THE CLINICAL SIGNIFICANCE OF THE BASAL METABOLIC RATE IN PREGNANCY.

by

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INTRODUCTION.

It has been known for many years that diseases of the thyroid gland produce alterations in the basal metabolic rate. The disturbance of the respiratory metabolism after removal of the thyroid experimentally in animals was noted very early by various observers - Maier (1897); Baldoni (1899); Smith (1894); Michaelson (1889). The results of these investigators, however, were vitiated by the fact that they failed to appreciate the effect of the simultaneously removed parathyroids. Later it was shown by many workers, among whom may be mentioned Juschtschenko (1923), Cramer and McCall (1917) Grafe and von Redwitz (1922), that even when this error was avoided, a diminution of the respiratory metabolism resulted from thyroidectomy.

The first clinical observation of the effect of the thyroid on metabolism

was that of Müller (1893) who, from a study of the food-intake and the body-weight changes in a patient with exophthalmic goitre, came to the conclusion that the tendency towards emaciation was explicable only on the grounds of a high metabolism. Two years later Magnus - Levy (1895) found in severe cases of myxoedema, a lowering of the metabolic rate to as much as 50 per cent below normal, while in cases of exophthalmic goitre, he observed a marked increase of the metabolism. Magnus - Levy also demonstrated the increase in metabolism after the ingestion of thyroid extract. These early clinical findings of Magnus - Levy were followed in subsequent years, by confirmatory results obtained by many other investigators.

Du Bois (1916) found out by calorimetric studies that very severe cases of exophthalmic goitre showed an increase of metabolism of 75 per cent or

more above normal. Less severe cases showed increases up to 50 per cent above normal.

In a cretin 36 years of age he found a heat production about half that of a child of the same size and weight and about 20 per cent below the normal for an adult of the same surface area. Three and a half days of treatment with thyroid extract raised his metabolism to normal.

Means and Aub (1919) found abnormally low metabolic rates in severe cases of myxoedema and noted an increase in metabolism following thyroid therapy to or above normal. Later, Means and Burgess (1922) wrote "We believe that in doubtful thyroid cases, provided that, in the first place a true basal rate is secured, and, provided that certain well-recognised causes for increased metabolism, such as fever, acromegaly, leukaemia and severe anaemia are excluded, the finding

of an increased basal metabolic rate is strong presumptive evidence of hyperthyroidism. In a similar way, provided that such conditions as starvation, hypopituitarism, and hyposuprarenalism are excluded, a low metabolic rate is strong evidence of hypothyroidism. To that extent, then, the metabolism test is distinctly useful in differential diagnosis. Like all other laboratory tests it should only be interpreted with due regard to all other clinical and laboratory findings, and with due regard for its limitations and pitfalls."

Basal Metabolism - Historical Survey.

The study of the heat-output of the animal organism may be said to have begun with the investigations of Crawford (1779) in Glasgow, and Lavoisier and de la Place (1780) in Paris. These two investigations seem to have occurred almost simultaneously, but considering

the difficulty of communication at that time, there can be little doubt that they were independent. Pride of place goes probably to Crawford, his experiments being reputed, according to the preface of the second edition of his "Experiments and Observations on Animal Heat", to have been performed in Glasgow in the year 1777 and communicated to the Royal Medical Society in the following year. The first edition of his treatise is said to have been published in 1779, while Lavoisier and de la Place's experiments were first published in 1780.

Both Crawford and the French investigators, in their experiments, attempted to measure the heat given off by a guinea-pig and also the amount of carbon dioxide produced by the same animal. For this purpose, Crawford used a water calorimeter, Lavoisier and de la Place a calorimeter containing ice, the heat evolved in the calorimeter being

measured by the weight of water resulting from the melting of the ice. Having made their observations on the animal, they then observed how much heat was produced in the burning of carbon or of a tallow candle within their calorimeters, and, applying the results so obtained, found, in their animal experiments, that a fair agreement existed between the heat produced by the animal and its carbon dioxide excretion.

Their interpretation of these results differed, however. Crawford, an adherent of the 'phlogiston' theory, believed that the animal was capable of abstracting heat as such from the air that it breathed, and that it was this air-borne heat which it gave off from its body. He said that "Since it has been proved that elementary fire is absorbed from the air in the process of respiration, and since the quantity that is thus absorbed is not only adequate to the

effect which we have been endeavouring to explain, but also proportional to it, we may safely conclude that it is the true cause of animal heat." While he spoke thus of 'elementary fire' he said:- "I do not mean to assert that elementary fire is really capable of being chemically combined with bodies. Before this can be admitted it must be proved that heat is a substance; and I do not know that any experiments have hitherto been published which demonstrate the materiality of that principle."

Lavoisier, on the other hand, regarded the animal heat as being derived from heat produced in the lungs by the transformation of the 'pure air' into 'fixed air'. The air respired therefore served two functions; it took away the precursor of the 'fixed air' from the blood, of which an excess, as Lavoisier said, would be very injurious; at the same time, the change of pure air

to fixed air was a combustion, similar to the combustion of carbon, occurring within the lungs themselves. By this combustion, heat was developed, without flame because the heat was rapidly absorbed by the moisture of the lungs, and, becoming transferred to the blood, was carried through the whole animal system.

Somewhat later, Lavoisier and Séguin (1789) investigated the differences between the working and the resting metabolism. While details of the apparatus used are not available, it is probable that they made use of a method similar to those in use at the present time, as drawings show the subject provided with a mask. Although their results were not quantitatively accurate, Lavoisier and Séguin demonstrated an increase in metabolism during work and after the consumption of food. It is interesting to note that Lavoisier estimated both the CO_2 production and

the O_2 intake, and that, during the resting experiments, required that the subject be in the fasting condition, in a state of muscular repose, and surrounded by an environmental temperature of 26°, on a thermometer with a scale of 80 divisions; precisely the conditions demanded in an estimation of the basal metabolism at the present day.

Lavoisier's conception of the animal heat being due to a combustion in the lungs was refuted by Lagrange (1791) on the grounds that, if a sufficient quantity of heat were generated to account for the whole output of heat, the lungs would reach such a high temperature as would cause their destruction. Considerable controversy raged around this point until 1839, when Magnus (1837), from his work on the blood-gases, came to the conclusion that combustion occurred in the capillary system throughout the whole body.

Some years previously the Academie des Sciences in Paris had offered a prize for the best essay on the origin of animal heat, a prize which was competed for by Despretz and Dulong and was won by the former. Despretz whose work was published in 1824, showed that, in rabbits and cats, 74 per cent to 90 per cent of the animal's heat-output could be accounted for by the combustion of carbon and hydrogen within its body. Dulong, whose work was not published until 1841, though his essay was read before the Academy 19 years earlier, from similar experiments, concluded that 69 per cent to 80 per cent of the animal's heat was due to combustion going on within it.

In 1842 Mayer enunciated the principle of the law of conservation of energy, and emphatically refuted the theories of Liebig, that, in the animal organism, physical force or energy could

be produced by an unknown 'vital' force. The controversy thus started directed many investigators towards the problem of studying the intake and output of energy in the animal body, this type of experiment culminating in the classical work of Rubner. Rubner (1885), in Voit's laboratory, began making a series of calorimetric researches into the heat value to the body of the various proximate principles of the food, and ultimately, in his own laboratory at Marbur, devised an accurate animal calorimeter for dogs, with which he demonstrated conclusively that, if accurate computations of the energy-intake in the food were made, and the heat-output were equally accurately measured, the law of conservation of energy could be shown to hold for animals (Rubner; 1894). About this time Atwater (1897) began to devise a calorimeter which could measure the heat-output in man, and, with the assistance of Rosa, a

physicist, constructed a chamber capable of measuring heat produced within it with an error of only 0.01 per cent. With such an apparatus, Atwater and Benedict (1902) demonstrated that in the average daily results for forty days in their subjects, the difference between the energy as calculated from the food combusted and the energy as actually measured was only 0.2 per cent, an irrefutable demonstration of the truth of the law of conservation of energy in man.

Definition of Basal Metabolism.

The term 'Basal Metabolism' arose as a translation of the German word 'Grundumsatz' originally used by Magnus-Levy, one of the very earliest workers on basal metabolism and its pathological variations.

The aim of a basal metabolic determination, as ordinarily done, is to measure the metabolism of the subject when

it is at a minimum value. To this end, one must diminish, as far as possible, the three factors that increase the heat-output, which, as shown by Lavoisier (1789) in the first metabolic determinations ever made, are, (1) the performance of muscular work; (2) the digestion and absorption of food; and (3) a low environmental temperature.

The term 'basal metabolism' as commonly used, is therefore defined as the heat-output, expressed in large calories per sq. meter of body surface area, of an individual lying at muscular repose, twelve to fifteen hours after a meal, and sufficiently covered to be comfortably warm. One must, however, differentiate between the 'basal metabolism as so defined and true basal metabolism, the real value of which has never been assessed. The true basal metabolism corresponds to the minimum chemical activity compatible with the

maintainance of life, a minimum, which, in actual fact, is never measured, since a subject, even though restricted within the conditions laid down in the above definition, maintains his cardiac, respiratory, and renal functions at a level considerably in excess of that absolutely essential to life, and moreover, though by the above restrictions apparently surrounded by an environment devoid of stimulation, he is probably still under the influence of many stimulating factors too subtle for our recognition or control.

The adjective 'basal' implies something fundamental and unchangeable, but, in this sense, 'basal' as applied to metabolism is a misnomer, for not only are the inter-individual variations considerable as has been shown by many workers on the subject and particularly by Benedict and Harris, but even the values obtained from the same individual

under the best conditions of technique still present considerable variations.

Krogh (1916) has objected to the term 'basal metabolism' on this very ground of inconstancy and suggests that the term 'standard metabolism' should be substituted for it. According to Krogh "the basal metabolism of an organ is not a constant quantity but can be modified experimentally by varying the external conditions and may probably vary also from internal causes." Basal metabolism as ordinarily defined measures both the real basal metabolism plus the energy expenditure resulting from the co-ordinated effects of the various functional activities of the organism (cardiac, respiratory, and renal) in the resting condition. The value of the real basal metabolism in this sense, Krogh estimates at 75 per cent of the basal metabolism as ordinarily measured. While Krogh's contention with regard to

nomenclature is probably theoretically correct, the term basal metabolism is now so universally used for the metabolic output as measured under the conditions of the above definition, that its alteration is inadvisable, especially when one considers that the assessment of its true value will probably remain impossible of achievement.

Lefèvre (1920) has objected to the application of the term 'basal' to the metabolism as measured under the above conditions on somewhat different grounds. He points out that the metabolism as so measured expresses not only the minimum amount of energy necessary for the maintainance of the subject, but also includes the small amount of energy necessary to maintain the subject's temperature at body-heat in an environment which is usually about 16° C. Lefèvre therefore insists on basal metabolic measurements being carried out with the

subject immersed in a bath of water at 36° C., whereby the effect of reaction against a surrounding temperature lower than that of the body is eliminated. The estimations of Janet (1923) and Hermann (1923) show, however, that, provided the subject is maintained in a comfortably warm condition by means of suitable coverings, the differences between estimations so made and those carried out in a bath at 36° C. are so small as to be negligible in practice. According to Hermann the basal metabolism expressed per kgm. per hour varied between 0.963 and 1.008 cals. with a mean value of 0.986 cals.; Lefèvre's estimations gave as a mean value the very similar figure of 0.98 cals.

Apart from the above objections the term 'basal metabolism' is generally accepted by physiologists and clinicians to indicate the metabolic rate of a subject at rest, sufficiently covered to

be comfortably warm, and in the post-absorptive condition, i.e., twelve to fifteen hours after the last meal.

Body Size and Metabolic Rate.

The problem in relationship between body size and metabolic rate has been discussed for more than one hundred years. The most important contributions to the question come from comparative studies on the whole animal kingdom.

The huge amount of literature in this field makes it impossible to give a complete quotation from all the studies on this question. More complete references are found in the interesting monographs by Brody (1945), Kleiber (1947), and Hemmingsen (1950). A few of the milestones in the studies of metabolism however can be briefly mentioned.

Sarrus and Rameaux (1919) seem to have been the first to give a general formulation for the relationship between body size and metabolic rate. They draw,

from the circumstance that the body temperature for homothermal animals is constant and the same for different species, the conclusion that the production of heat must be proportional to the area of the body surface from which the heat loss occurs. Their theory is an attempt to apply Newton's law of cooling on this physiological problem. Bidder and Schmidt (1852) stated that "the fasting metabolism must be nearly the same in animals having the same body volume, surface and temperature; the larger the body-surface, the body-volume and temperature remaining constant ..... the higher will be the metabolism as determined by the laws of static heat. Of course a sharp mathematical treatment of this phenomenon can be thought of only after very numerous and exact experimental determinations on animals of most varied form, size and temperature."

Meeh (1879) discussing the ratio

of surface to volume in any object, showed that, since the surface area was proportional to the square of one of its linear measurements (say the radius of a sphere) and the volume proportional to the cube of the same measurement, the surface must be a function of the power of the volume. In symbols:

$$S = V^{2/3} \times K$$

K being a constant for any particular shape of object, having one value for, say, a sphere, another for a cylinder and a third for the human form and so on. Since, in animals, the density of their tissues was believed to be a constant, the body-weight was substituted for V in the above formula so that it becomes $S = W^{2/3} \times K$. Later studies by a long series of investigators, among which especially the names Richet (1889); Rubner (1883); and Voit (1901) must be mentioned, seem to support the theory which in literature often is called

Rubner's law, or surface area law.

