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THE INTERACTION OF PREGNANCY AND ASSOCIATED DISEASE*

BY

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Until the early part of this century, when the importance of ante-natal care began to be realized, the subject of general medical diseases associated with pregnancy rather fell between two stools. While not wholly in the province of either the obstetrician or the physician, these diseases were generally regarded as "complications" of pregnancy and treated as such by the obstetrician. Nowadays the obstetrical specialist is almost always also a gynaecologist, and the strongly surgical trend of his gynaecological work directs him more to the study of surgery than of medicine. Recently the growth of endocrinology in relation to gynaecology has been leading him back in some degree to medicine, but I think it is true to say that the obstetrician and gynaecologist who has reached the charge of hospital wards has rarely been able to keep pace with the developments of modern medicine. That being so he ought to (and usually does gladly) seek the co-operation of a physician in regard to cases of pregnancy and labour associated with general disease. For the main burden of what I have to say to you is that the old view of these diseases as complications of pregnancy has now come to be recognized as looking at matters from the wrong end, and that these cases ought usually to be regarded as instances of pregnancy complicating general disease.

The train of my thought on this subject was started by reading about a year ago a brief and modest article in the *American Journal of Obstetrics and Gynecology* in which Drs. Allen and Bauer of Chicago summarized an analysis of 9,696 consecutive uterine pregnancies in their hospital service. Their conclusions were statistically tabulated, but they were also put into words which arrested my attention like a slogan. Thus: (1) "It was five times more dangerous for a woman affected with a medical disease to bear children than it was for a healthy woman"; (2) "A child born to a woman suffering from a medical disease was twice as apt to be stillborn as a child born to a healthy mother."

Statistics in Great Britain

This raised the question in my mind whether the association of general diseases with pregnancy was as significant a factor in relation to maternal mortality and morbidity in this country. I knew of no statistics comparable to those of Drs. Allen and Bauer because, while in American cities almost every woman goes to hospital for her confinement and their statistics of a consecutive series of cases may therefore be regarded as a very fair sample of the population, in this country the patients who go to the maternity hospitals are still only a variable proportion

of the population and represent a somewhat selected population. In the search for information on a large scale, from which alone a reliable estimate could be formed, I turned to the Interim and Final Reports of the Committee on Maternal Mortality and Morbidity in England and Wales, published in 1930 and 1932; and to the Scottish Report on the same subject, published in 1935 by Drs. Douglas and McKinley of the Department of Health for Scotland.

These reports together cover some 8,000 deaths, of which just under 25 per cent. were attributed to associated diseases rather than to any obstetric factors. In addition to this I sought information from two other sources. In the first place Dr. Charlotte Douglas of the Department of Health for Scotland kindly gave me access to the schedules concerning maternal deaths in Scotland which have occurred *since* the 1935 report was drawn up, and these were analysed for me by Dr. Dorothea Lang. Of 2,136 deaths she attributed 861—that is, 40 per cent.—to associated diseases. I regard this as probably too high an estimate, but it must be remembered that in making such an analysis there is a large personal equation, and that the schedules are often so sketchily filled up that in many cases more than one opinion might well be formed as to the primary cause of death. In the second place Dr. Lang also analysed the deaths in the Royal Maternity Hospital, Edinburgh, within the last fourteen years. Of a total of 462 she attributed 134, or 29 per cent., to associated diseases.

Here, then, we have four series of maternal deaths, two officially and two unofficially analysed; on the lowest computation 25 per cent. and on the highest 40 per cent. of the totals are attributed to associated diseases. That gives us a general idea of the dimensions of the problem. In passing it is of interest to note that in each of these series of deaths the same three disease groups are found to dominate the picture almost to the exclusion of anything else—namely, heart disease, non-tuberculous respiratory disease, and kidney disease.

