work of Bierich,⁷ and of Bierich and Rosenbohm,⁸ however, concerning the mode of extension of cancer of the skin, induced in mice by tar, is of considerable interest in this respect. These observers found that there are certain characteristic changes in the collagen fibres preceding infiltration.

Experiments with acids and bases and mixtures of these with salts were made on the dorsal skin of mice, and changes in the collagen fibres were produced; but, according to these authors, the only reagent which produced exactly the same change as that seen in the presence of cancer was lactic acid. Alkalis produce an entirely different appearance.

This work, if confirmed, is highly significant in view of the lactic acid produced by malignant growths, and by the trophoblast, especially in the earlier stages of pregnancy.

The Hydrogen-ion Concentration of Foetal Tissues.

The pH Value of the Placenta.—Experiments have been conducted to obtain information concerning the pH value of the placentae of rabbits. In each case the placental tissues were examined by means of the glass electrode, employing the technique of Kerridge,¹³ after having been placed into liquid air immediately on excision. The pH measurements of the rabbit's placenta in different stages of pregnancy are shown in Table II.

TABLE II.

Number of days pregnant...	20	23	26	29
pH of placentae ...	6.12	6.59	6.76 6.87	6.97

It will be seen that the placenta has an acid reaction, and that over a period of pregnancy from twenty to twenty-nine days the pH value rises considerably, the placenta tending towards a neutral reaction at full-term. In the case of a human placenta obtained at full-term by a Caesarean operation the pH value was found to be 6.99, which is practically that of neutrality. One of us (H. M., unpublished) has demonstrated that malignant neoplasms also show a pH value on the acid side of neutrality.

The pH Values of Foetal Somatic Tissues.—The reactions of foetal tissues of a number of rabbits at different stages of development have been examined, and results have been obtained similar in extent and variation to those recorded in the case of rabbits' placentae. In every case the pH value of the foetal tissues examined was lower than the pH value of the corresponding maternal tissue.

Thus far we have considered the pH values of different foetal somatic tissues, and we have seen that in all cases these are considerably lower than the maternal tissues. We have also examined the placenta. Moreover, we have shown that the placental metabolism with regard to the production of lactic acid by aerobic glucolysis resembles that of malignant tissues which are also acid in nature.

We now pass on to the consideration of the foetal blood as compared with the maternal. The pH values of the bloods from umbilical veins and arteries and from the maternal arteries and veins at full-term have been examined, together with their sugar and lactic acid contents. The oxygen content and alkali reserve have also been estimated. It is to be noted that somatic tissues, whether maternal or foetal, exhibit a lower pH value than the blood supplying the tissues concerned. The amniotic fluid, too, has been studied.

The Glucose Content of the Foetal Blood and Amniotic Fluid.

It occurred to us that considerable light might be thrown on the nature of the carbohydrate metabolism of the foetal tissues if the glucose content of the blood entering and leaving the foetus were estimated at the same time as the corresponding values of maternal arterial and venous blood.

The earliest work on the simultaneous determination of glucose values in arterial and venous blood in the adult appears to have been done by Claude Bernard in 1877.⁶ Since then many workers, including one of us,²³ have confirmed his findings. We have already drawn attention to the investigations of Slemmons,²⁴ who found a slightly lower value in the foetal than in the maternal circulation. Unfortunately it was impossible to obtain sufficient blood from the various sources to perform complete chemical analyses in any single case, but we have had enough material to calculate a mean value for the glucose content of arterial and venous bloods in the maternal and foetal circulations, respectively, from a series of cases; the results are recorded in Table III. In all cases the glucose was estimated at once by Folin and Wu's method.

TABLE III.—Glucose Values.

Number of Case.	Maternal Artery.	Maternal Vein.	Umbilical Vein.	Umbilical Artery.
11	131	117	72	66
12	95	84	71	60
14	127	127	109	99
*16	88	89	75	48
21	100	97	89	81
23	110	105	81	70
Mean values...	112.6	106.0	84.4	75.2

* Caesarean section. This case is excluded from the mean.

It will be seen from these results that the arterial values—the umbilical vein functioning as an artery—in each case are richer in glucose than the corresponding venous values, that the difference in arterial and venous values is greater and more constant in the foetal circulation than in the maternal circulation, and that the maternal blood contains considerably more glucose than the foetal blood.