The main characteristic of this theory is that the prime factor is supposed to be the loss of heat to the surrounding. The production of heat must then be regulated so that body temperature may be maintained. The consequence of this aspect was that the area of the body surface must be measured or calculated as accurately as possible. Numerous attempts to determine the area of the body surface from simple biometric data have been made. The formula for surface area in man of Du Bois (1916) is an example of these attempts. This resulted from the work of E.F. Du Bois and his cousin Delafield Du Bois who actually measured the surface area of several individuals by an ingenious photographic method, and worked out from those measurements the now well-known empirical formula that

$$\underset{\text{in sq. cms.}}{\text{Surface Area}} = \underset{\text{in kilos}}{(\text{Weight})^{0.425}} \times \underset{\text{in cms.}}{(\text{Height})^{0.725}} \times 71.84$$

The Du Bois's claimed for this formula an average error in the calculation of the surface area of only ± 1.5 per cent with a maximal variation of ± 5 per cent, as against 16 per cent and 36 per cent respectively for the same values in the Meeh formula. At the same time Du Bois and his associates determined the basal metabolism of a number of individuals of varying weight, height, and age and published a table showing the average heat-output per square meter of surface (calculated according to their own formula) for the two sexes at varying ages from 14 to 80. These have been widely used as the Du Bois standards; an accuracy of ± 10 per cent being claimed for them.

Objections against the so-called surface area law appeared early in the discussion. When von Hoesslin (1888) made the experiment to keep similar dogs at different surrounding temperature, it

appeared that these dogs maintained approximately the same standard metabolic rate, but the dog kept in a cold environment developed a protective fur. When, later on, it was shown through numerous investigations that also cold-blooded animals showed about the same relationship between body size and metabolic rate, the difficulties for the explanation of metabolic rate as governed by the heat loss were obvious.

Hoesslin (1888) pointed out that in organisms a series of functions, for instance absorption of food, are surface functions, and consequently must be more proportional to surface area than to body weight. Later on, Dreyer et al (1912) showed that the sectional area of the aorta and the trachea of animals of different size are approximately proportional to $M^{2/3}$. (M= weight).

In his fundamental work "Respiratory Exchange of Animals and Man", Krogh (1916)

opposes the more or less teleological character of the arguments for the surface area law. Krogh (1916) writes: "In the opinion of the writer the reasons against Rubner's view are very strong, and the line of inquiry initiated by Dreyer is much more likely ultimately to clear up the relationship between size and metabolism. The metabolism should not therefore be expressed per sq.m. or any other unit of surface but as a function of W^n. For warm-blooded animals 'n' can be taken, at least provisionally, as "2/3". In this quotation, W is used as the symbol for total body mass.

In later comparative studies, many investigators have used Krogh's system for designating metabolism and have calculated the value of 'n' in the equation: Metabolism = $k.M^n$.

These studies have given important results. It has appeared that the exponent 'n' for adult warm-blooded animals

is between .75 and .70, according to Kleiber (1947) and Brody (1945). Furthermore, it has appeared that the same value of 'n' is also valid for comparison between different cold-blooded animals with a minimum total body mass of about 1 mg (for data see Hemmingsen, 1950). In this case the value of 'k' is different from that valid for warm-blooded animals. Zeuthen (1953) who studied the marine microfauna, has found that 'n' = .95 for small metazoa to organisms containing about 1 mg. nitrogen. For protozoa he found that 'n' = .7. Hemmingsen (1950) furthermore extended the comparison to plants and showed that the carbon dioxide production of the aerial leafless parts of beech trees followed the same function as the metabolism of cold-blooded animals.

Benedict (1938), who contributed to the discussion with a large amount of carefully collected data of standard metabolism in different species, did not

agree with the way of expressing metabolism as a function of M^n. His opinion is that "this method of presenting the data completely masks metabolic differences within the species and distorts or obscures striking differences between species." Further he writes that " ... all attempts by mathematical means to secure a uniform expression of basal metabolism findings on different animal species are utterly futile."

Krogh's and Benedict's views are not only different opinions in a question of matter, but they also represent two entirely different scientific ways of thinking. There does not seem to be any doubt about which is the most productive method if the purpose of science shall be something more than the collection of as many separate detailed data as possible.

Concerning the explanation of why the exponent is closer to 2/3 than to 1, the discussion has not given any more definite results. One explanation is that the fact

that big animals have a lower metabolic rate per unit of body mass than small animals is the result of natural selection. The empirically found relationship between body size and metabolic rate is supposed to have a "survival value". Kleiber (1947) gives this thesis the following formulation: "In natural selection, those animals prove to be better fit whose rate of oxygen consumption is regulated so as to permit the more efficient temperature regulation as well as the more efficient transport of oxygen and nutrients." It appears doubtful how this thesis can apply to standard metabolic rate, since this is a pure product of laboratory conditions. If we should go out into nature and try to find an animal under standard conditions, that is fasting during complete muscular relaxation, we would have to search for a long time. This behaviour in animals would mean a definite negative "survival value".

Just under one condition, and that is during the period of sleep, the conditions approach those existing in metabolic experiments in the laboratory. When the climatic conditions make maintainance of the body temperature difficult, different protective mechanisms are taken advantage of by various species. The migrating birds seek a warmer climate, and the hibernating animals lower their metabolism and body temperature. The large animals might have the problem of maintaining body temperature low enough, but the important thing is that they are able to maintain body temperature even though they have a higher metabolic rate than the standard. For the elephant, whose life is one continuous meal, body temperature must be maintained under the conditions of eating and searching for food, which includes muscular activity. It is characteristic that Benedict (1936) in his study of the physiology of the elephant, found only

one among sixty-three elephants which could be used for metabolic studies, and this one was adapted to the life in New York City. The remark of Zeuthen (1953) that "... the basal metabolism in mammals - as in other animals - is adapted to the needs of the species to a lesser extent than the species are adapted to the metabolism derived according to their body size and the phylogenetic history of their whole groups" contains a more important view of this problem.

Other scientists tried to solve the problem by studying energy output of tissues isolated from animals of different sizes. Krebs (1950) draws from his studies of tissue respirations the conclusion that "The characteristic differences in the basal rate of heat production in animals of different size are to be attributed mainly to variation in the Q_{O2} (Q = density of water) of the musculature." Von Bertalaffy and Pirozynsky (1953) however, could not

confirm the conclusion of Krebs (1950) but found in direct comparative studies of the tissue respiration of the musculature that this did not decrease with increasing body size to an extent which would explain the value for the exponent 'n'. These authors, also discussing other possibilities for explaining the value of 'n', arrived at the conclusion that "none of the explanations proposed (decline of total metabolic rate as based upon decrease of the rate of tissue respiration, upon thermoregulation, upon decrease of Q_{O2} of musculature, upon the relative decrease of 'metabolically active' organs, upon age) is consistent. It appears that the decline in basal metabolic rate depends on regulative factors lying in the organism as a whole".

These attempts to explain the value of 'n' all have one thing in common, they presuppose a biological explanation

for the deviation of the value of 'n' from the figure 1. The value n = 1 seems to be considered as the most natural one. Already Hoesslin (1888) has objected to this way of looking at the problem, and has written: "Diejenigen, die annehmen, das Natürlichste wäre, der Umsatz verhielte sich wie die Körpergewichte der verschiedenen Thiere und nicht wie die Querschnitte, müssen die Voraussetzung machen, es lasse sich im Körper leicht eine Einrichtung denken, welche bewirke, dass in der Zeiteinheit durch den physiologischen Quershnitt des Körpers eine Blutmenge strome, die nicht proportional der Grösse des Querschnittes, sondern proportional der des Körpergewichtes selbst wäre. Es liesse sich dies jedoch überhaupt nur unter ganz gewaltigen morphologischen Aenderungen und vollkommenem Verzicht auf die Aehnlichkeit im Bau verschieden grosser Thier erreichen, bein grossen

Gewichtsunterschieden aber ist es ganzlich unmöglich."

Later on Lambert and Teissier (1927), and Teissier (1928) made a fundamental theoretical analysis of the problem. They originated from the hypothesis that the quotient between the times required for equivalent physiological events, for instance the time for a heart beat, in animals of different size equals the quotient between corresponding anatomical lengths. They found that the only relationship between the total energy output of animals of different size, which is consistent with the approximation that animals of different size are uniform, is the quotient of the respective masses raised to the power 2/3.

The present knowledge of the relationship between body size and standard metabolic rate derived from comparative studies may be summarized in the following way. With increases in

body size, the standard metabolic rate per kilo body mass decreases. The influence of body size is best expressed by the relationship standard metabolic rate equals $k.M^n$, where the value for 'n' is between $\frac{2}{3}$ and $\frac{3}{4}$. There does not exist any generally accepted biological explanation for this empirically found value for 'n'.

In recent years, in view of obvious unavoidable inaccuracies of previous standards of measurement, attempts have been made to relate changes in body functions to body mass as a whole. Behnke (1953; Behnke, A.R., Osserman, E.F. and Welham, W.C. 1953) found it useful for some purposes to introduce the concept of the "lean body mass" hoping to find in it a relatively constant structure, a common denominator of all body forms, with which comparisons would be meaningful and to which physiological factors such as basal metabolic rate could be reduced.

This hope at least to some extent has been realised, and the concept has been and doubtless will continue to be put to useful purpose. Siri (1956) believes it to be a better basis than body weight for correlation and intercomparison of physiological measurements.

Measurements of human body density, or "specific gravity", have been undertaken since the middle of the 18th. Century, and older investigations are summarized by Boyd (1933). All these measurements were influenced by the unknown quantities of gases in the body, especially in the lungs. Therefore, there did not exist any possibility of utilizing the method of Archimedes to determine the composition of the body with respect to various components with different densities. No other conclusion from the older measurements could be drawn than "that obesity tends to decrease specific gravity" (Boyd). The first

measurements of the volume of the lungs in connection with determination of total body volume were made by Behnke (Behnke, A.R., B.G. Feen and W.C. Welham, 1942). After measurements on 99 male test subjects in the age range of 20 to 40 years, Behnke (1953) arrived at the conclusion that "Excess fat ... is viewed as the prime factor governing the level of specific gravity".

Behnke's interpretation of his data is based on the opinion that the organism consists of a "lean body mass" of uniform composition and of a variable amount of "adipose tissue". Since these two masses have different values of density, the relationship between "lean body mass" and "adipose tissue" may be calculated from the gross body density. Behnke's concept of "lean body mass" has been criticized by Keys & Brozek (1953) but von Döbeln (1956) interprets their results as being evidence of support for the original

idea of Behnke.

The gross body composition with respect to the different tissues has been known since the fundamental anatomical studies of Bischoff (1863) and von Liebig (1874). Unfortunately, the data of Bischoff and von Liebig have been overlooked in modern discussions on the same question. One recent study on the body composition is published by Forbes (Forbes, R.M., A.R. Cooper and H.H.Mitchell. 1953.).

Apparently the data of Bischoff, von Liebig and Forbes et al, support Behnke's concept of a "lean body mass" of approximately uniform composition. "Lean body mass" (L.B.M.) can be defined as the total mass of the body minus the mass of adipose tissue. This does not mean that L.B.M. is entirely free of fat. It contains fat, for instance, in the central nervous system and especially in the bone marrow. This type of fat Behnke labels

as "essential lipoids".

Fat tissue has an important characteristic which makes it differ from "essential lipoids". This characteristic is that if fat is added to or taken away from fat tissue, both weight and volume change. If fat, on the other hand, is taken away from the bone marrow, another substance must be added because the volume is anatomically determined. If fat from the bone marrow is used, the total body weight will increase. In emaciation the fat from the yellow bone marrow is used by the body, and is substituted by a gelatinous substance which is poor of fat. It is not known at what stage of emaciation this phenomena appears.

Now the L.B.M. is composed of soft tissues, including body fluids (blood) and skeleton. In order to determine the density of L.B.M., knowledge of the densities of the components is required.

The heaviest components of L.B.M., are muscles, skin, blood, liver, nervous tissue, and skeleton. According to von Döbeln (1956) muscles make up about 48 per cent of L.B.M., the skin about 8 per cent and the liver and nervous tissue each about 3 per cent. He estimates the blood volume as determined by Sjöstrand (1949) to be about 9 per cent of L.B.M.. Finally, the skeleton makes up about 21 per cent.

Of the measurements found in literature on the density of muscle tissue, the value of 1.043 is given by Nadeshdin (1932).

Only one value for the density of the skin is found in literature. In the year 1832, Schübler and Kapff (1832) determined the specific gravity of "allgemeine Bedeckung ohne Fett" to 1.057 which, computed to normal skin temperature of 30° C. will be a density of 1.053. The density of blood at body

temperature is about 1.052. The density of liver tissue, calculated from the determinations of Nadeshdin is 1.059 and for nervous tissue is 1.035. The remaining parts of L.B.M. consist of different organs. According to the measurements of Nadeshdin (1932) the values of density for these organs cannot differ very much from that of muscle tissue.

On the basis of the density figures and the figures for the composition of L.B.M. previously stated, it can be estimated that the L.B.M. contains 56 per cent tissue with the density 1.043, 8 per cent with the density 1.053, 9 per cent with the density 1.052, 3 per cent with the density 1.059, and 3 per cent with the density 1.035. Now the density of all the soft tissues together (Ds) may be computed. Because the total volume equals the sum of the volumes of the components,

thus:-

$$\frac{79}{Ds} = \frac{56}{1.043} + \frac{8}{1.053} + \frac{9}{1.052} + \frac{3}{1.059} + \frac{3}{1.035}$$

$$Ds = 1.045.$$

The main inaccuracy in this computation is due to the unreliability of the value for the density of the skin. According to Forbes et al (1953), the skin contains 57.71 per cent water, while the water content of muscle tissue is 70.09 per cent. Supposing that the density of the skin is the same as that of muscle tissue dried to 57.71 per cent water content, we would obtain a value for density of 1.068. If in the computation above, 1.068 is inserted instead of 1.053, Ds would be 1.047. Another inaccuracy is due to normal variations in the water content of the body. This, of course, would be of particular importance in pregnancy. It is known that body weight measured under standard conditions may

vary from one day to another up to .5 kg. The main reason for this must be variances in water content. This influences the density of the soft tissues of L.B.M. within .5 units. Consequently the density of the soft tissues of L.B.M. can be estimated to 1.045 with a possible range of variation of about 2 units.

Determinations of the density of the whole skeleton are not to be found in literature, but von Döbeln (1956) believes the density to lie somewhere between 1.25 and 1.30.