The death of the mothers in these cases is not the whole of the tragedy; there is also the comparative fruitlessness of the fatal pregnancies; in other words, the effect of the diseases upon the pregnancies, or upon the health of the child if born alive, is the corollary to the dangerous effect of pregnancy upon the disease. The English reports give no information on this important point, but in the 1935 Scottish report, covering over 2,000 maternal deaths, we found that in only 40 per cent. was the child born alive. In the other 60 per cent. the mother had either died undelivered or before her death had aborted, or had been delivered prematurely or had given birth to a still-

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born child or to a living child which had not survived for more than a comparatively few days. That figure, of course, includes a very large number of obstetrical emergencies, and is not confined merely to cases of associated disease. But if we confine our attention to the latter and choose the main disease groups we obtain these figures:

Maternal Deaths due to:	Foetal Deaths:
Heart disease	59 per cent.
Non-tuberculous respiratory disease	70 "
Renal disease (including pyelitis)	68 "
Tuberculosis	55 "
Anaemia (? + malnutrition)	42 "

The corresponding figures for the 2,136 maternal deaths in Scotland investigated since 1935 showed:

Maternal Deaths due to:	Foetal Deaths:
Heart disease	65 per cent.
Non-tuberculous respiratory disease	57 "
Renal disease (including pyelitis)	60 "
Chronic and acute nephritis alone	76 "
Anaemia, malnutrition, debility	46 "
Tuberculosis	60 "

From the humane point of view this aspect of the problem is perhaps less important, but from the national standpoint in these days of a falling birth rate it is very significant.

Now it is obvious that to analyse any number, however large, of maternal deaths is by no means an accurate method of assessing the actual incidence of associated diseases, because it takes no cognizance of the patients who suffer from these diseases but survive. There is, so far as my knowledge goes, no accurate means of assessing the actual incidence of associated diseases in pregnancy, and I can present no figures parallel to those of Allen and Bauer. An attempt was made to gain some knowledge on this point in connexion with the investigation on which the 1935 Scottish report was based, for in the course of their analysis of the mortality figures the investigators felt that "much of the information could not be fully used without comparable details for mothers who survived. Accordingly an inquiry into the circumstances attendant upon all births in Scotland over a period of six months was instituted. It was purely voluntary, and the schedules were completed by the doctor or midwife." The returns, which were in many respects incomplete and imperfect, covered 39,205 births, and one rough conclusion which may be drawn is that in 10 per cent. of the mothers there was a definite deterioration in health during pregnancy, most of which was attributable to the coexistence of general diseases. How far this deterioration was permanent I have no means of knowing.

These morbidity figures for Scotland showed that the proportionate incidence of the more important disease groups was parallel to their proportionate roles in the mortality figures, with the striking exception of heart disease. Thus the incidence of non-tuberculous respiratory disease (including in order of frequency influenza, bronchitis, asthma, and pneumonia) was 3 per cent.; that of kidney disease 3.3 per cent.; and that of heart disease 0.9 per cent. It is surely a very striking commentary on its dangers that heart disease should be below 1 per cent. in its incidence in over 39,000 pregnancies in Scotland, and yet in both the English and the Scottish reports should be found responsible for over 4.9 and 7.5 per cent. respectively of the total maternal deaths from all causes, both obstetrical and medical, and in each series for about 25 per cent. of the deaths attributed to associated diseases.

So much, then, for the importance of these associated diseases in pregnancy. I have tried to show that they

account for something between one-quarter and one-third of maternal deaths, and that in those mothers who survive they cause definite ill-health in some 10 per cent. of cases. Lastly, they are accountable for a huge wastage of foetal and neo-natal life.

Some Interesting Problems

My next point is that the association of medical diseases and pregnancy presents us with some peculiarly interesting problems. Disease means that some organs are partially disabled. Pregnancy means that increased demands are put on all the mother's organs. Therefore, if pregnancy occurs in a woman who is already suffering from disease it superimposes conditions of strain upon already disabled organs; while if disease originates after the pregnancy has already begun it introduces an element of disablement to the pre-existent conditions of strain. Further, it may be assumed that the pregnancy-strain element is capable of being assessed with some approach to accuracy, while the influence of the disease is generally less capable of measurement. We are therefore dealing with the interaction of two sets of factors—one more or less known, the other more or less unknown—and the situation partakes of the character of a clinical experiment. To watch how the diseased organs behave under the new conditions becomes a fascinating study, while to determine whether the experiment may safely be allowed to continue or whether and just when it must be interrupted calls for the exercise of a wide knowledge and a nice judgment.