It is interesting to note that in the determination of lactic acid the opposite state of affairs is found: a low glucose value invariably accompanies a high lactic acid value, and conversely a high glucose value accompanies a low lactic acid value. This may be seen at a glance in Table IX. The assumption is that lactic acid is formed at the expense of glucose. The sugar content of a series of specimens of amniotic fluid from the parturient woman gave a mean value of 18 mg. per 100 c.cm.

The Lactic Acid Content of Foetal and Maternal Blood.

The lactic acid content of blood obtained from the umbilical vein and artery in cases of normal labour was determined; and, owing to the difficulty of obtaining blood from the uterine vessels, except in cases of Caesarean section, blood was also collected from the vein and artery in the arm of the mother at the time of delivery. A modification of Clausen's¹¹ method, as used by Warburg (private communication), was employed. The method gave a yield of 93 per cent. lactic acid when standardized against pure zinc lactate. The results obtained are given in Table IV.

TABLE IV.—Lactic Acid in mg. per 100 grams of Blood.

Number of Case.	Maternal Artery.	Maternal Vein.	Umbilical Vein.	Umbilical Artery.
1	—	42	74	87
2	25	30	47.5	62
3	34.5	—	35	42
4	33	42	65	73
5	29.5	25	37.5	63.5
6	24	27	52	48
7	35	45	54	101
8	22	24.5	34	39
9	16.5	26	40	41
10	25	49	43.5	65
11	32	42	65	63
12	48.5	49	75.5	97.5
13	56	54	64	77
14	42	45.5	73	100
15	—	35	42	61
Mean ...	32.5	38	54	68

It will be seen that the lactic acid concentration in the foetal circulation is considerably higher than that in the maternal circulation. Further, the concentration of lactic acid in the blood leaving the foetus (the umbilical artery) is greater, except in three cases (6, 9, and 11, where the differences lie within the limits of experimental error), than that entering. It must, however, be remembered that the umbilical arterial blood is venous in function and composition, and that in the general maternal circulation the venous blood contains more lactic acid than the corresponding arterial blood.

The results obtained from cases in which Caesarean section was performed (Table V) suffice to show that the high lactic acid content in the foetal circulation is not due to special circumstances attending delivery. The pH values of the bloods are also given in Table V.

TABLE V.—Lactic Acid in mg. per 100 grams of Blood. Cases of Caesarean Section.

No. of Case.		Maternal Artery.	Maternal Vein.	Umbilical Vein.	Umbilical Artery.	Ovarian Vein.
16	Lactic acid... pH ...	28 7.44	35 7.34	42 7.07	50 7.03	36 7.19
17	Lactic acid... pH ...	28.5 7.34	29 7.30	71 7.12	—	34 7.30

In connexion with the lactic acid values given above for human cases, it is interesting to note that Loeser,¹⁷ employing the method of Mendel and Goldscheider,¹⁸ in two cases, found the lactic acid content of the umbilical vein to be higher than that of the mother's arm vein, and that of the umbilical artery to be slightly higher than that of the vein. All the determinations by Loeser show a lower level of lactic acid content than ours.

Bokelmann,⁹ using Clausen's method, finds that the lactic acid content of the blood from the mother's cubital vein immediately before and after parturition averages

45 mg. per 100 c.cm. The variations are similar to those observed by us, although the values are for the most part higher than ours.

Measurements of the pH Values of Umbilical and Maternal Blood.

Measurements have been made of the pH values by means of the glass electrode. In order to prevent loss of carbon dioxide each sample of blood was kept under liquid paraffin. The pH values for a number of cases after normal labour are included in Table VI.

TABLE VI.—pH of Umbilical and Maternal Blood at 18°C.

Case No.	pH Values.			
	Maternal.		Umbilical.	
	Artery.	Vein.	Vein.	Artery.
6	7.33	7.33	7.17	(6.57)
7	7.43	7.43	7.19	—
18	7.31	7.27	7.14	7.02
8	7.28	7.28	7.15	7.03
20	7.25	7.29	7.13	7.00
15	—	7.29	7.10	—
19	—	—	7.14	7.04
Mean ...	7.32	7.31	7.15	7.02

It will be seen that whilst there is but a slight difference in the pH values of the blood from the maternal vein and artery—the vein having a slightly lower pH value—there is an appreciable difference between these and that of the blood from the umbilical vein and artery, both of which are more acid in this respect than the blood in the maternal circulation.