The density of the L.B.M. can now be calculated from the data of body composition and density of different tissues, not as an actual figure but within limiting values. Total density of the human body can be determined by one of two methods. One method consists of weighing and volume determinations independent of each other; the second, that of hydrostatic weighing.

In the former method the Formula:

$$D = M/V$$

is used, where M = mass and V = volume, but in this method great technical difficulties arise in connection with the volume determination.

The second method is the more practical method and in this case D is determined from the formula:

$$D = \frac{Ma}{Ma-Mw} \cdot Q + \left(1 - \frac{Ma}{Ma-Mw}\right) \cdot 1.2 \cdot 10^{-6}$$

where Ma - weight in air
Mw - weight in water
Q - density of water
1.2×10^{-6} - density of air.

This latter method is described in detail by von Döbeln being the method used in his experiments to determine the L.B.M. of his subjects.

As a result of his study he suggests that in future studies on the influence of body size on standard metabolic rate, the fat-free body mass raised to the power 2/3 be used as a reference standard. This view is also shared by Miller &

Blyth (1952).

While it has been attempted to relate basal metabolism to surface area, body weight and lean body mass in mammals both in male and in females in the non-pregnant state, it is obvious that where any one of the standards is applicable it does not necessarily follow that the same standard will be applicable to a female in the pregnant state. Indeed there is no known standard at present which is entirely applicable in that state without some possible fallacy or inaccuracy being present.

The linear comparison of body weight alone with basal metabolic rate cannot possibly produce accurate results since the body weight in pregnancy is subject to variable fluctuations not only from an irregular increase in protoplasm, but also as a result of variations in fluid balance and in the amount of fluid retained during the pregnancy. This would be particularly

true in the case of pre-eclamptic toxaemia and eclampsia where there is increased water retention.

In addition, the maternal body-weight bears no relation to the weight or metabolism of the foetus and placenta and membranes.

The relationship between lean body mass and basal metabolism while appearing to be the most accurate of all standards of comparison cannot readily be applied, at the moment, to the pregnant organism, where unknown weights, volumes and densities of foetal tissue, amniotic fluid and placental tissue exist. Indirect methods of measurement of total body composition such as the use of antipyrine, (Brodie, B.B., Axelrod, J., Soberman, R., & Levy, B.B. 1949), Deuterium (Schloerb, P.R., Friis-Hansen, B.J., Edelman, I.S., Sheldon, D.B., & Moore, F.D. 1951), and Tritium (Prentice, T.C., Siri, W.E., & Joiner, E.E. 1952), are likewise inapplicable in pregnancy

although it is hoped that a reliable method based on work of a similar nature to that as employed in the non-pregnant may be produced for accurate and safe measurement of lean body mass during pregnancy.

The use of surface area as a reference standard although not wholly satisfactory, would therefore appear to be the most convenient method available at the present time for calculating basal metabolic rate during pregnancy.

Estimation of Metabolic Rate.

The employment of carloric values of oxygen based on the assumption that a fixed percentage of the total calories arise from protein metabolism was suggested by Magnus-Levy (1907). It is realised that for many purposes it is unnecessary and impracticable to make the "exact" protein correction for the urinary Nitrogen. A standard correction on the assumption that protein produces

about 12½ per cent of the total calories is suggested by Weir (1949). The error introduced, even of the percentage, is somewhat different and practically negligible. Widdowson (1947) has pointed out that the results of dietary surveys in various parts of the world all go to show that the majority of mankind take 10-15 per cent of their calories in the form of protein. In various environments in different parts of the world Johnson and Kark (1947) found a range of 11-13 per cent. It does not necessarily follow that there is a similar constancy in the percentage of calories arising from protein metabolism within the duration of any given metabolic determinations, but Wishart (1928) found a marked parallelism between daily variations in basal metabolism and variations in output of Nitrogen in the urine.

The finding that the determination of metabolic rate requires only the

measurement of the volume of the air expired and its oxygen content according to Weir (1949) introduces the possibility of new techniques for its estimation. Indeed newer methods are already being developed.

Recognised Methods.

Estimations of metabolism may be carried out either by the direct or by the indirect method, and the latter of these methods may be performed with a closed-circuit or open-circuit type of apparatus.

In the direct method, the subject is placed within an artificially ventilated chamber fitted with a complex system of cooling water-coils. From a comparison of the temperatures of the water circulating in these coils before it enters and after it leaves the chamber and a measurement of the amount of water which has passed through the coils, the heat eliminated by the subject may be directly estimated. Such a method offers several advantages.

There is no disturbance in breathing produced by the attachment of the subject to the apparatus by means of a mask, mouthpiece or nose pieces; since arrangements can be made for the introduction of food and withdrawal of the excreta, experiments of almost any duration are possible; thirdly the heat-output is directly measured and interesting comparisons may be made between the heat-output as found, and the heat-output as calculated from the food-stuffs metabolised during the period of the experiment.

Very efficient heat-insulation of such an apparatus from the surrounding air has to be provided for, the plan adopted being to surround the chamber with a double wall, the intervening space being occupied with electrical resistance-heaters, each heater being thermo-electrically controlled by the temperature of the corresponding section of the wall

of the chamber. Such a complex arrangement makes the apparatus very costly to instal and maintain and necessitates the supervision of several operators during the running of each experiment. Also, in such an apparatus the volume of the chamber is very large compared with the volumes of oxygen utilised and carbon dioxide excreted by the subject, and, since the former is measured by the diminution in volume of the air within the chamber, slight changes in barometric pressure or in moisture-saturation may readily vitiate this estimation. Apart from these disadvantages, and the further one, that, in general, complexity of apparatus leads to greater liability to error, this method is probably the method 'par excellence' for the estimation of metabolism.

In the indirect method, an estimate is made of the amounts of each of the proximate principles undergoing combustion

in the body, the protein being estimated from the amount of nitrogen in the excreta, and the carbohydrate and fat from the excess of oxygen utilised from, and carbon dioxide added to, the breath after making allowance for the gaseous exchange due to the combustion of the protein. The relative amounts of carbohydrate and fat undergoing combustion are estimated from the value of the R.Q. Having so obtained data as to the quantities of the proximate principles being catabolised, the heat output of the subject is then computed by multiplication of the amount of each food-stuff by its calorific factor. Usually the direct measurement of the heat output in a respiration chamber is combined with such an indirect calculation of the heat-output from the respiratory exchange and the nitrogen excretion. That a good agreement exists between the two methods has been shown by Benedict (1919).

The estimation of the respiratory

exchange by the indirect method may be carried out either with a closed circuit or open circuit apparatus. In the closed-circuit type, the subject is placed in or connected with a circulating stream of air in a closed system from which the CO_2 eliminated is absorbed and measured as formed, and O_2 is added to replace that consumed in measured quantities so as to maintain the volume of the system constant. Probably the earliest and best known type of this apparatus was Benedict's Universal Respiration Apparatus (1912). Later several portable forms of it were designed by Benedict and his co-workers, one modification which was extensively used for clinical work was the Benedict-Roth-Collins Apparatus (1922). Recording apparatus of this type has continued to be used in the estimation of basal metabolic rate up to the present day. It is considered to be the most important of the simpler methods of estimating basal metabolic rate (Bell,

Davidson, and Scarborough, 1956). This apparatus consists of a spirometer, the bell of which is of uniform bore, and with its counterpoise working alongside a graduated scale or recording its movements graphically on a drum. Two tubes opening within the spirometer are extended outside of it to join one another at the subject's mouthpiece. Each tube is provided with a valve, the valves being so arranged that the expired air must pass to the spirometer by one tube while the inspired air is drawn from the spirometer by the other. Interposed in the course of the expiratory tube, and, for compactness actually housed within the bell, is a soda-lime CO_2 absorber. The CO_2 eliminated by the subject is therefore absorbed before the expired air reaches the spirometer from which the same air is rebreathed. The volume of the system will diminish, due to the absorption of O_2 by the subject, and this O_2-absorption will therefore be

registered by the fall of the spirometer bell, which may be traced graphically on the drum or read off on the scale as a result of the rise of the counterpoise. No provision is made in this apparatus for the measurement of the R.Q.; all that is measured is the absorption of O_2 and in estimating the metabolism indirectly therefrom a constant R.Q. of 0.82 is assumed.

In apparatus of the open-circuit type, the subject is supplied, either in a chamber or by means of a mask or mouth-piece with a stream of fresh atmospheric air. The total volume of the out-going expired air is measured and an aliquot portion analysed for carbon dioxide and oxygen. From the differences between the carbon-dioxide and oxygen content of the expired and the inspired atmospheric air, the amounts of these gases produced and utilised by the subject can be arrived at. Such methods differ mainly in the

mode of collecting the expired air, and in the manner of performing the analysis of the aliquot portion of the same. In this country the commonest type of such a method is the Douglas-Haldane; the expired air is collected in a canvas-covered rubber bag as devised by Douglas (1911) and the analysis of the air-sample carried out on some form of the air-analysis apparatus originally devised by Haldane (1918) for the analysis of mine gases.

With regard to this type of estimation it may here be noted that four possible observations may be made during the experiment, only three of which are required for the estimation of the heat-output, since the fourth may be calculated from the other three. These four observations are:- (1) the volume of atmospheric air inspired; (2) the volume of expired air; (3) the carbon dioxide added to the inspired air by the subject;

and (4) the oxygen taken from the inspired air. The usual procedure is to observe the last three and to calculate the first, which, in the Douglas-Haldane method, is virtually done in the correction of the apparent respiratory quotient to a true respiratory quotient. Of the whole procedure, the most time-absorbing part of the procedure is the oxygen-analysis, and, therefore, it would be an advantage to be able to substitute for this the observation of the inspired volume. Unfortunately the difficulty here arises that accurate measurement of the inspired volume demands some form of water-meter, which offers a resistance to inspiration, thereby altering the metabolism of the subject. Such a measurement might be carried out by some form of recording spirometer, which can be made almost devoid of resistance, and this idea was developed by Hagedorn (1924) in a recording differential spirometer. Owing, however, to the comparative inaccuracy

of such additive spirometric readings this type of apparatus is only suitable for clinical work where only gross differences in the metabolism are to be measured.

Since the introduction of the simpler and portable types of recording apparatus, and the publication of standards of metabolism by Du Bois and Benedict countless series of metabolism studies have been reported from all parts of the world. These studies have included comparisons between the different coloured races, and effects on metabolism of variable climatic conditions and geographical position.

In 1951 a statistical study of the recorded energy expenditure in man was carried out by Quenouille (Quenouille,M.H. Boyne, A.W., Fisher, W.B. and Leitch, I., 1951). In this, the published series of many workers were subjected to a strict scrutiny and certain conclusions were

drawn from the study. Before the data could be included in the survey the work had to conform to certain simple requirements including one that "the method used to estimate basal metabolism preferably should be one of those generally accepted as capable of giving reliable results. In effect this ruling amounted to drawing a line at or about 1914, with the work of Benedict".

As a result of a study of the records of basal metabolism of over 8,600 subjects, equations were derived from which to predict basal metabolism in calories for 24 hours and from these, prediction tables for the two main racial groups distinguished, were produced.

The relation of basal metabolism to stature was suggested as being more complex than that expressed in the Du Bois formula, or by any simple function of weight or of height and weight together. Temperature, humidity -

racial differences appeared to play a part in influencing the results.

Pregnancy and the Thyroid Gland.

The role of the thyroid gland in pregnancy has long been the subject of interest, but its exact function and bearing on the pregnant state is still not clearly understood.

That swelling of the thyroid gland takes place more or less regularly in pregnancy was recognised by the ancients and has been known to physicians for a long time. Over one hundred years ago, Schweger and Bardeleben (cited by Davis, 1935) demonstrated an enlargement of the thyroid gland in pregnant dogs.

Since then many writers have found a variable incidence of thyroid enlargement in association with pregnancy. One of the reasons for the lack of agreement is that the ease with which one might palpate the thyroid gland would depend to a large extent on the thickness

of the subject's neck and to the presence or absence of fat.

One of the problems has been whether the increase in size of the thyroid gland is due to true hypertrophy and hyperplasia of the secretory tissues or whether it is only transitory hyperaemia. In certain animals, e.g. the cat, a hyperaemia only is observed. Engelhorn (cited by Davis, 1935) however, has demonstrated an increase in epithelial cells, increased secretion and storage of colloid. He observed these changes in humans, rabbits and guinea pigs. Most observers agree with these findings.

Schwartz (cited by Davis, 1935) has observed striking changes in guinea pigs. A series of thyroids from pregnant guinea pigs were removed at various stages of pregnancy. About the end of the first trimester, there is marked hyperplasia of the interfollicular tissue with slightly increased storage of colloid. At the

middle of gestation, hyperplasia of the interfollicular tissue is even more marked and a further slight increase in colloid storage occurs. During the period corresponding to between the fiftieth and fifty-fifth day of gestation, the colloid spaces are markedly distended with colloid, and the interfollicular tissue is much compressed and thinned out. At term, however, colloid storage has markedly decreased and the interfollicular tissue again becomes more prominent but much less so than in mid-pregnancy. From these findings, it is clear that there is increased function of the thyroid gland in many instances during pregnancy.

Garry & Wood (1946) affirm that the increase in metabolism which normally occurs in pregnancy undoubtedly puts an additional strain on thyroid function. Likewise Arnold (1940) believes that pregnancy makes greatly increased demands on thyroid activity, both in the mother

and in the foetus and suggests that foetal overweight is due to foetal thyroid deficiency. Since Magnus-Levy (1904) studied the basal metabolism of a pregnant woman, there has been a voluminous literature regarding the role of the thyroid gland in normal pregnancy. According to Seitz (1929), the combination of enlargement of the thyroid gland, the increase in the iodine content of the blood, increase in basal metabolism and the clinical deterioration which is observed in hyperthyroid patients all point to an increase in thyroxin production by the thyroid gland during pregnancy.