It is not necessary to recall to your recollection all the physiological changes in the maternal organism produced by pregnancy. The fact that only the woman of perfectly sound health of body and mind can adapt herself to the new conditions without suffering from some symptoms of difficulty is familiar to us all, as is also the significant fact that such a woman feels triumphantly and exuberantly well during pregnancy, presumably because all her organs are working under high pressure, so to speak, yet without undue strain. But so complex is the necessary adaptation that if disease exists the affected organ is liable to suffer further detriment, while in other cases an occult weakness may become revealed for the first time during pregnancy. May I try to illustrate my thesis by one or two examples?

Cardiac Disease

Consider, for example, diseases of the heart, most commonly chronic endocarditis of rheumatic origin. For my purpose it matters not what the exact nature of the heart lesion is, nor even whether the organic defects are or are not fully compensated. The point is that soon after pregnancy begins the heart enters upon a period of progressive strain which may last for several weary months and culminate in the severe muscular effort of labour.

That the normal heart is able to bear the strain of pregnancy and labour is obvious, and I do not suppose that with healthy patients we often give any thought to the matter. But that astute and painstaking observer the late Sir James Mackenzie has told us that even the healthy heart does give indications of the strain of pregnancy. Probably all of you who are especially interested have read his classical monograph on *Heart Disease and Pregnancy*—a little book which is full of wisdom of a much wider application than its immediate subject, salted with devastatingly candid criticisms of both obstetricians and physicians. That sagacious old Scot, in some respects so reminiscent of Thomas Carlyle, based his statement characteristically on his own personal observation of such signs as the restriction of the response to effort, on the

slight tendency to oedema at the bases of the lungs recognizable only on careful auscultation, on the tendency to overfilling of the veins of the lower limbs, and on the pulsation of the jugular veins. He summarizes his views in these words: "It is perfectly evident that in the pregnant state, towards the later months, the heart is embarrassed in healthy women; for the woman is not capable of so much exertion as she was accustomed to undertake, and becomes breathless during efforts which at other times would not have inconvenienced her." If we accept Mackenzie's statement then, *a fortiori*, the diseased heart is bound to manifest more obvious reactions to the same conditions, and it is the detection and proper evaluation of these that is the practical problem.

Now it is no part of my purpose to discuss the methods of detecting incipient heart failure, of preventing its development, or of treating it when once declared. These points are familiar to you all. I would, however, just summarize the experience we have had in the Royal Maternity Hospital, Edinburgh, where Dr. Rae Gilchrist acts as our advisory physician. On the whole that experience in the last twelve years has tended to imbue us with a tempered optimism, provided we get these patients under our supervision early in pregnancy. For we never see in such women the advanced degree of congestive heart failure often found in women admitted as emergency cases later in pregnancy. This is obviously *a point of very wide application*, for if congestive heart failure can be avoided by adequate treatment and supervision under the conditions of strain imposed by pregnancy, then all the more can similar care avert heart failure in non-pregnant patients. Dr. Gilchrist attributes such success as we have achieved to prolonged rest in bed, to the use of large doses of digitalis on modern lines, and to the exhibition where necessary of the extraordinarily efficacious diuretics of the mercurial type such as salyrgan, neptal, and novurate.

A second point is that the study of heart disease in pregnancy demonstrates impressively the enormous power of even a *damaged* heart to adapt itself to a gradually increasing burden, and even to post-operative shock and anaesthesia, provided congestive failure is not present. The key to that statement surely lies in the words "a gradually increasing burden," for it is a physiological truism that all our organs have an amazing power of adaptation provided the stress is applied gradually.