The lower pH values observed in the umbilical blood, as compared with the maternal blood, agree qualitatively with the lactic acid estimations; furthermore, the pH of the umbilical artery is appreciably lower than that of the umbilical vein, and this also agrees with the fact that the lactic acid content of the blood from the umbilical artery is usually higher than that from the vein.

The Lactic Acid Content and pH Value of Amniotic Fluid.

As illustrative of the current teaching in regard to the reaction of the amniotic fluid, Whitridge Williams²² may be quoted. He states: "According to Hoppe Seyler, the amniotic fluid is clear, *alkaline* in reaction . . ." (italics ours). A few analyses similar to those described above have been carried out with full-term human amniotic fluid. The results given below confirm the findings of Mendeléeff¹³ in regard to the pH value of this fluid; it is undoubtedly acid in reaction.

TABLE VII.—The Lactic Acid Content and pH Value of Amniotic Fluid.

Case No.		Umbilical Vein.	Umbilical Artery.	Amniotic Fluid.
21	Lactic acid	—	—	56
	pH	—	—	5.93
22	Lactic acid	—	—	32.1
	pH	—	—	5.67
19	Lactic acid	42.5	64	63
	pH	7.14	7.04	6.50

So far as these figures go there does not seem to be a complete relation between the pH value of amniotic fluid and its lactic acid content.

As already mentioned, the sugar content of a series of specimens of amniotic fluid from the parturient woman gave a mean value of 18 mg. per 100 c.cm.

The Alkali Reserve and the Oxygen Content of Foetal Blood.

The hydrogen-ion concentration of a fluid such as the blood, which contains only weak acids and their salts, has been shown to be equal to $\frac{(H_2CO_3)}{(NaHCO_3)} \times K$, where K is a constant, and the brackets denote concentrations. The significance of this equation is more apparent if it be written as follows: $K = (H) \times \frac{(NaHCO_3)}{(H_2CO_3)}$. If there is an increase in the hydrogen ions, which we have shown to be the case in foetal blood, there must be a decrease in the fraction $\frac{NaHCO_3}{H_2CO_3}$, since the value of K does not alter. This can be effected in two ways, either by decreasing the amount of $NaHCO_3$, or by increasing the amount of H_2CO_3 .

The amount of $NaHCO_3$, which is present in the blood is termed the "alkali reserve," and it is calculated as the amount of CO_2 which can be taken up by blood at a pressure of 40 mm. of CO_2 —that is, the tension of CO_2 , normally existent in the alveolar air.

We have succeeded in determining the alkali reserve of the blood in both the umbilical artery and vein by Van Slyke's method. Our object has been to determine whether the increase in the hydrogen ions which we have observed is due to alterations in the numerator or the denominator of the fraction in question. It might conceivably be due to either, and, if there were an increase in H_2CO_3 only, we should expect to find a normal or relatively high alkali reserve, in response to an attempt by nature to increase the $NaHCO_3$ of the blood with high tensions of CO_2 .

As a matter of fact, we have found a low alkali reserve in the foetal blood as compared with the maternal (Table VIII). This we consider to be due to neutralization of $NaHCO_3$ by excess of non-volatile acids, and we know that there is a higher level of lactic acid in the foetal blood (Table IV). We therefore conclude that the depletion of the alkali reserve observed is in whole or in part dependent on the presence of excess of lactic acid.

It will be noticed that the alkali reserve of the umbilical artery is higher than that of the vein. This is just the reverse of the values found in the maternal circulation, but we must remember that the umbilical vein is really arterial in function, and the umbilical artery venous.

The oxygen contents of foetal bloods have also been estimated by Van Slyke's method, and they are found to approximate corresponding values in the maternal circulation, in those cases that have breathed. Here again we must bear in mind the fact that the umbilical vein is arterial in function. It will be noted that although the oxygen content of the foetal circulation is much less than that of the maternal circulation in the cases in which the foetus did not breathe, the difference between the values obtained for arterial and venous blood is the same.