Anselmino and Hoffmann (1930) in the first of their publications demonstrated that the pregnant animal degrades considerably more carbohydrate to lactic acid than a non-pregnant animal under like conditions. They concluded that this increased lactic acid

production was referable to raised thyroid activity.

A constant characteristic of the metabolic activity of the thyroid hormone is an increase in acetone bodies in the hyperthyroid organism. The level of ketone body formation depends on the size of the disposable glycogen store, which is known to decrease materially under thyroid activity. Abelin and Jordi (1932) demonstrated that the feeding of thyroid and the injection of thyroxin into rats resulted in a threefold increase of acetone bodies in the urine. This finding was also noted clinically in hyperthyroid conditions. Porfes and Novak (cited by Davis, 1935) observed that withdrawal of carbohydrates in pregnancy resulted in a much higher acetone body level in the urine than in non-pregnant women under like conditions.

Numerous authors agree that the basal metabolic rate at term is increased

from 10-30 per cent above normal.

Anselmino and Hoffmann (1931) injected rats and mice with pregnancy serum and found that carbon dioxide production, and therewith the basal metabolic rate increased markedly whereas those injected with non-pregnant serum showed no change in metabolism. Here again the greatest increase was noted with samples of serum taken in the last month of pregnancy, while samples taken during the puerperium were much less active. Foetal blood was inactive, giving no such increase. Thyroxin administration caused the same reaction as serum from pregnant animals.

An increase in the metabolic processes, such as is found in the pregnant state, must set up a greater demand on the circulation. There is uniform agreement that the minute volume of the heart is increased in pregnancy and according to Davies, Meakins and

Sands (1924) this increase is in proportion to the increase in metabolism, the two being closely related. Linhard (1932) found that heart minute volume was highest just before labour with a subsequent fall in the puerperium. The increase in minute volume is also typical of thyroid activity.

In studies of the carbohydrate metabolism and the thyroid state, one of the most constant observations is that of a decreased glycogen level in the body following the administration of the thyroid hormone.

Anselmino and Hoffmann (1930) injected mice with pregnancy serum, then killed the animals and determined the liver glycogen. The liver was prepared by Pfluger's method and the sugar determined by the method of Hagedorn Jensen.

These experiments indicated that a substance was present in the blood serum of pregnant women which caused a fall in

the glycogen content of mouse liver. Further experiments also showed that this substance was present in increasing concentrations as pregnancy progressed from the second month, and that there was a rapid decline during the puerperium. Another important finding was that foetal blood caused only one third as much glycogen reduction as maternal blood. It was concluded that the increase in carbohydrate metabolism of the pregnant female, which had, previously been attributed to the needs of the foetus and the growing maternal organs, was brought about by an active substance in pregnancy blood serum. This substance could itself, influence carbohydrate metabolism as indicated by their series of experiments.

A general consideration of symptoms and findings per se makes pregnancy a "hyperthyroid state". According to Soule (1932), the pregnant women is in a

physiological condition in which there is hyperfunction of the thyroid.

It is an established fact that pregnancy is associated with a considerably elevated metabolic rate. This had been recognised by clinical observation for many years. The earliest determinations are quoted by Root and Root (1923) as a relative and absolute increase in the oxygen consumption per kilogramme of body weight, early in pregnancy. Similar observations were described by Baer (1921) and Cornell (1923). The latter found a 29-35 per cent increase with a sharp post-partum fall.

Plass and Yoakam (1929) studied patients with abnormal glands and found that the ante-partum increase of basal metabolic rate was directly proportional to the degree of disease.

Kraul and Halter (1924), and Litzenberg and Carey (1929), further substantiated these findings in their

reports of decreased metabolic rates in instances of decreased genital function, dysmenorrhoea and sterility.

There is therefore abundant evidence of the existance of thyroid hypertrophy during normal pregnancy, in the writings of Cornell (1923), Plass and Yoakman (1929), Bram (1922), Raycraft (1930), Davis (1929), Straus and Daley (1926). There were investigators, however, who did not agree with these findings, notably Kraus (1924) of Berlin. This worker stated that the results of ephedrine injection tests for thyroid function showed a depressed rather than an intensified thyroid activity during pregnancy. In support of this view he reports three cases of patients dying intra-partum in which the histological picture of the thyroid gland was that of hypothyroidism.

A relationship between the anterior pituitary and thyroid activity has clearly been shown to exist. Bugbee (1931) and

his associates in discussing the function of the anterior lobe of the pituitary gland mention the work of Foster and Smith which showed that removal of the whole pituitary gland caused a 35 per cent reduction of the metabolic rate. This could be restored by daily transplantation of anterior pituitary gland, transplantation of posterior pituitary being without effect. This work with that of other investigators, such as Schwartzback and Uhlenhuth (1927) and Crew and Wiesner (1930), confirms the view that one of the hormones of the anterior pituitary activates the thyroid gland. This is interesting in view of the hypertrophy of the anterior portion of the pituitary gland in pregnancy and it is presumed therefore that thyroid hypertrophy is secondary to anterior pituitary hypertrophy, or at least to increased anterior pituitary activity.

Similarly there might be hyperplasia of the posterior pituitary as suggested by

the possible existence of an excess of anti-diuretic substance in the urine of women suffering from pre-eclamptic toxaemia (Anselmino & Hoffmann, 1931: Theobald, 1933-34:).

The importance of the thyroid gland and its function in relation to obstetrics and gynaecology cannot be overestimated.

This relationship of the thyroid gland to the sex glands is evidenced by thyroid enlargement concurrent with menstruation, puberty, pregnancy and the menopause, and also by the fact that goitre occurs more frequently in the female.

It has been known for years that a certain type of uterine haemorrhage is associated with hypothyroidism and that it may be corrected by the administration of dessicated thyroid. Litzenberg, Meaker and others (1932) have found that thyroid dysfunction may be an important factor in sterility.

It is therefore probable that basal metabolism studies in obstetrics and gynaecology are of greater importance than at present realised and it is believed that this should be examined more frequently in obstetrical and gynaecological patients.

The uterus, tubes and ovaries are all richly supplied by the sympathetic ganglia of the pelvis and will function entirely independently of the central nervous system. These functions are apparently further governed in part by the action of certain hormones or secretions of the ductless glands acting directly or indirectly through stimulation of the sympathetic nervous system.

It is not surprising therefore in view of the physiological and pathological changes that occur during pregnancy in the human body, that deviation from the normal non-pregnant state can be found in the various ductless glands as an

expression of their response to the abnormal stimulus brought about by pregnancy. Thus it is seen that the anterior lobe of the hypophysis may be greatly enlarged, even to twice its normal size (Falta, 1915), due to over-growth of the chief cells which dominate the eosinophilic and basophilic cells forming about 80 per cent of the total cells. Gross changes in the adrenals are less evident but there is evidence that the cortical portion is markedly increased (Seitz, 1913). The ovary presents the unusual corpus luteum of pregnancy and the Graafian follicles fail to develop during that period. Other less evident functional changes in the interstitial cells may well be present. In addition there is evidence that the thymus, parathyroids and Islets of Langerhans of the pancreas are also functionally altered by the pregnant state.

The thyroid gland is one of the most

noticeably altered of the endocrines during pregnancy.

The intimate relationship between the thyroid glands and the pelvic organs is stressed by Porter (1909) who reports a case of hyperemesis gravidarum cured by thyroidectomy. In certain invertebrates the thyroid is a sexual organ and empties its secretions through a duct into the genital tract. The thyroid is relatively larger in women than in men and according to Falls (1929) women are five times more prone to develop thyroid disease than men.

Stowe (1909) reports a case which developed acute exophthalmic goitre secondary to tuberculosis of the pelvic organs, the patient dying in labour.

Goodell and Conn (1911) report a case in which a goitre was produced by pelvic tuberculosis and cured by panhysterectomy.

Ward (1909) and others have suggested that a failure of the thyroid gland to

increase its activity during pregnancy is one of the causes of eclamptogenic toxaemia.

Ward (1909) found that the use of a saline extract of the thyroid gland taken from a normal human thyroid seemed to affect favourably one case of hyperemesis gravidarum. He feels that the injection of saline extracts of human thyroid glands may favourably alter the metabolism in patients who have eclamptogenic toxaemia or hyperemesis gravidarum.

With such diversity of opinion as to the true role and state of the thyroid gland in pregnancy it was decided to carry out a series of investigations on pregnant women using a single method.

The method chosen was that first described and used in pregnancy in 1897 by Magnus Levy (1904), viz. the estimation of basal metabolic rate from oxygen consumption.

Much has been written regarding the

usefulness and accuracy of this method of studying thyroid function.

Although essentially a test, simple in nature, it would appear that the interpretation of the results is much less simple than the performance of the test.

Since the original work of Magnus Levy (1904) many investigators have used the test with very varied results. (Root & Root, 1923; Cornell, 1923; Plass & Yoakam, 1929; Carpenter & Murlin, 1911; Hughes, 1934; Cornell & Baer, 1921:)

The basal metabolic rate has been estimated under practically every circumstance in which the human body is likely to be placed - the seasonal fluctuation in basal metabolism (Gustafson & Benedict, 1928); racial differences (Steggerda & Benedict, 1928; Eijkmann, 1896; 1921), variations due to differences in physique, occupation and climate have all produced interesting and useful information (Eijkmann, 1896; 1921;

Delcourt-Bernard & Mayer, 1925; Takahira, Kitasawa, Ishibashi & Kayano, 1924; Cathcart & Orr, 1919).

The usefulness of the estimation of basal metabolic rate in pregnancy has been discussed by various workers who have carried out series during pregnancy (Baer, 1929; Plass & Yoakam, 1929; Watrous & Blakeley, 1952; Peters, Marr & Heinmann, 1948), and although some consider the procedure as being of doubtful value (Watrous & Blakeley, 1952; Peters et al, 1948), there are many writers who consider that estimation of basal metabolic rate has some value in certain conditions and stages of pregnancy (Baer, 1929; Kraul & Halter, 1924; Litzenberg & Carey, 1929), indeed Colvin and Bartholomew (1939) believe that the procedure should be routine in all primigravidae at an early stage in the pregnancy.

The study consisted of two main

parts, clinical and experimental. The clinical section consisted of series of experiments conducted on normal pregnant women at all stages of pregnancy. The effects of age, parity and maturity on the basal metabolic rate were observed. Later, shorter series were conducted on the abnormal states of pregnancy and in the puerperium.

The clinical part of the work was carried out in the wards of the Glasgow Royal Maternity and Women's Hospital and the experimental section was conducted in the Research Laboratory of that hospital.

Part 1.

Basal Metabolic Rate in Normal Pregnancy.

Method.

Before commencing the experiments considerable thought was given to the true meaning of basal metabolism. It was felt that while satisfactory results or at least low results, uninfluenced by extrinsic factors such as anxiety and emotion could be obtained by heavy sedation of the subjects, the results thus obtained could not be truly basal readings since depression of cellular activity had advanced to a stage such that the state of unconsciousness had been produced, nor could they be compared with standards unless those standards had been obtained under similar circumstances.

It was therefore decided that if possible the results should be achieved without the use of heavy sedative drugs. With this end in view the following

technique was adopted:-

The estimations were carried out on the Benedict-Roth recording spirometer and were conducted personally at the same time on each of three consecutive mornings. The subjects for investigation if not already in hospital, as in the series of complications of pregnancy, were admitted during the afternoon of the day preceding the first of the tests.

Investigations were usually conducted on two subjects simultaneously, as it was found more convenient to confine the patients to a cubicle, with two beds, by themselves where they were undisturbed by other patients and by the nursing staff. Later in the afternoon of their admission the patients were each shown the recording apparatus. The apparatus was explained to them and the procedure was described in detail and then the apparatus was connected to each in turn for a short period so that they might better understand

the workings of the machine. Thereafter the patients were confined to bed for a period of twelve hours prior to the carrying out of the test. No food or fluid was given after 8.30 p.m. on the night prior to the test, and at that time, each patient received a sedative consisting of Pentobarbitone ("Nembutal") in a dose of 1½ grains by mouth. A screen was placed between the two patients in readiness for the test in the morning and the patients were encouraged to go to sleep. They were not disturbed again until after the test had been completed. This was normally carried out at 8.30 a.m. on the following morning.

The recording apparatus was kept in the cubicle beside the patients throughout the course of the experiments so that by the end they were thoroughly familiar with it and were completely unafraid of it.

On each of three consecutive mornings

at 8.30 a.m. before the patients had been disturbed by any of the nursing staff the Oxygen consumption of each subject was recorded over a period of fifteen minutes. As little disturbance as possible was made during the tests. At the end of each test the temperature of the water in the outer chamber of the spirometer was noted and the barometric pressure noted in millimeters of mercury.

The height in centimeters and the weight in kilograms were obtained in each subject at the termination of each test. The surface area in each case was calculated using the formula of Du Bois (1927 P.121).

$$A = 71.84 \times H^{0.725} \times W^{0.425}$$

Where A is surface area in square centimeters, H. is height in centimeters and W. is weight in kilograms.

The oxygen consumption of the subject as measured by the spirometer was converted to that obtaining at standard temperature and pressure.

It has been established under experimental conditions that the calorific value of a litre of oxygen, assuming a respiratory quotient of 0.82, is 4.825 calories. If, as stated by Spiga-Clerici (1937) and quoted by Garry & Wood (1945-46) the respiratory quotient is unaffected by pregnancy, the puerperium and lactation, one can calculate from this the basal metabolic rate of women during pregnancy and the puerperium.

The results are expressed in large calories per square meter of body surface per hour (Kcals./sq.m. per hour).

A similar technique was followed on each occasion of test except that on the night preceeding the third test no sedative was given. It was found during the course of the experiments that except in a few cases who were obviously nervous and anxious, a true basal reading could be obtained without the use of any sedative drugs. With a few exceptions the readings

of the second and third days were within ± 5 per cent of each other. The reading obtained on the first day was always discarded as unsuitable as this was invariably greater than subsequent ones due to anxiety and other extraneous causes. The respiratory excursion was usually found to be greater also on these occasions indicating that the rise was in all probability caused by nervous elements and therefore not a true basal reading. The actual basal metabolic rate was usually calculated from the third reading unless it had been noted that the patient had shown signs of anxiety and nervousness when the second reading, if lower then the third, was taken.