Thirdly, we have been impressed with the futility of any operative procedure in the presence of congestive heart failure. It is the straw that breaks the camel's back. As our experience has increased we have found ourselves gradually doing fewer Caesarean sections in heart cases, because we have seen that ordinary labour is surprisingly well borne. The labours of cardiac patients are indeed often remarkably and inexplicably easy. A fair proportion of them occur prematurely, and in these the small size of the baby makes for an easy labour. But even at full time the labour is often unexpectedly easy.

Fourthly, the danger is not always completely over when the labour is passed. In patients who have shown any pronounced degree of heart failure before labour, exhaustion of the cardiac reserve sometimes occurs suddenly and fatally a few days later. Care must therefore not be relaxed.

Fifthly, it is remarkable how slight is the embarrassment induced by pregnancy in cases of congenital heart disease. This teaches us that the prognosis must be better for such of these individuals as reach puberty than might be supposed. Congenital cases are but a small percentage

of the total coming under observation in any ante-natal clinic, but we have not seen one go on to any sign of congestive failure. This contention is to some extent supported by individual cases reported in the literature—for example, Firket's patient, a woman with combined mitral stenosis and auricular septal defect, who had eleven uneventful pregnancies and three abortions and lived to be 74 years of age.

Lastly, our experience seems to show that death from congestive heart failure in young or middle-aged married women could be prevented or postponed if, after one or two pregnancies, more of them were sterilized. It not infrequently happens that having weathered one or two pregnancies successfully a woman, after an interval of some years, during which in all probability contraception has been practised, presents herself at the hospital about the sixth month or later with early signs of heart failure. Such cases do badly: sterilization earlier might well have prolonged the life of such a patient.

Anaemia

I turn next to anaemia as a subject in which medicine and obstetrics have found much common ground in recent years and in which the contact has been the means of considerably advancing knowledge. The fact that the tissues of women in pregnancy are unduly filled with fluid has long been observed, and the old clinicians used to attribute it to what they described as "the plethora of pregnancy."

When the study of the blood began to be placed on a scientific basis it was recognized that in pregnancy the increase in the quantity of the body fluids was due not strictly to "plethora" but rather to a dilution of the blood by an increase in its fluid constituents. In recent years numerous observers have carried out repeated systematic observations of the blood of pregnant women at frequent intervals throughout the whole period of gestation and the puerperium, and from these observations it appears that there is uniformly a definite fall both in the number of red cells per cubic millimetre and in their haemoglobin content. This fall occurs towards the end of the third month, reaches its lowest point about the seventh month, and persists to about a fortnight before term, when conditions usually improve. Within a fortnight after delivery there is a rapid improvement, which continues during the next few months, and by six months after delivery the blood should be once more in a normal condition.

We have also come to appreciate in recent years how very real are the demands which the upbuilding of the foetus makes upon the mineral constituents of the maternal blood through the placental interchanges, and that unless the mother's diet contains an adequate supply of these substances her blood and tissues will become depleted of them to an extent which may cause more or less serious symptoms. The "harmonious symbiosis" which may be said to describe the relation of mother and foetus in a healthy pregnancy under perfectly hygienic conditions thus degenerates into something indistinguishable from foetal parasitism in the undernourished mother. The principal demands are for iron, calcium, and phosphorus. The possible depletion of the mother's tissues in respect of calcium is well known in connexion with the teeth and with the disease of osteomalacia, while more recently it has been considered as a possible explanation of uterine inertia in labour. If in spite of drawing upon the mother's resources the foetus remains short of calcium and phosphorus the result is seen in a predisposition to

rickets after birth. But in relation to anaemia our main interest is concerned with iron; for while there is no direct transference of blood from the mother to the foetus, yet the latter has to derive from the former the materials for making its own haemoglobin. This, as Strauss and Castle point out, means the equivalent of a definite blood loss in every pregnant woman, even in the absence of any actual haemorrhage. Moreover, as the same authorities have proved, "no matter how anaemic the mother, the infant is born with a normal amount of haemoglobin."