TABLE VIII.—Alkali Reserve and Oxygen Content of Foetal Blood. (Mean Values.)

	Oxygen Content, vols. per cent.		CO ₂ Combining Power, vols. per cent.	
Maternal artery (radial) ...	18.87		40.45	
Maternal vein (median cephalic)	15.44		43.45	
	A.	B.	A.	B.
Umbilical vein	18.78	9.02	36.9	37.7
Umbilical artery	17.6	5.85	37.7	40.0

A = Those that have breathed. B = Those that have not breathed, including two cases of Caesarean section in which the blood was obtained before the delivery of the child.

Table IX summarizes the related findings in the foregoing investigations. The connexion of the production of

lactic acid with the diminution of sugar, the oxygen content and alkali reserve, together with the pH values, are all of importance in drawing final conclusions concerning the mechanisms involved.

TABLE IX.—*Summarizing Table of All Experiments.**
Human cases—mean values.

	Glucose mg. per cent.	Lactic Acid, mg. per cent.	Oxygen, vols. per cent.		Alkali Reserve.		pH.
Maternal artery ...	112.6	32.5	18.87		40.45		7.32
Maternal vein ...	106.0	38.0	15.44		43.45		7.31
			A.	B.	A.	B.	
Umbilical vein ...	84.4	54.0	18.78	9.02	36.9	37.7	7.15
Umbilical artery ...	75.2	68.0	17.6	5.85	37.7	40.0	7.02

* In all the cases summarized in this table parturition was normal, except for the administration of anaesthesia in some.

A = Those that have breathed. B = Those that have not breathed.

Discussion of Results.

These investigations, designed primarily with the idea of examining as far as possible the function of the placenta in regard to the glucose metabolism and the production of lactic acid in aerobic conditions, which has been shown to be a special function of malignant neoplasms, have yielded interesting results.

First, the placental tissues have been examined in regard to aerobic glycolysis *in vitro*, and the chorionic epithelium alone has been found to have an action similar to that observed in the case of malignant neoplasms.

Secondly, the pH values obtained in regard to the placenta agree very closely with those obtained by one of us for malignant tissues (unpublished), and, moreover, it has been demonstrated that the younger the placenta the lower the pH value.

Thirdly, the blood concerned in the foetal circulation at full-term has been studied. It is much more difficult to draw final conclusions from observations made in this connexion, for the actual excretion of lactic acid into the maternal circulation cannot be deduced.

There are for decision two main issues: the extent to which the foetal metabolism is responsible for the lactic acid in the blood of the umbilical vessels, and the part, if any, played by metabolism of the chorionic epithelium in this respect.

With regard to the first, the view may be held that the chorionic epithelium at full-term acts merely as a semi-permeable membrane (as is suggested, for instance, by Lochhead),¹⁶ and at this period has neither selective activities like the renal epithelium, which is capable of concentrating urea, nor anabolic functions like the mammary epithelium, which after birth carries on the metabolic functions probably possessed by the placenta earlier in the gestation period. If, then, it be possible to exclude such active processes in regard to the syncytium of the full-term placenta, we may draw the conclusion that the lactic acid content of the umbilical vessels is then mainly of foetal origin.

The argument to be adduced in such circumstances is as follows:

The differences between the blood of the umbilical vein and artery obtained at delivery allow us to state that from each 100 c.cm. of blood passing through the foetus, the foetus on the average abstracts 3.2 c.cm. of oxygen and 9.2 mg. of sugar; 14 mg. of lactic acid are excreted, and the pH is lowered from 7.15 to 7.02.

Diffusion across the chorion is not an instantaneous process, and it must be expected, therefore, that the level in the umbilical circulation of a substance which is being actively removed by the foetus should be lower than its level in the maternal circulation. This is actually found to be the case for oxygen and sugar, while for lactic acid, which is being excreted by the foetus, the converse holds good.