In order to have a basis for comparison it was necessary to study the basal metabolic rate in normal women in the non-pregnant state. Ten normal, healthy, non-pregnant subjects aged between 20-25 years were studied. As in

TABLE 1.

Table 1.

Subject	Basal Metabolic Rate (Kcals./Sq.m./Hour) in Healthy Non-Pregnant Adult Women.
A	30.41
B	32.63
C	33.32
D	29.67
E	29.21
F	30.81
G	29.88
H	30.71
I	31.80
J	32.80
Mean Average	31.72

the pregnant series, the third of three consecutive readings of oxygen consumption was taken and from this the basal metabolic rate was determined. The mean value of the ten results was calculated as shown in Table 1. This figure of 31.72 Kcals./sq.m. per hour was taken as the average Basal Metabolic Rate for normal non-pregnant women within the reproductive period of life. This figure compares favourably with the standards for Basal Metabolic Rate in women given by Robertson and Reid (1952).

TABLE 11.

Table 11.

Stage of Pregnancy in Lunar Months.							
3	4	5	6	7	8	9	10
32.98	33.30	32.35	33.30	35.52	36.47	34.57	36.47
33.30	34.25	33.62	36.47	37.42	39.33	36.79	38.06
33.62	34.25	36.16	36.47	37.74	40.16	40.80	38.10
	34.89	36.47	36.79	38.10	40.48	40.80	38.69
	35.20	36.47	37.11	38.10	40.48	41.11	39.33
	36.16	36.79	37.42	38.69	40.80	41.23	39.65
	36.47	37.11	38.06	39.33	41.55	41.89	39.65
	36.79	38.06	39.01	39.33	42.82	42.18	40.16
		38.69	41.11	44.09		42.18	40.48
		41.11					41.89
							44.72
							45.67
33.30	35.16	36.68	37.30	38.62	40.26	40.17	40.24

The results shown are expressed in K calories per sq. meter of body surface per hour.

Figures in last line represent Mean Values.

Table 11. Shows fluctuation of basal metabolic rate during normal pregnancy.

Results.

a) Relationship of Stage of Pregnancy to Basal Metabolic Rate.

The series of normal pregnant women studied consisted of sixty women at various stages of pregnancy, from the 3rd lunar month onwards. No measurements were made at earlier stages of pregnancy than this owing to the lack of suitable subjects.

From the results obtained the mean value for the basal metabolic rate in each lunar month of pregnancy from the third month onwards, was determined (Table 11). The mean values were plotted on graph paper and a curve as shown in Figure 1 was produced.

It will be observed that the Basal Metabolic Rate rises from 33.30 Kcals./ sq.m. per hour, the level at the third lunar month of pregnancy (an increase of 1.58 Kcals./sq.m. per hour or 5 per cent, in excess of the non-pregnant figure of 31.72 Kcals./sq.m. per hour) at a uniform

Figure 1.

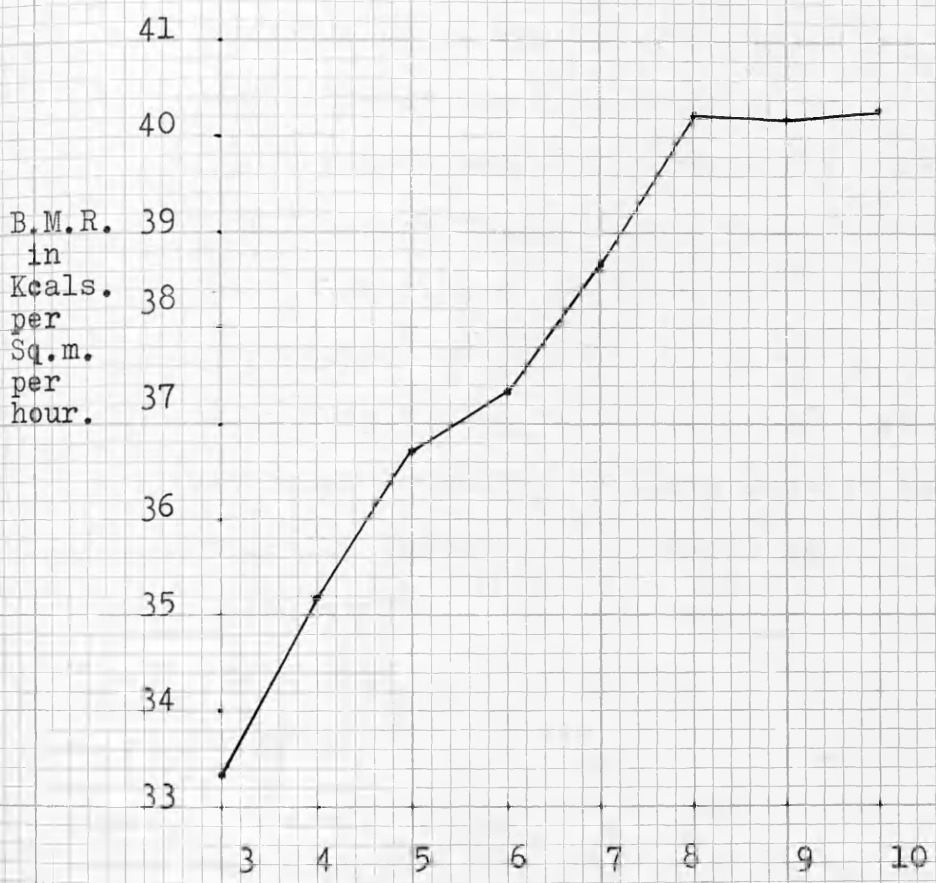

Figure 1. shows graphical representation of the changes in Basal Metabolic Rate (B.M.R.) during normal pregnancy. Twelve of the subjects were observed on two separate occasions during the same pregnancy thus giving 72 sets of observations from 60 subjects studied.

rate to reach a level of 40.26 Kcals./ sq.m. per hour at the 8th lunar month. Thereafter the level remains almost constant until the termination of pregnancy at the 10th lunar month. Whether this was simply concomitant with the frequent findings of a fall in body weight associated with the approaching termination of pregnancy or whether there was in fact some demonstrable alteration in basal metabolism associated with the onset of labour were interesting speculations. It was therefore decided to investigate more precisely the immediate pre-labour stage of pregnancy.

Six subjects were admitted to hospital a few days prior to their estimated dates of delivery.

A technique similar to that already described was adopted but in this series the subjects were given a sedative (Pentobarbitone 1½ grains) only on the first night in hospital and the basal

Figure 11.

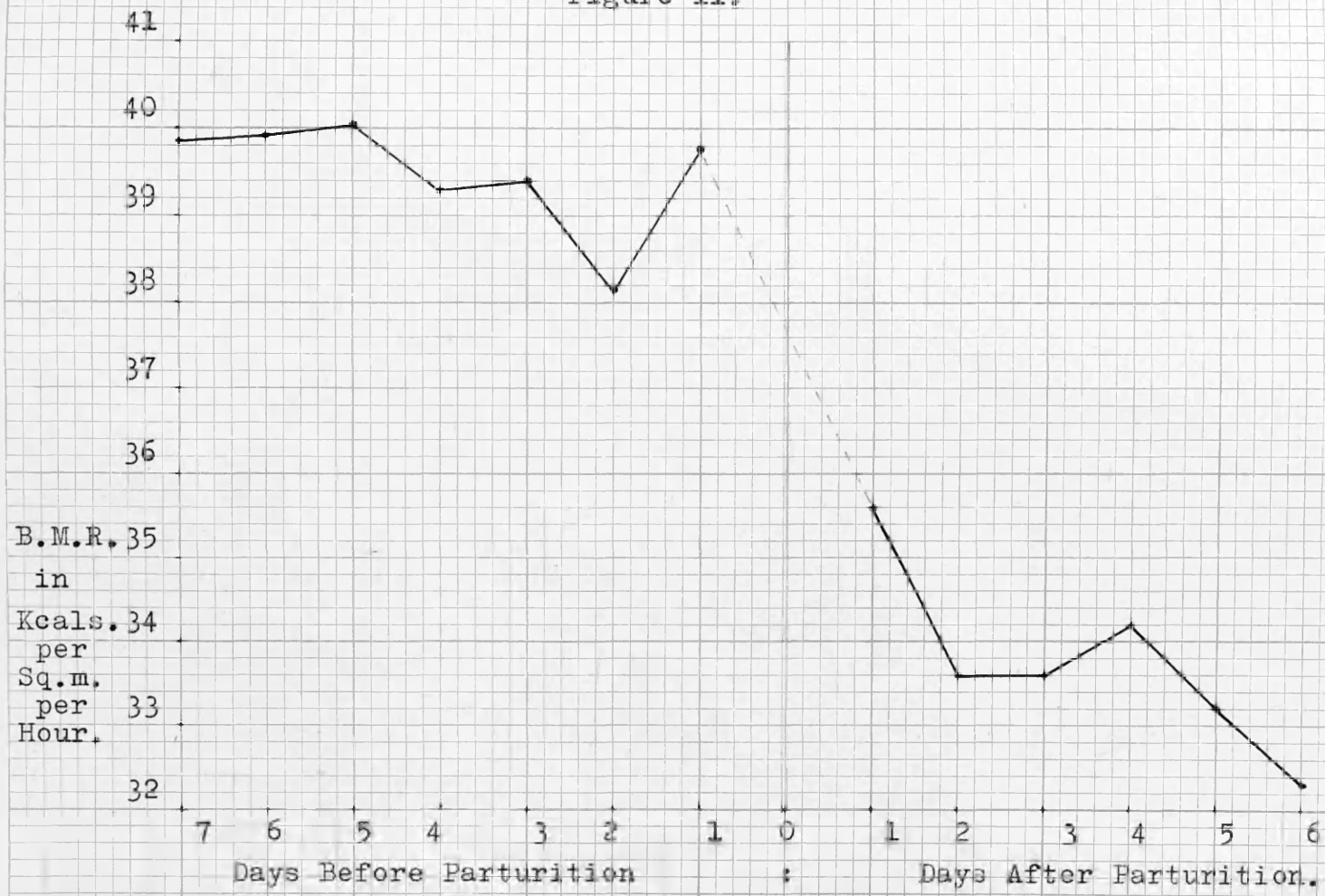

Figure 11. shows fluctuation in Basal Metabolic Rate (B.M.R.) before and after parturition.

TABLE III.

Table III.

Days Before Parturition.	Basal Metabolic Rate in Kcals./sq.m./hour.				
	Subject 1.	Subject 2.	Subject 3.	Subject 4.	Mean Value.
7	38.06	39.33	41.11	40.80	39.82
6	39.33	38.10	39.01	43.13	39.89
5	40.16	40.80	40.16	39.01	40.03
4	37.74	39.01	40.80	39.65	39.30
3	37.42	38.69	39.65	41.89	39.41
2	35.84	39.65	38.06	39.01	38.14
1	36.79	41.55	39.33	41.55	39.80
					39.49
Days After Parturition.					
1	34.25	38.06	35.52	34.52	35.59
2	34.57	32.03	32.67	34.89	33.54
3	35.20	32.98	34.25	35.84	33.57
4	34.25	33.62	34.54	34.89	34.32
5	33.62	32.98	34.25	33.94	33.20
6	33.30	31.40	31.72	32.89	32.33
					33.75

Table lll shows results of daily determinations of Basal Metabolic Rate in four subjects during seven days immediately prior to, and six days immediately following parturition.

metabolic rate was estimated daily in each case until the actual onset of labour.

The results obtained are shown in Table 111 and the mean values were plotted on graph paper. (Figure II) An analysis of variance shows that:

1) There is a significant difference in the Basal Metabolic Rate before and after parturition, the difference being that between 39.49 Kcals./Sq.m. per hour and 34.01 Kcals./Sq.m. per hour.

2) There is no significant difference between the values obtained for the Basal Metabolic Rate on the seven separate days before parturition but again as shown in Figure 111 a significant fall in Basal Metabolic Rate occurs after parturition.

Thus it can be said that no alteration in Basal Metabolic Rate occurs immediately prior to the onset of labour nor even during the last few weeks of pregnancy, and whatever is the factor

Figure 111.

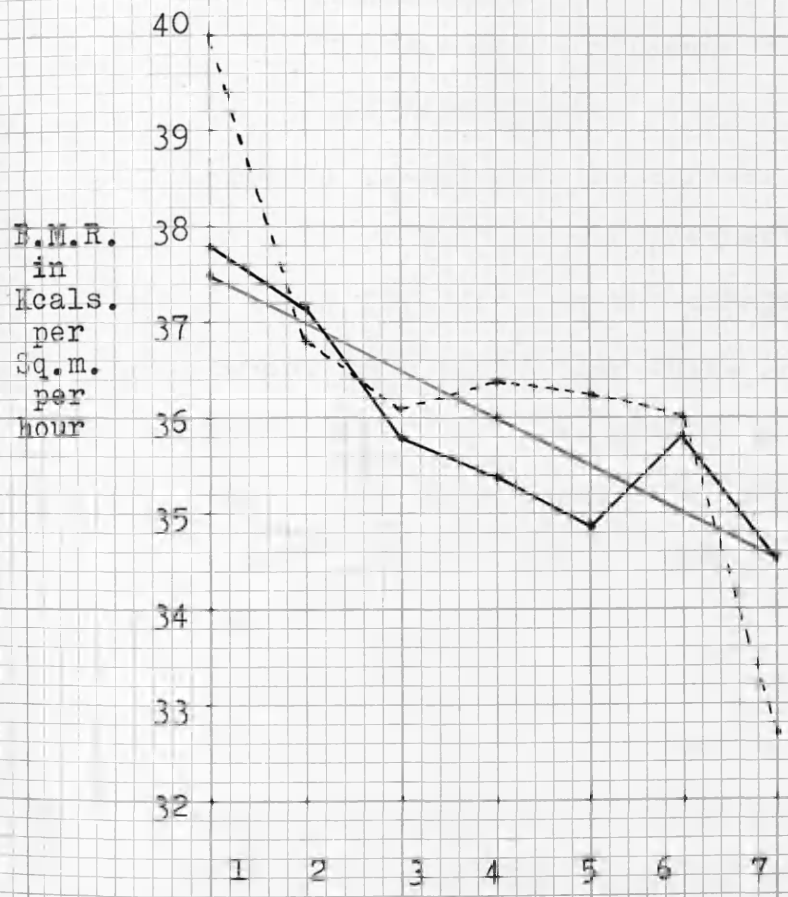

Figure 111 shows graphical representation of the changes in Basal Metabolic Rate (B.M.R.) in the first seven days following parturition. Heavy line indicates B.M.R. in normal puerperium. Dotted line shows B.M.R. in subjects with suppressed lactation. Blue line represents Regression Line.

which brings about the levelling out of the Basal Metabolic Rate during the latter weeks of pregnancy, this factor would not appear to be associated directly with the onset of labour.

b) Influence of Age on Basal Metabolic Rate in Pregnancy.