Bunge has shown that the milk of a bitch contains the same quantities of mineral substances as the tissues of its offspring except iron, which is present in the tissues of the offspring in a quantity six times greater than in the mother's milk. This store of iron gradually diminishes during the period of lactation, but increases again when the young animal begins to take a mixed diet. In other words, the offspring has a store of iron at birth for the purpose of supplying that substance during the weeks in which it is fed on its mother's milk, which is poor in iron. Hugounenq confirmed these findings in general with regard to the human foetus. Weight for weight the liver of the newborn child contains five times more iron than that of its mother, and this store is apparently accumulated in the last three months of its intra-uterine existence—a point to be linked up with the observation that the loss of red cells and haemoglobin is greatest at this period of pregnancy.

Still another factor has come to be recognized during observations upon pregnant women—namely, the influence of functional disturbances of the gastric secretions. Nearly thirty years ago Faber of Copenhagen showed that the proportion of total and of free hydrochloric acid in the stomach has a direct bearing upon the absorption of iron from the food. The proportion of acid in the stomach varies considerably in different individuals, but Strauss and Castle found that the great majority of the women they studied during pregnancy had a marked deficiency.

Here, then, we have abundant evidence that in pregnancy the haemopoietic system is labouring under a strain. In the healthy woman on an adequate diet it can adapt itself to the conditions of strain without either serious symptoms occurring or lasting damage being wrought. But if the woman be already suffering from anaemia when pregnancy occurs, or if her diet be inadequate in the essential constituents, we have again a condition of what I may call a clinical experiment superimposed by the occurrence of pregnancy.

Thus the physiological hydraemia of pregnancy, combined with dietetic deficiency and possibly some slight hypochlorhydria, may adequately account for the common but mild anaemia of the hypochromic microcytic type. Obviously there may be also other factors at work, such as unhygienic surroundings, and toxic conditions such as chronic nephritis, pre-eclamptic toxæmia, or pyelitis, as well as actual blood loss from obstetrical complications.

Occasionally we meet more severe anaemias of the same type—women with red counts of $3\frac{1}{2}$ millions or less and haemoglobin below 45 per cent.—which are essentially due to the same factors. But Fullerton of Aberdeen, who has studied the subject carefully, believes that in these cases the women were suffering from a definite anaemia before the pregnancy ensued. Both these forms are susceptible to treatment by large doses of iron with hydrochloric acid, fortified if necessary by a proper diet and hygienic surroundings.

The severe hyperchromic macrocytic anaemia of pregnancy is relatively rare in this country, although so common in India as to constitute one of the major dangers of reproduction. Both the clinical picture and the blood picture resemble Addisonian pernicious anaemia. The most important point of difference is that the disease clears up when the pregnancy ends and does not tend to recur (in the absence of another pregnancy), whereas true Addisonian pernicious anaemia of course has that tendency. Strauss and Castle have shown it to be due to much the same mechanism as true pernicious anaemia. It will be recalled that this involves an essential reaction between an intrinsic stomach factor present in normal gastric juice and an extrinsic dietary factor associated with vitamin B. In their cases Strauss and Castle found that in pregnancy the breakdown was due to the temporary absence of the intrinsic stomach factor combined with an iron deficiency resulting from foetal demands or dietetic errors, or both. Iron, liver extracts, and occasionally transfusion of blood are the lines of treatment, and not infrequently the pregnancy has to be interrupted.

Here again we have an example of the interaction of the physiological strain of pregnancy and the processes of disease. Here also, I submit, is a field for co-operation between physician and obstetrician.