As regards the pH level, this is lowered on passage through the foetus, probably mainly owing to the lactic

acid production, although the carbon dioxide resulting from respiration will doubtless contribute to the lowering. The bicarbonate concentration (alkali reserve) is probably slightly lower in the foetal circulation than in the maternal, while the pH is considerably lower; thus the carbon dioxide is higher in the foetal circulation, and we must, therefore, suppose that carbon dioxide is actively excreted to the maternal circulation.

The source of the lactic acid produced by the foetus at full-term is difficult to determine, since there is so little muscular movement and there is no evidence that at full-term foetal somatic epithelial tissues can glycolyse when well oxygenated. The chorionic epithelium can, of course, glycolyse, but at full-term in the human subject this tissue is reduced in amount, and therefore it may be surmised that its contribution of lactic acid is negligible compared with that of the foetus. If we had been considering a much earlier stage of pregnancy we should expect this state of affairs to be reversed; the trophoblast would be producing a relatively large amount of lactic acid, although at an early stage the foetus itself might show aerobic glycolysis in its somatic epithelial tissues.

There are two further points on which emphasis may be laid before a final conclusion is considered. First, it will be observed that the differences in lactic acid and oxygen contents between the foetal arterial and venous blood are of the same order as those which occur in the arterial and venous blood of the arm of the mother at full-term. The foetus is sufficiently supplied with oxygen, and there is no reason to suppose that its epithelial tissues glycolyse. Secondly, there is a period of many weeks' duration before the foetal circulation is established, when the chorion is particularly active, and in all probability shows its highest rate of glycolysis.

It is, however, as already indicated, difficult to arrive at a quantitative conclusion in the matter of the cause of the high lactic acid concentrations in the umbilical circulation at full-term, although there can be no doubt as to the importance of this finding.

SUMMARY AND CONCLUSIONS.

1. It has been shown that the chorionic epithelium behaves functionally like a malignant neoplasm.

(a) The pH value is on the acid side as compared with normal tissues, and the acidity is greatest in the earlier periods of pregnancy.

(b) This tissue, like cancerous neoplasms, has the power of aerobic glycolysis with the production of lactic acid. It has been suggested by Bierich that the infiltrating properties of malignant disease are due to the presence of lactic acid. If this be so, the same explanation probably obtains in regard to the invasive power of the syncytium.

2. A high lactic acid associated with a low glucose content has been found in the foetal blood; and a reduction in the pH, together with a diminution in the alkali reserve, has been demonstrated.

3. Certain foetal somatic tissues have been examined and have been shown to be acid in regard to their pH value.

4. The amniotic fluid has a low pH, and this is not entirely related to the lactic acid content.

5. There appears to be no deficiency in oxygen consumption so far as the foetus is concerned.

6. The source of origin of the lactic acid in the umbilical blood has been discussed.

7. The connexion between these findings and pathological states of the foetus and mother (toxaemias) has not yet been determined.

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HEREDITARY ICTERUS, OR FAMILIAL ACHOLURIC JAUNDICE.

BY

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THE following is a description of a family, some members of which show very distinctly an icteric tinge in the skin and conjunctivae. The title "hereditary icterus" would seem to be more accurate than the alternative "familial acholuric jaundice," for there was no splenic enlargement, and the jaundice does not affect either the duration or enjoyment of life.

Attention was first directed to a girl (IV 1), aged 10 years, about seven years ago. She was brought to me by her mother on account of jaundice. At the time this was thought to be an attack of catarrhal jaundice. There had been some slight malaise, but no prominent symptoms. On a subsequent occasion three years later she was seen on account of the same condition. In May, 1927, she was brought again for examination on account of jaundice and for an opinion as to her fitness for entry to a training college. She had now grown into a well made, strongly built young woman, full of vigour and with a zest for games. The skin and conjunctivae showed a distinct icteric tinge. The faeces were normal and the urine was free from bile. There was no enlargement of the spleen, and all the other organs were normal. Her mother informed me that when her daughter was bathing in the sea the parts of the body not covered by the bathing dress (neck, shoulders, and legs) became intensely red. It may be conjectured that this showed an abnormal sensitiveness of the skin to exposure to sunlight. A diagnosis of haemolytic jaundice was made, and a consultation was arranged with Dr. T. H. Oliver of Manchester. He saw her on June 2nd, agreed with the diagnosis, and arranged to have the blood examined at the clinical laboratory of the Manchester Royal Infirmary.