The variable influence of age on the human reproductive process and its outcome is universally agreed. Indeed the age of the patient frequently exerts a major influence on the management of labour in a particular case. It is well known that the older woman (age being the only variable and all other factors being equal) tends to have a more protracted and more hazardous labour than the younger woman. Indeed the very young adolescent is noted for having a particularly short and uncomplicated labour. Likewise fecundity is influenced adversely by advancing years.

It was felt that since age, particularly at the extremes of the

reproductive phase, as a single factor, exerted a measurable influence on the outcome of pregnancy that as such its relation to the basal metabolic rate, if any, deserved consideration.

Such an investigation was not likely to be simple since no matter how large a series was studied it would be difficult to obtain a number of results, sufficiently large to be significant, in which age was the sole variable factor. Other factors such as maturity of the pregnancy, parity and weight and stature of the subject might all influence the basal metabolic rate and so render interpretation of its relationship to age difficult or even false.

Nevertheless an attempt was made to determine such relationship from the results obtained in the initial series of sixty investigations. It was only possible to divide the small number of

TABLE IV.

Table IV.

Age Group. (Years)		Basal Metabolic Rate. (Kcalories/Sq.m.) per hour.
20-30		37.42
		39.65
		39.33
	Mean	38.80
30-40		41.23
		37.11
		40.80
	Mean	39.70

Table IV showing basal metabolic rate in two age-groups, 20-30 and 30-40 years. All readings at thirty-sixth week of pregnancy: average weight of subjects: 60 kilograms. height: 160 centimetres.

six cases where stage of pregnancy and parity and weight were approximately equal into two groups, i.e. between the ages of twenty - thirty and between the ages of thirty - forty years. There were no comparable cases whose ages were above or below the twenty - forty years range.

The results obtained are shown in Table IV and it would appear that during pregnancy, at least, age has little bearing on the metabolic rate in the twenty - forty years age group.

It is however, regretted that the series was so small, as it is obvious that a more accurate impression would be gained from the study of a much larger series.

c) Influence of Parity on Basal Metabolic Rate.

That the nulliparous woman differs from the multiparous woman in many ways cannot be denied. Although the difference

in behaviour during labour between the two classes is considered to be a purely physical one in that the tissues, in the case of the multiparous woman have previously undergone the physiological changes which those of the nulliparous woman are undergoing for the first time, the changes which do occur as a result of one pregnancy are not exactly repeated in subsequent pregnancies. Such changes are the considerably greater hypertrophy of breast tissue which takes place as a result of the first pregnancy than in succeeding pregnancies. Would it not be possible therefore for there to be similar excessive hypertrophy of other glandular tissue, including the thyroid gland, as a result of the first conception?

Likewise the generally accepted fact that pre-eclamptic toxaemia occurs more frequently in the first than in subsequent pregnancies might also indicate the possibility of a metabolic difference.

TABLE V.

Table V.

	Primigravidae.	Multigravidae.
Basal Metabolic Rate in Kcalories per sq. metre per hour.	42.82	41.11
	41.23	41.55
	39.01	41.23
	38.10	37.11
	39.65	43.77
	36.47	38.10
Mean.	39.55	40.48

Table V showing comparison between basal metabolic rates of primigravidae with those of multiparae. Results were obtained between the thirty-fourth and thirty-eighth weeks of gestation.

A scrutiny of the results previously obtained, with these aforementioned questions in mind was therefore considered worth while.

From the "normal" results obtained at one particular stage in pregnancy, viz. at the four weekly period, from the thirtyfourth to the thirtyeighth weeks, it was possible to compare the basal metabolic rates of six women who were pregnant for the first time with the rates of six women who had had one or more previous pregnancies. In the light of previous findings the age of the patient was considered as having no bearing on the results and was therefore ignored. These results are shown in Table V.

From the results obtained the metabolic rate appears to be unaffected by multiparity, there being no statistically significant difference between the Mean Values for the two

groups. Nor is there any appreciable difference in the basal metabolic rate as a result of one or of several previous pregnancies. This would suggest that any variation in basal metabolic rate during pregnancy is a result of changes in metabolism during the course of and as a result of the existing pregnancy.

Discussion.

A study of the methods of determining the basal metabolic rate used by previous workers has shown that the recording spirometer measuring the oxygen consumption appears to be the apparatus most convenient and generally accepted. Indeed since the introduction of the Benedict-Roth apparatus already described, for determining respiratory exchange this apparatus has been used in the routine investigation of the basal metabolic rate which according to Wayne (1954), is still the standard laboratory investigation used by most clinicians in an attempt to

confirm or refute a diagnosis of thyrotoxicosis.

The technique employed has however varied considerably. Earlier workers including Hanna (1938) accept a single reading as the basal metabolic rate. Robertson and Reid (1952), suggest that two consecutive readings, under ideal surroundings, that agree within 5 per cent should be obtained before accepting any figure as the basal metabolic rate.

The difficulty of obtaining two such readings prompted Bartels (1949) and others to use sedative drugs in an attempt to eliminate the effect of extraneous circumstances on the basal metabolic rate particularly in emotionally unstable patients. Bartels reported a series of patients in whom the basal metabolic rate was determined after sleep had been induced by the intravenous administration of Sodium Thiopentone. In normal patients the

basal metabolic rate dropped an average of 13 per cent whereas in hyperthyroidism there was little drop in the basal metabolic rate. Of more significance was a group of patients with greatly elevated metabolic rates due to various nervous states, in whom rates dropped to normal under Sodium Thiopentone anaesthesia, indicating absence of hyperthyroidism. Bartels states "This method of metabolism testing induces a perfect basal state - the resulting rate being void of all nervous and muscular factors".

The obvious disadvantage of this method is, the necessity of having a trained anaesthetist present at each test, and the dangers of Thiopentone anaesthesia, resulted in the use of other less potent sedative drugs.

Rapport, Curtis & Simcox (1951) suggested a safer method: the intravenous injection of pentobarbitone

sodium ("Nembutal") which induced only sleep and so avoided the risks of anaesthesia. They showed that the basal metabolic rate so obtained agreed with the clinical diagnosis in 91 per cent of two hundred patients - a much higher correlation than they obtained with the basal metabolic rate of patients awake. The results so obtained they designated the somnolent metabolic rate.

A similar technique was employed in seventy three patients by Fraser and Norden (1955) and in fifty three patients oral Amylobarbitone Sodium (Sodium Amytal) was given.

.The results they obtained were similar in both cases and closely corresponded to those of Rapport et al (1951). Fraser and Nordan (1955), regard the estimation of the basal metabolic rate during sleep as eliminating one of the main sources of error in assessing thyroid function by measurement

of the oxygen consumption but admit that ideally it should not be necessary to put patients to sleep to induce a basal state. They describe a distinct disadvantage of their method in that the patients remain drowsy and occasionally restless for the rest of the day.

Bartels (1950) in discussing basal metabolic rate and plasma cholesterol as aids in the clinical study of thyroid function suggested methods for recording a true basal metabolic rate. He believed that Pentobarbitone 1½ grains should be given on the night before and again one hour before the test was carried out in nervous and emotional patients. If this failed to produce a basal result he then advised the use of Thiopentone.

In addition to the obvious disadvantages of the Sodium Thipentone in its being a general anaesthetic and so incurring the risks accompanying an anaesthetic, Thiopentone shares with

Pentobarbitone and Amylobarbitone the fact that they depress cellular activity and therefore must depress the normal metabolism of the cells. Likewise each of these drugs undergoes detoxication which begins as soon as the drug enters the body. For this purpose a metabolic process is initiated and so further upsetting the basal metabolism. Whether or not the one process of metabolic depression counterbalances the other of drug detoxication is a matter for conjecture but the fact remains that the value obtained under the circumstances described cannot be a true basal reading and may in fact rather be "sub-basal". Such a method could however be adopted provided that sufficient standards were available which had been obtained under exactly similar circumstances. There would still be as a source of error the varying tolerance of patients to the drugs used, although this would probably

occur so infrequently as to cause no serious disadvantage.

After the consideration of the advantages and disadvantages of the various methods it seemed reasonable to the writer that by increasing the number of estimations to three taken consecutively the greatest extraneous source of error, viz. anxiety and emotion, would be eliminated by an understanding of and practice in the proceedure and that a true basal metabolic rate would be then obtained. The use of pentobarbitone was merely to ensure adequate sleep on the first two nights of the tests.

In complete contrast to the use of sedatives in determining the true basal metabolic rate Robertson (1944) in a series of basal metabolism estimations carried out on out-patients believed that a reproducable metabolism measurement could be obtained if the subject attended for the test on at least two mornings

under normal conditions. The lower of two readings which were within 5 per cent was taken as the basal level. If the second day tests were higher than those taken on the first day, further attendance was advisable until a constant reading was obtained.

In some clinics it is the usual custom to carry out only a single determination without any preliminary practice, thus excluding the element of training (Boothby, Berkson & Dunn, 1936). Those authors however add that the initial reading is accepted "unless at the time of the test and before its calculation it was noted as unsatisfactory for reasons of restlessness, observable nervous tension or an elevated temperature".

This suggests the obvious limitations of the method and selection of cases would be necessary before reliable results could be obtained.

The series of experiments just described was carried out for several reasons:- 1) By carrying out a large number of estimations, to find the most suitable and accurate technique which would give a true basal reading of metabolism. 2) To determine reliable values for the basal metabolic rates of normal pregnant women for comparison with those of abnormal and complicated pregnancies. 3) To compare a large series of estimations of basal metabolic rate in normal pregnancy with the results obtained by other workers in the field. 4) To endeavour to provide a satisfactory explanation for the changes which take place in the basal metabolic rate as a result of pregnancy.

Examination of the basal metabolic rates of the sixty normal pregnant women at varying stages in pregnancy tends to confirm the results of earlier workers.

By the third lunar month, at which

stage the earliest investigations were carried out, the basal metabolic rate had began to rise above normal limits, from the figure of 31.72 Kcals./Sq.m. per hour, taken as standard to 33.30 Kcals./Sq.m. per hour. The increase in basal metabolic rate is maintained until by the eighth lunar month the maximum level somewhere in the region of 40.26 Kcal./Sq.m. per hour (equivalent to 24% increase) is reached. After this point the basal metabolic rate continue at an almost constant level till the termination of pregnancy.

It was hoped that this levelling out of the basal metabolic rate, if investigated more thoroughly might be an indication of the onset of labour but repeated daily estimations on a small number of subjects failed to show any significant change immediately prior to the onset of labour.

Since Magnus Levy described the

results of his estimations of metabolic rate carried out in 1897, on one patient through pregnancy where he found that the oxygen consumption in the eighth month was 17 per cent higher than that of the third month, a considerable number of investigations has been reported. Conclusions as to the behaviour of the basal metabolic rate in pregnancy have been drawn from both large and small series. Conflicting statements have resulted regarding not only the actual findings obtained but also the explanations given to account for the changes. The difficulty, as already stated, would appear to lie in the interpretation of the results.

Much of the early work was summarized by Javert (1940). He constructed a graphic composite of the findings by Baer (1921), Sandiford and Wheeler (1924), Plass and Yoakham (1929), Hughes (1934), Hanna (1938), Colvin and

Bartholomew (1939) in the form of a probable basal metabolic rate curve in normal pregnancy.

This curve shows no change in the basal metabolic rate until approximately the twenty second week when a very definite rise is observed. This rise has been explained in at least three different ways. Two explanations are reasonably satisfactory. Sandiford and Wheeler (1924), believe that it is due to the increase of protoplasmic mass, the rise in basal metabolic rate being proportional to the combined mass and surface areas of the mother and foetus. In other words they believe that the rate of metabolism per unit of tissue is not increased. This view has been questioned, however, by Rowe and Boyd (1932), who challenged the basis of Sandiford's and Wheeler's calculations; but Rowe and Boyd are themselves unable to explain the change in basal metabolic

rate. As further evidence against the explanation of Sandiford and Wheeler (1924), Javert (1940) points out that in his series of eighteen hypothyroid patients the basal metabolic rate was essentially the same in the last two trimesters and in the post partum period. This observation he believes is evidence against the explanation that the raised basal metabolic rate is due to the increased protoplasmic mass of mother and foetus.

A second explanation is that the rise in the basal metabolic rate in the latter half of pregnancy is secondary to thyroid hyperplasia. The fact that there is palpable enlargement of the thyroid gland in many pregnant patients has been offered as support for this explanation. According to Hanna (1938), 40 per cent of pregnant women have palpable enlargement of the thyroid gland. Other observers quote the figure as being as high as 80 per cent. This has not been the experience

of the writer. In the present study each of one hundred normal pregnant subjects was subjected to a clinical examination which included palpation of the thyroid gland. Only 7 per cent of the subjects showed palpable enlargement of the gland. No other clinical signs of hyperthyroidism were observed. Further argument in favour of thyroid hyperplasia as a cause of increased basal metabolic rate was suggested by Javert (1940), who observed in his study of hyperthyroidism and pregnancy that the basal metabolic rate was not reduced following delivery of the products of conception. From this he concluded that thyroid hyperplasia and not active protoplasmic mass affects the basal metabolic rate. Since the enlargement of the gland occurs chronologically well in advance of the rise in basal metabolic rate this argument for hyperplasia as an explanation seems quite untenable.