Polyneuritis

This modern conception of certain anaemias as deficiency diseases naturally led my thoughts to another sometimes associated with pregnancy—namely polyneuritis, in regard to which a similar aetiological claim has been put forward. This is generally regarded as a rare condition, but it is probable that it sometimes escapes diagnosis and that its rarity is more apparent than actual. Most often it occurs in a woman who has been suffering for a considerable number of weeks from hyperemesis gravidarum, so that it usually makes its appearance about the fourth or fifth month of pregnancy. The early symptoms are vague and mainly subjective—extreme weakness and hyperaesthesia of the skin—and there is only too much reason to believe that these have occasionally been looked upon as merely further hysterical manifestations in a woman thought to have been suffering from so-called neurotic vomiting. When actual paresis of the muscles appears and tendon reflexes disappear the condition becomes much more recognizable. Still later there ensues a state of mental confusion and obfuscation, of the type found in association with alcoholic neuritis (Korsakoff's syndrome) and characterized by loss of a sense of place and time and of recent memory. Regarded as a rare form of pregnancy toxæmia and treated as such even to the point of therapeutic abortion, polyneuritis in pregnancy has proved a very fatal condition. Plass and Mengert collected twenty-eight cases from the literature, with a mortality of no less than 68 per cent. My own experience is very limited, but I can recall four cases which corresponded to the description given, although an accurate diagnosis was made in only one. One of these patients died during an induced delivery, and the others very slowly recovered after the artificial termination of pregnancy.

Theobald first drew attention to the striking similarity between this disease in pregnancy and the endemic form of polyneuritis known as beriberi. It is stated that the pathological degenerative changes in the nervous system are identical in the two conditions. Beriberi is accepted as being due to a deficiency of vitamin B₁, which is now accordingly spoken of as the antineuritic factor.

Now experiments on animals show that during pregnancy there is a transference of vitamin B from the mother's tissues to the foetus, as well as to the mammary glands, for the functions of which it is essential. In a healthy woman on an adequate diet this drainage of vitamin B can be compensated without the appearance of deficiency symptoms. But if the woman is vomiting severely, a vitamin B starvation is caused along with starvation in respect of all other elements of diet, and in some cases a polyneuritis may apparently result. On the other hand, dietary deficiency alone may cause it in pregnancy, for the condition is much commoner in those parts of the world in which beriberi is endemic—that is, in which a large proportion of the population exist on a diet deficient in vitamin B. In these latter cases the superimposition of what I have called the experimental conditions of pregnancy with its increased demand for vitamin B may thus reveal for the first time a pre-existing but hitherto occult deficiency in the mother's tissues. Lastly, some evidence is slowly accumulating of the good results of prompt treatment of the condition by a diet rich in vitamin B or by concentrated extracts of the vitamin.

Such is the argument. Whether we can as yet adopt this new view in its entirety may be open to debate. What is not in doubt, as it seems to me, is that it offers a small but most interesting field for co-operative research by neurologists and obstetricians, and teaches us, when we are treating prolonged cases of hyperemesis, to keep a watchful eye upon the nervous system and to see to it that an adequate supply of vitamin B is provided in such diet as the patient is able to assimilate.

Diabetes

Diabetes mellitus is another disease sometimes associated with pregnancy in which the interaction of the physiological and the pathological conditions provides an interesting study. It is, I think, undoubtedly true to say that the discovery of insulin and the increasing understanding of the whole subject of carbohydrate metabolism which has followed it have robbed the association of pregnancy with diabetes of its former terrors. But that does not mean that the association is no longer fraught with considerable risk to the mother and even more to the foetus. For one thing, the treatment of diabetic women with insulin is making the association much more frequent than before. In pre-insulin days it was definitely rare, because the diabetes brought about a depression of ovarian activity and an atrophic condition of the whole genital tract which militated against the occurrence of conception. Nowadays if, under insulin, the diabetic woman can be kept in approximately normal health, her whole endocrine system, apart from the pancreas, may function as in a normal woman, and there is nothing to prevent conception. The evidence of diabetic clinics is clear on this point.

The occurrence of conception in a diabetic woman is, however, another example of physiological conditions of extra strain being superimposed upon a disease. If we consider the influence of pregnancy upon the carbohydrate metabolism of the healthy woman we find evidence of strain or at least of a disturbance of the normal conditions. Apart from the accepted increase in the basal metabolic rate, which is probably linked up with increased endocrine activity, the most obvious example of this is the frequency with which sugar appears in the urine during pregnancy. For this, as you are aware, there are several possible explanations. The sugar may be lactose, about which I would only say that while

lactosuria is common enough in the puerperium it is not in our experience very common in pregnancy. Moreover, the recognition of lactose by the appropriate tests does not by any means exclude, and may even mask, a more significant glycosuria, unless tests are applied for glucose also.