As I was aware that the girl's father (III 2), aged 49, also had a yellow tinge in his skin and conjunctivae, Dr. Oliver agreed to see him and arrange for a blood examination. After examination on June 16th Dr. Oliver decided that the father had the same condition as the daughter, but in a lesser degree. The father has a sister, aged 50, who has a yellow skin. She had an operation for gall stones some years ago, but no information is obtainable as to whether stones were found or not. She still has the yellow tinge in her skin.

The father informed me that he had a brother (III 4) living in another town who was quite pale and free from yellowness in the skin. I arranged to examine both brothers together in the daylight and so make a comparison. This was striking; the one was indeed a yellow man, while the other was a pale-face. Owing to the kindness and interest of Dr. Oliver, the pale brother's blood was examined at the Manchester Royal Infirmary. The results of the three blood examinations are given in detail. On making further inquiry into the history of the family, the father of my first patient informed me that his father,

who died in 1909, aged 64, had a yellow skin, but that his mother was pale and clear-skinned. He also remembers that his father's mother was yellow-skinned (she died in 1897, aged 78), and that his paternal grand-uncle was yellow-skinned. He died aged 81. My informant cannot remember his father's father.

A pedigree chart based on this information and on the facts observed can be constructed as follows (the members of the family who had yellow skins are indicated by an asterisk):

In estimating the value of the father's (III 2) observations on his grand-uncle and grandmother (I 1 and I 2) account of their advanced years must be taken into consideration, for they would then show some of the yellowing due to age, but this factor can be discounted in the other affected members in the pedigree.

Blood Examinations for Fragility of Red Corpuscles and Bilirubin Content of Serum.

IV 1.			III 2.			III 4.		
Solution Sod. Sulphate.	Haemo-lysis.		Solution Sod. Sulphate.	Haemo-lysis.		Solution Sod. Chloride.	Haemo-lysis.	
2% ...	10%		2% ...	5%		0.46% ...	Beginning	
1.75% ...	20%		1.75% ...	15%		0.4% ...	100%	
1.5% ...	40%		1.5% ...	25%				
1.4% ...	50%		1.4% ...	40%				
1.3% ...	70%		1.3% ...	70%				
1.2% ...	80%		1.2% ...	90%				
1.1% ...	90%		1.1% ...	100%				
1.0% ...	100%							

IV 1 shows increased fragility of corpuscles because haemolysis is not usually complete until solution is equal to 0.75%. Blood serum: 10 units of bilirubin—van den Bergh's indirect reaction. Urine: No bile salts or bilirubin.

III 2 shows increased fragility of corpuscles. Haemolysis is not usually complete until solution is equal to 0.75%. Blood serum: 5.7 units of bilirubin—van den Bergh's indirect reaction. Urine: No bile salts or bilirubin.

III 4 shows very slight increase in fragility of corpuscles. Blood serum: 1.4 units of bilirubin.

Commentary.

There will be general agreement that we have here an abnormal yellowing of the skin which has been transmitted through four generations. This yellowing is due to an abnormal increase of bilirubin in the blood serum arising from the destruction of abnormally fragile red corpuscles. The increase is greatest in IV 1, less in III 2, and almost normal in III 4.

According to van den Bergh the bilirubin content of normal human serum varies from 1 in 1,000,000 to 1 in 400,000, and taking as his unit 1 in 200,000, it would appear that the normal physiological limit varies from 0.2 to 0.5 of a unit, with an average of 0.3. Thus IV 1 has thirty times, and III 2 seventeen times, the average amount of bilirubin without signs of ill health, except the icteric tinge in the skin and conjunctivae. III 4 has five times the average amount, and in him the skin colour appears quite normal.

In 1905 Gilbert and Lereboullet¹ estimated the bilirubin content in the blood serum of 60 persons (31 men and 29 women), and came to the conclusion that there was a condition of simple familial cholaemia wherein the bilirubin content of the serum was more than double that in the normal physiological state. Although they used the term "familial" they did not show that the condition can be transmitted through the generations by genetic continuity. They also remarked that persons so affected showed the characteristics of the "*bilieux tempérament*." These are commonly supposed to be instability, ill temper,