Furthermore, Peters and his associates (1948) working on the precipitable iodine in serum found that the iodine level which they believed to reflect accurately the activity of the thyroid gland did not parallel the basal metabolic rate changes in the latter half of pregnancy and suggested that this was evidence that the rise could not be attributed to hyperplasia or increased activity of the thyroid gland.

A third explanation unrelated to thyroid activity is offered by Zuntz (1936) who stated that the rise, in part at least, represented the additional work imposed by interference of the enlarging uterus with the mechanics of respiration.

Arguments against this explanation are the finding in a later series, that, in a case of hydramnios where there was marked distension of the uterus, the basal metabolic rate was not unduly raised. Likewise the fact that in the normal

puerperium, as will be explained, later, after the initial fall in basal metabolic rate a constant rise occurs between the third and sixth days. If the rise were a result of an upset of respiratory mechanism one would expect an increase in basal metabolic rate and in the former and no significant rise in the latter condition.

A comparison of the results obtained in primiparous patients with those of multiparous patients shows that there is no difference between the two groups in respect of basal metabolic rate (Table V). Therefore it might be stated that whatever may be the stimulus producing the rise in basal metabolic rate during pregnancy, this cannot be transmitted either wholly or in part from one pregnancy to the next.

This would gain support in the fact that thyroid hypertrophy, noticeable as thyroid enlargement during pregnancy, undergoes regression at the end of

pregnancy so that no enlargement is detectable on clinical examination.

On perusal of the literature on the subject, no reference to the effect of repeated pregnancy on the basal metabolism was found. This seemed surprising in view of the wide diversity of opinion as to the effect of pregnancy on the abnormal gland of hyperthyroidism. According to Clute & Daniels (1930) hyperthyroid patients have, when the disease sets in, normally a history of fewer pregnancies than normal for their age. On the other hand Stewart and Menne (1933), in their studies of thyroid function during pregnancy observed the frequent occurrence of fulminating hyperthyroidism in women with histories of repeated pregnancies and suggested that the repeated excitation of the thyroid gland might eventually result in functional thyroid imbalance.

There are other authors who have

even gone so far as to say that pregnancy has a favourable effect on the disease (Astwood, 1951; Beck, 1912; Gardner-Hill, 1929; Hyman & Kessel, 1927).

A study of the results of a comparison between the basal metabolic rates in the twenty - thirty and thirty - forty age groups reveals no apparent difference between the rates in the two groups. It is presumed therefore that there can be little difference in the basal metabolic rates of the different ages during the reproductive years. This is in agreement with the findings of Berkson and Boothby (1936) who investigated the influence of age between twenty and forty years and found little variation and likewise Boothby, Berkson and Dunn (1936), using different methods found a little variation in the twenty - forty age group. This compares favourably with the view of Baer (1921), Zuntz and Loewy (1916), who found no

difference in their own metabolic rates between the ages of forty one and sixty three and twenty six and forty eight respectively. Again Loewy (1923) comes to the same conclusion. Du Bois (1929) however interprets their results as showing a gradual decline in metabolism with advancing years.

Cornell (1923) on the other hand suggested that there was a gradual increase in the metabolic rate with advancing age of the patient. Subsequently Lusk and Du Bois (1924) reported metabolism measurements on themselves over a number of years and showed uniformity in metabolism of the former. The drop in Lusk's metabolism in later years was attributed to a loss of physique due to much reading and writing.

It is clear that there has been a division of opinion as to the influence of age on the basal metabolic rate and it

is equally clear that, with so many variable factors complicating the results, the determination of that influence is not simple. It would appear from the results obtained in the present series, that if the basal metabolic rate is influenced at all, by age, this is of so little moment as to remain undetected in other than an extensive series.

The position is aptly summarised by Benedict (1928) who states that in a study of the influence of age on a group of people of various ages, it is practically impossible to rule out all other factors and have age the only variable. This was attempted by Benedict and Hendry (1921) and later by Benedict (1923), but it was found difficult to obtain groups of girls of similar height, weight and age. Long continued experiments with the same individual are consequently the best in any age study.

Part 2.

The Basal Metabolic Rate in Abnormal or Complicated Pregnancy.

This section of the work was directed towards the study of the behaviour of the basal metabolic rate in the various commoner abnormalities or complications associated with pregnancy, to observe and attempt to explain any deviations from the normal values as obtained in the earlier part of the work.

The various conditions studied were Twin Pregnancy: Pre-eclamptic Toxaemia: Cardiac Disease and Intra-Uterine Death of the Foetus.

A review of the literature on the subject of basal metabolism in pregnancy with reference to the causation of the increased rate found in pregnancy makes it clear that opinion differs widely as to the role played by the foetus in affecting

such an increase.

Rowe and Boyd (1932), as a result of their studies of this particular problem suggest that the excess heat production is apparently the result of a complicated and unknown mechanism, engendered by the state of pregnancy but involving factors other than those of the foetal tissue alone. On the other hand Sandiford and Wheeler (1924) believed that the increased rate of heat production in pregnancy represented the heat production of the newly formed protoplasmic tissue, composed largely of the foetus, and to a less extent of maternal tissue.

This being so it would be expected that a study of the basal metabolic rate during multiple pregnancy would reveal a proportionate increase.

Baer (1921) suggests that the estimation of basal metabolic rate might be used as a means of diagnosing twin pregnancy and also intra-uterine death

of the foetus. Watrous and Blakely (1942), although they did not study the influence of multiple pregnancy in the series, did in fact attempt to relate the weight of the offspring to the basal metabolic rate of the mother. They found no correlation between the two figures.

It was therefore thought desirable to carry out as many observations on the basal metabolic rate in cases of multiple pregnancy as was conveniently possible. It was hoped that if the basal metabolic rate was a measure of the increase in active protoplasmic mass in the maternal organism, this would become more apparent under such circumstances. Similar considerations lead to the study of intra-uterine death and its influence on the basal metabolic rate; thus a decrease in the basal metabolic rate coinciding with the death of the foetus might be observed as was supported by Cornell and

Baer (1921). Much more has been written regarding the relationship between the basal metabolic rate and pre-eclamptic toxaemia but again the views expressed on this subject are varied.

Stander and Peckham (1956) compared the basal metabolic rate in seventeen cases of pre-eclamptic toxaemia with that of thirteen normal cases and found that the basal metabolic rate was slightly higher in pre-eclamptic toxaemia than in normal pregnancy. Cornell found that the metabolism reading gave no information regarding the degree of toxaemia.

On the other hand, Colvin and Bartholomew (1939) found some correlation between the basal metabolic rate and the severity of the toxaemia.

Other investigators, Bloss (1937), Taylor (1928), and Hughes (1934) noted a greater incidence of toxaemia of pregnancy showing hypothyroidism early in pregnancy but offered no explanation of the

mechanism by which this was produced.

Less frequent perhaps in its incidence than pre-eclamptic toxaemia, yet a serious complication of pregnancy is the onset of cardiac failure. While certain advances have been made in the study of this complication of pregnancy there are still many perplexing problems to be solved.

Cardiac failure, although occurring most frequently at a stage in the pregnancy concurrent with the maximum changes in blood volume and cardiac output, the thirty second week, nevertheless does occur on occasions, at a much earlier stage in the pregnancy and before such physiological changes have become significant. It is possible that such failure of the heart might be brought about by interference with metabolism as a result of changes in general metabolism and endocrine activity.

Rosenkrantz and Marshal (1947), in

studying basal metabolism in hypertensive vascular disease without cardiac insufficiency found a direct correlation between basal metabolic rate and blood pressure.

Although cardiovascular disease as a complication of thyrotoxicosis has become progressively less frequent in its occurrence, there are numerous references to the combination appearing in series of cases of thyrotoxicosis.

Himsworth (1944) observed two cases of auricular fibrillation in thirty three cases of hyperthyroidism. Nussey (1944) also noted several cases with auricular fibrillation in his series.

The influences of an anti-thyroid drug, Thiouracil on cardiovascular complications of thyrotoxicosis has been studied by several workers including Grainger, Gregson & Pemberton (1945) and Cookston and Staines (1949). These workers noted a significant improvement

in a number of their cases.

The results of the use of Thiouracil in cardiovascular disease unassociated with thyrotoxicosis are however more conflicting. Raab (1943), found treatment to be effective in seven out of ten cases of angina pectoris. Ben-Ascher (1945) also noted improvement in a similar condition while Grainger et al (1945) found little or no response to Thiouracil in cases of hypertension not associated with thyrotoxicosis.

In the present study of the basal metabolic rate in pregnancy complicated by cardiac disease an attempt was made to classify the patients according to the classification of cardiacs of the American Heart Association, a classification approved of in this country by Gilchrist (1931), McIlroy and Rendel (1931), MacLennan (1933), and MacRae (1948) and others.

Thus not only a study of the basal

metabolic rate in pregnancy complicated by cardiac disease would be possible but the influence, if any, of the varying degree of severity of cardiac failure on the basal metabolic rate would be observed.

Method.

The method used in estimating the basal metabolic rate in the abnormal stages of pregnancy was similar in every way to that used in the initial series of normal pregnancy and the writer was equally satisfied with the accuracy of the results obtained.

The estimations were invariably carried out during the time when the patient was in hospital for some particular reason pertaining to her abnormal condition.

The basal metabolic rates obtained in the individual groups were tabulated separately and were compared with the corresponding figures for basal

TABLE VI.

Table VI.

Stage of Pregnancy in weeks.	Basal Metabolic Rate in Kcalories per Sq. metre per hour. SINGLE PREGNANCY.	Basal Metabolic rate in Kcalories per Sq. metre per hour. TWIN PREGNANCY.
35	37.42	49.55
36	41.23	45.04
36	39.65	44.40
36	39.33	36.79
38	40.80	47.58
40	39.01	41.89
40	40.48	45.35
Mean Average	39.70	44.80

Table VI showing comparison of basal metabolic rate in single and multiple (twin) pregnancy.

metabolic rate obtained at a similar stage in normal pregnancy.

Results.

a) Basal metabolic rate in multiple pregnancy (Twins).

A total of seven cases of normal twin pregnancy are included in this series. The diagnosis of twin pregnancy was in each case confirmed radiologically, before the case was included in the series and only patients in whom no other abnormality existed, were used as subjects. The basal metabolic rate was estimated in the manner described and the results obtained were compared with the basal metabolic rate of normal pregnancy at a similar stage, where only one foetus was present.

These results were tabulated and are shown in Table VI. It will be noted that in this case individual results of normal single pregnancy were taken and an average figure was obtained from them.

This figure, even for such a small number of cases, was so close to the figures obtained from the graph that it was deemed unnecessary to use individual figures in future comparisons.

It will be observed from a study of Table VI that the difference between the mean values for the basal metabolic rate in twin pregnancy and in pregnancy where only a single foetus is present compared at the same stage of pregnancy, is highly significant ($P < 0.01$).

The rate in twin pregnancy is considerably greater than, but is less than twice, that obtained in pregnancy where only one foetus exists.

b) Basal Metabolic Rate where Intra-uterine Death of the Foetus has occurred.

Several difficulties were encountered in the collection of this series of cases. The diagnosis of intra-uterine death of the foetus is not always easy. This is particularly so

in the earlier months of pregnancy where foetal movement might not be readily appreciated and when the foetal heart is not clearly heard. Even in the latter months of pregnancy the cessation of foetal movements and the inability to hear the foetal heart do not always signify death of the foetus. The diagnosis in such cases is often helped by radiological examination but even by this means one is not always certain of the diagnosis unless definite overlapping of the skull bones (Spalding's Sign) is observed.

Only such cases where a definite Spalding's Sign had been demonstrated were included in the series and it was therefore with some difficulty that, and after some considerable time had elapsed before, a series of six cases was amassed.

The basal metabolic rates were compared with the rates of normal pregnancy for a similar length of pregnancy. In

TABLE VII.

Table VII.

Stage of Pregnancy in Weeks.	Basal Metabolic Rate. Kcals./sq.m. per hour. Normal Pregnancy.	Basal Metabolic Rate. Kcals./sq.m. per hour. Intra Uterine death of Foetus.
25	36.47	36.79
36	40.48	35.84
30	38.06	32.67
28	37.42	34.25
34	39.65	33.30
24	36.47	34.89
Mean	38.06	34.62

Table VII showing basal metabolic rate where intra uterine death of the foetus has occurred. The figures for the basal metabolic rate in normal pregnancy were obtained from the graph (Figure I).

the case of the Intra-uterine foetal deaths, duration of pregnancy was calculated from the first day of the last menstrual period to the date of the cessation of foetal movements where this was noted by the patient or when the original diagnosis, not necessarily the confirmatory one, was made. These results and comparisons are shown in Table VII.

It would appear from examination of the individual results that the basal metabolic rate is significantly reduced to almost pre-pregnancy levels in cases where intra-uterine death of the foetus has occurred. ($P < 0.01$).

c) Basal Metabolic Rate in Pre-eclamptic Toxaemia.

In the series of experiments on patients suffering from pre-eclamptic toxaemia of pregnancy, strict standards for the diagnosis of the condition were adopted. This resulted in the rather

TABLE VIII.

Table VIII.

Stage of Pregnancy in weeks.	Basal Metabolic Rate in Normal Pregnancy. Kcals./sq.m. per hour.	Basal Metabolic Rate in Kcal./sq.m. per hour. in Pre-Eclamptic Toxaemia.
40		49.93
40		41.55
40		42.18
37		45.67
38		40.80
38	39.65	40.48
40		40.48
35		41.89
38		43.13
40		41.23
Average		42.73

Table VIII showing a comparison between the basal metabolic rate in normal pregnancy and the basal metabolic rate in pre-eclamptic toxaemia. The average figure of 39.65 Kcals. was taken from the graph (Figure I) to represent the basal metabolic rate in the 35-40 weeks group of normal pregnancies.

small number of patients suffering from a relatively common complication being included in the series.