In the second place, the glycosuria may be of the so-called alimentary type, or, as Skipper prefers to call it, "the impaired carbohydrate tolerance of pregnancy." This is due to the liver being less able than usual to synthesize and retain glycogen, so that the ingestion of any considerable quantity of carbohydrate is followed by hyperglycaemia and glycosuria. So commonly is this condition found in the first three months of pregnancy that it was propounded as a diagnostic test for early pregnancy by Frank and Nothman, and the so-called adrenaline and phloridzin tests are essentially just modifications of it. But none of these tests has the degree of specificity and uniform accuracy necessary for that particular purpose. While not of itself serious, alimentary glycosuria is important, because it is almost impossible to differentiate it from a mild but true diabetes *during pregnancy*. After delivery the glycosuria of true diabetes persists, the other disappears.

In the third place, glycosuria in pregnancy may be, and probably most commonly is, due merely to a lowering of the renal threshold for sugar. The cause of this increased permeability of the kidney is not understood, but it is legitimate to speculate that it is connected with the activity of the anterior pituitary lobe.

There is still another apparently physiological point to be considered—namely, the frequency with which acetonuria occurs in pregnancy. Lambie in his masterly review of the subject states that acetonuria occurs in more than 30 per cent. of normal pregnancies. It indicates, of course, that there is a disturbance in the normal proportion of fats and sugars undergoing simultaneous combustion in the body and a significant rise in the ratio of ketogenic to anti-ketogenic substances. Lambie attributes the acetonuria in part to the lowered carbohydrate tolerance which we have discussed and in part to the demands of the foetus for carbohydrate. But whatever be the exact explanation of the phenomenon there is no question that it complicates in some measure the ease of estimating the significance of a glycosuria, just as it increases the difficulty of controlling the condition by diet and seriously increases the risk of coma in actual diabetics.

I need not dwell upon the dangers of pregnancy to the diabetic mother, because whereas Matthews Duncan in a famous communication in 1882 painted a very gloomy picture, and Whitridge Williams in 1909 collected sixty-six cases with a maternal mortality of 27 per cent. at or shortly after labour (mostly in coma) and an additional mortality of 23 per cent. within two years, yet the records since 1923, when insulin became available, tell quite another story. Thus Skipper collected 118 cases with an immediate maternal mortality of only 9.3 per cent., and in thirty-three cases under his own observation at the London Hospital there was no immediate mortality. In the Royal Maternity Hospital in Edinburgh during the last ten years we have had twenty-one patients with diabetes, two of whom have been under our care for two pregnancies each. Of these twenty-three cases, three left the hospital before delivery and have not been traced. But among twenty deliveries in eighteen patients there was no maternal mortality, although it has been impossible to follow the patients up and find out the ultimate results.

While, therefore, the outlook for the diabetic mother has enormously improved, there has been no corresponding improvement regarding the influence of diabetes upon the pregnancy, for the foetal mortality still remains tragically high. Abortion is very common in diabetics, and intra-uterine death in the later weeks adds to the toll; while not infrequently its undue size causes the death during delivery of many a foetus which has survived until term, and yet others die shortly after birth. In Williams's pre-insulin series of cases the foetal mortality, including abortions, was 41 per cent. In 136 pregnancies collected by Skipper the foetal mortality was 45 per cent., and in the thirty-seven pregnancies which he himself observed it was 40.5 per cent. In our twenty pregnancies in the Royal Maternity Hospital in Edinburgh the foetal mortality was 35 per cent.

Priscilla White, writing from Joslin's special clinic in Boston, gives an interesting series of figures. In cases in the pre-insulin era the stillbirth and abortion rate was 44 per cent. After the introduction of insulin there was a reduction in the foetal mortality to 34 per cent., while in cases under the direct and careful observation of the clinic it amounted only to 23 per cent. "Stillbirths and the macerated foetus of the giant type," she writes, "are nearly as characteristic of diabetic pregnancies which are allowed to come to term as they were in the pre-insulin era." Her solution of the problem is the delivery by Caesarean section of "the fully developed but chronologically premature infant." Whether we agree with that view or not, her figures, and those others that I have quoted, are an eloquent plea for the careful ante-natal supervision of such patients by a physician well versed in the management of diabetes, and a clear proof that all such cases must be treated on strictly individual lines and not by any mere routine. For treatment to be fully successful it seems to me that co-operation between the obstetrician and the physician is a *sine qua non*.

Conclusion

I have chosen these three or four diseases to illustrate my thesis that their association with pregnancy can be understood only in the light of the physiological strain of pregnancy. Other examples might equally well have been chosen. I was tempted, for instance, to refer to the temporary benefit in phthisis brought about by the physiological ascent of the diaphragm, compressing the lung and closing up cavities; and to the disastrous relapses which follow the abrupt and ruthless removal of this factor when the uterine tumour suddenly subsides after labour. I was tempted also to refer to kidney diseases, in which the physiological strain is so subtle and so uniform that, as Gibberd has succinctly expressed it, "pregnancy is the best test of kidney function." But these are large subjects, and to have indulged myself would have been to put a wholly unwarrantable tax upon the kindly patience with which you have listened to me.

If I have succeeded in interesting you in my main thesis you will find additional interest in working out its application in these and in other conditions at your leisure.

The London hospitals have received during the past year a present of over 5,000 gramophone records by the courtesy of the B.B.C. and the record manufacturing companies. These records, which have been used for broadcast purposes, are delivered to the hospitals free by the Gramophone Company in accordance with a schedule drawn up by King Edward's Hospital Fund for London in collaboration with the B.B.C.

CALCIUM AND PHOSPHORUS DEFICIENCIES IN A POOR HUMAN DIETARY

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Dietary surveys and experiments on the feeding of milk and other supplements to children and adults suggest that the diets of various classes of the population both in this and in other countries may be deficient for the maintenance of health. These observations in groups of human beings have led to experiments in which rats were fed on diets similar to those in common use among people whose nutritional state was being studied. One of the best-known of these experiments is that of McCarrison (1926-7), in which a striking parallelism was shown between the health and physique of rats and the health and physique of different tribes in India whose diets were fed to different groups of rats.

In an experiment of this type Orr, Thomson, and Garry (1935) maintained a large colony of rats for two and a quarter years on a diet which approximated the average diet eaten by a working-class community in Scotland as ascertained by dietary survey (Davidson *et al.*, 1933). Another colony received the survey diet with the addition of green food and unlimited milk. Four generations of animals were reared. The rats on the human dietary supplemented with green food and milk were quite normal, and in all respects were equally as healthy as rats kept on the Rowett Institute stock diet (Thomson, 1936). On the other hand, with a similar environment and heredity, the animals fed on the survey diet alone showed a slightly impaired reproductive capacity, a considerably increased death rate, a retarded rate of growth, a lowered haemoglobin content of the blood, and a clinically poorer condition. It was thus shown that the addition of green food and milk converted a deficient human diet into one that was adequate, though Orr and his co-workers were unable to state which factor or factors in this diet were responsible for the benefits obtained.

An analysis of the diet showed that it was very deficient in calcium and phosphorus, and the addition of green food and milk greatly increased the content of these elements. The hypothesis that this deficiency might be a major factor in the difference in health and physique of the two groups of rats was strengthened by the fact that numerous experiments with large animals have demonstrated that calcium and phosphorus lack is a common cause of deficiency disease, retardation of growth, and low viability in young at birth (Osborne and Mendel, 1918; Elliot, Crichton, and Orr, 1922; Elliot and Crichton, 1926). Orr (1930) has reviewed the influence of mineral salts in stock feeding, showing the benefits of adding calcium and phosphorus in various forms to the rations of pigs, cattle, and poultry. Similar deficiencies may occur in human diets. A survey made of 607 diets in Scotland in 1926-7 (Orr and Clark, 1930) showed that as family income fell the diet became poorer in calcium. In 205 of the families the intake was less than 0.3 gramme per head per day. In a feeding experiment with the children of these families it