Only patients in whom the blood pressure was elevated above 140/90 millimeters of mercury and who had slight to moderate oedema of the extremities were included. These strict standards were adopted to ensure that the changes in basal metabolic rate in pre-eclamptic toxaemia only was studied and that no case of essential hypertension was included. No case of eclampsia occurred during the course of this series of experiments and therefore no results for eclampsia were obtained.

The results of the basal metabolic rate estimation of the ten patients comprising the series were tabulated as in Table VIII and were compared with the basal metabolic rates of normal pregnancy at a similar stage in the pregnancy.

On examination of the results

obtained it appears that there is a significant difference between the basal metabolic rate in pre-eclamptic toxaemia and normal pregnancy ($P < 0.01$), this difference being an average increase of 3.08 Kcal./Sq.m. per hour in pre-eclamptic toxaemia.

d) Basal Metabolic Rate in Pregnancy complicated by Cardiac Disease.

This study consisted of the estimation of the basal metabolic rate in twelve pregnant patients in whom a cardiac complication existed. All had some degree of mitral stenosis but in all except two cases the exercise tolerance, the most important factor from the point of view of the pregnancy, was good. The patients therefore fell into the category II of the American Heart Association classification of cardiacs and only two patients were of Group III having a poor exercise tolerance.

TABLE IX.

Table IX.

Grade of Cardiac Disease (New York Classification).	Maturity of Pregnancy in weeks.	Basal Metabolic Rate in Kcals./ Sq.m./Hour Normal Pregnancy.	Basal Metabolic Rate (Kcals./ Sq.m./Hour) in Pregnancy complicated by Cardiac Disease. Grade 1	Grade 11
II	38	39.65	42.82	
II	32	39.01	38.06	
II	38	39.65	35.84	
II	39	39.65	37.74	
II	34	39.33	52.97	
II	29	38.06	37.74	
II	36	40.80	36.78	
II	30	38.06	36.47	
II	29	38.06	37.74	
II	40	39.33	32.03	
III	40	39.33		40.48
III	38	39.65		45.99
Mean		39.22	38.82	43.28

Table IX showing the basal metabolic rate in pregnancy complicated by cardiac disease.

The small number of patients with a severe degree of cardiac involvement, although a favourable reflection on the satisfactory ante-natal care, was regretted as it was felt that any variations from the normal basal metabolic rate were most likely to occur in the more seriously affected cases.

The results obtained were tabulated as in Table IX according to the cardiac grading and were again compared, with the normal results previously obtained.

The only conclusion which can be drawn from the figures obtained in this experiment is that the basal metabolic rate appears to be unchanged in pregnancy complicated by cardiac disease, where cardiac failure is not a feature, as compared with the results in normal pregnancy. No significant difference was found to exist between the mean Basal Metabolic Rate of subjects with Grade II Cardiac Disease complicating pregnancy

and the mean Basal Metabolic Rate in normal pregnant women.

On comparing the mean Basal Metabolic Rate of Grade III cardiac subjects with that in normal pregnancy however, a difference of 4.04 Kcal./Sq.m. per hour was observed.

This revealed a significant difference between the values compared.

Discussion.

a) Foetal Influence on Basal Metabolic Rate.

There have existed for many years a lack of decision as to whether the purely maternal metabolic rate is raised during pregnancy; that an increase in total energy expenditure occurs is undisputed. The prime difficulty in considerations of the maternal rate has been the necessity for making critical assumptions concerning the metabolic rate of foetuses. The problem has been reviewed by Newton (1952) who concluded

that the majority of evidence favoured the belief in an increased maternal metabolism in most species studied. Support of a more direct nature is given to this conclusion by the findings of Dewar (1953) that the metabolic rate is raised in mice with retained placentae but in the absence of foetuses, which were physiologically pregnant. That the raised metabolic rate is due to an increase in activity is unlikely, however, for both Slonaker (1924) and Wang (1924) observed decrease in the activity of rats during pregnancy.

Rowe and Boyd (1932) in an attempt to assess the part played by the foetus in causing the rise in basal metabolic rate in pregnancy investigated the heat production in a series of seventy-seven women throughout the last six lunar months of pregnancy. They found that during the third and fourth months of gestation there was a decline in the

energy requirement from a normal to a subnormal level, the latter being reached in about four weeks. From that point onwards they noted a steady increase in the basal metabolic rate amounting to 13 per cent or more in excess of that conditioned by the gross increase in body weight. As a result of an analysis of their results and calculations they were unable to support the view that the excess basal metabolic rate was contributed primarily by the foetus. They concluded that the excess heat production is apparently the result of a complicated and unknown mechanism engendered by the state of pregnancy but involving other factors than those of foetal tissue alone.

Sandiford and Wheeler (1924) in an earlier communication reported an exhaustive study of the basal metabolism of a normal woman before, during and for six lunar months after pregnancy and

from their results and from the study of the results of previous investigators concluded that the energy production of a unit mass of the mother's protoplasmic tissue remained unchanged throughout the course of pregnancy, and that such increases in the total heat production which occur are due to the increasing mass of active protoplasmic tissue consisting in larger part of the foetal tissues and in lesser part of maternal structures.

Javert (1940) however disagrees, having found in his study of hyperthyroidism in pregnancy that delivery of the products of conception failed to reduce the basal metabolic rate. He suggests that the increase in basal metabolic rate, usually found in pregnancy is not due to the foetus but to thyroid hyperactivity.

On the other hand Dewar (1953) as the result of a study of the total metabolism of the mouse after pseudo-

parturition and parturition suggests that the fall in weight following pseudo - or normal parturition is largely due to a loss of water, and this rapid and irreversible loss bears no apparent relation to protein losses. The removal of the placenta is the signal for the termination of a water-retaining mechanism. The closely correlated irreducable sodium losses further indicate that the water held in pregnancy is probably extra cellular.

It was found that the weight loss was proportional to the energy expenditure and that although after parturition and removal of the foetuses there was a fall in total energy expenditure, the metabolic rate expressed as Kcal./gm. body weight/ 24 hours before and after parturition showed no definite change.

Furthermore, the metabolic rate before parturition was found to be noticeably lower than that in mice with living placentae only and in whom the

foetuses had previously been destroyed by crushing. A possible explanation of this is that the foetal metabolic rate per unit body weight is lower than that of the mother, thus tending to mask any increase in the maternal rate which might occur.

From the results of the present series of estimations of basal metabolic rate in twin pregnancy it would appear that the foetus does in fact play some part in causing the rise in basal metabolic rate in pregnancy.

An increase of some 3 Kcals./Sq.m. per hour would appear to be due to the presence of a second foetus. That this increase is not twice the increase found in normal single pregnancy (7 Kcals./Sq.m. per hour) would suggest that although foetal influence is great there must be some other factor, as suggested by Rowe and Boyd (1932) contributing to the rise.

The results of the investigations

in cases of intra-uterine foetal death make an explanation more complex. In this case an actual reduction of basal metabolic rate of 3.44 Kcals./Sq.m. per hour (= 11 per cent) was noted. This would suggest that following the death of the foetus, if the foetus is not responsible for the entire rise in basal metabolic rate some other factor which is anti-thyroid in its effect comes into action. That placental activity regresses after the death of the foetus is a known fact and it is postulated that the factor which is responsible for the additional hyper-metabolic effect, originates in the placenta and in normal pregnancy stimulates thyroid hyperactivity.

Support to this belief is given by the findings of Dewar (1953) that an average decline in total energy expenditure of about 12 per cent occurred in the three to four days after pseudo-

parturition in the mouse while finding that the metabolic rate was raised in the same animal with retained placentae but in the absence of foetuses i.e. physiologically pregnant.

It is of significance that placental function, in a hormonal respect, begins at or about the twelfth week of pregnancy, at about which stage, an initial rise in basal metabolic rate is observed.

A similar fall in the basal metabolic rate in association with foetal death in late pregnancy was noted by Baer (1921) in women who were otherwise normal.

Connell (1923) on the other hand failed to find such a correlation between foetal death and basal metabolism.

Nevertheless results of investigations relating to intra-uterine death of the foetus and to twin pregnancy demonstrate a definite relationship between the foetus and the increase in

basal metabolic rate. At the same time the relationship is not direct and this would suggest that some other factor causes a stimulation of metabolism. Almost certainly this factor resides in one or other of the marked endocrine changes which take place during pregnancy.

b) Hormonal Influence.

It is now well known that the metabolic rate is mainly controlled by the thyroid gland acting largely under the influence of the thyrotropic hormone of the anterior pituitary. (Samson Wright 1952). Many problems associated with thyroid function have been elucidated in recent years by the use of radio-active isotopes although this is unsuitable as a method for investigations in the human in the pregnant state. Until recently it had been assumed that the active secretion of the thyroid gland was thyroxin, which is tetraiodotyrosine.

It is now known that the active component of the gland is triodothyronine (Gross and Pitt-Rivers, 1953: Asper, Selenkow & Plamondon, 1953).

Similarly in recent years the thyrotropic hormone has been isolated in relatively pure state from the anterior pituitary gland and it has been shown that where the thyroid gland is removed or destroyed, the secretion of thyroid hormone increases thus showing the direct relationship between this hormone and thyroid activity (Samson Wright 1952). A reciprocal action is suggested by Evans, Simpson & Pencharz (1939) and Roy (1947) who found maximal anterior pituitary growth effects highly dependent on thyroxin.

It has been known for some considerable time that the basal metabolic rate of normal women shows a definite cyclical variation (Hitchcock & Wardwell, 1929). Since the highest metabolism is

usually observed in the week before and in the week after the menstrual period, when the corpus luteum and the follicle appear to be very active, it seems possible that such a rise is due to the secretions from these structures.

In support of this hypothesis, that the basal metabolic rate is affected by the ovarian hormones, there is the evidence that women with faulty ovarian hormones are likely to have low basal rates (Litzenberg & Carey, 1929; Randall, 1934; Thurmann & Thompson, 1930). Furthermore bilateral oophorectomy in women usually results in a lowering of basal metabolism to 7-20 per cent below normal (Allen, 1932). Collett, Smith and Werkenberger (1937) found a lowering of basal metabolic rate of 12-30 per cent following castration in women. King (1926) however in a large series of cases found the basal rate of such women close to normal levels.

The literature dealing with the effect of oestrogen upon the basal metabolism (Allen, (1932); Zondek (1930); v.Arvay and Meyer (1932)), is somewhat confused.

Some authors (Kochmann, 1926; Anselmino, 1934) suggest that the basal metabolism is raised by some ovarian hormone other than oestrogen. Pratt (1936) also suggests a special thyrotropic hormone of the ovary as does Anselmino (1934). von Arvay (1933) states that in ovariectomised rate the basal metabolic rate is raised by oestrogen administration only if the uterus is left intact and suggests that the increase observed in basal metabolic rate is caused by increased oxidation in a uterus sensitised to pitocin by the presence of oestrogen.

Moore and Price (1932) found the secretion of both gonadotropic and growth hormone inhibited by oestrogen. Lane

TABLE X.

Table X.

	Basal Metabolic Rate Kcals./Sq.m. per hour. before Oestrogen.	Basal Metabolic Rate Kcals./Sq.m. per hour. after Oestrogen.
1	43.45	40.16
2	39.65	34.54
3	44.09	43.45
4	35.52	32.35
Mean	40.68	37.63

Table X showing the effect of Oestrogen administration in the basal metabolic rate.

(1935) found that small oestrogen injections stimulate, while heavier dosages inhibit, the production of gonadotropic hormones.

The inhibition under heavy oestrogen dosage is explained by Halpern and d'Amour (1936), as being due to an overstimulation of the pituitary which brings about a period of overgrowth at the expense of secretory activity.

It is therefore probable that a similar effect on the thyrotropic hormone is exerted by oestrogen. The depressant effect of large doses is suggested by the results shown in Table X obtained following administration of large doses of oestrogens, a dosage similar to that used to inhibit lactation.

The difference between the mean values for the results obtained in the same subjects before and after administration of oestrogens was found to be statistically significant ($P < 0.05$).

In support of this contention, Sherwood and Bowers (1936) working with rats and Starr and Patton (1935) working with women, have shown that prolonged oestrogen administration reduces the basal metabolic rate in hyperthyroidism and suggest that the effect is by way of the hypophysis.

c) Pre-eclamptic Toxaemia of Pregnancy.

The frequent occurrence of toxaemia as a complication of pregnancy with its serious consequences both to mother and child has resulted in countless and exhaustive researches into the aetiology of the condition.

Several workers have demonstrated a relationship between toxaemia of pregnancy and an alteration in basal metabolic rate. Bartholomew and his co-workers (Bartholomew & Kracke, 1932; Bartholomew & Parker, 1934; Bartholomew & Kracke, 1936; Bartholomew & Colvin, 1938), as a result of several studies

found evidence to support the theory that toxaemia of pregnancy was probably due to toxic products of autolysis of acute placental infarcts which in turn were the result of a specific type of vascular disease of the placental arteries brought about by the combined factors of hypercholesteraemia of pregnancy and the trauma of foetal movements on the exposed placental vessels.

Bloss (1937) found an increased tendency to toxaemia among women who had low metabolic rates early in gestation. He also noted that the placentae from women with hyperthyroidism late in pregnancy, showed much degenerative change with haemorrhage and infarction.

Taylor (1928) likewise noted a tendency to eclampsia among women with low metabolism early in pregnancy. Neither, however, gave any explanation

of the mechanism by which this association between toxaemia and hypothyroidism is produced.

Although only one case under the age of twenty years appears in the author's series, it is generally accepted that pre-eclamptic toxaemia occurs more often in adolescent primigravidae than in primigravidae of the older age groups.

Talbot, Wilson & Worchester (1937) in the study of basal metabolism, state that in adolescence, particularly between the fifteenth and sixteenth years the basal metabolic rate is at a particularly low level. Hurxthal (1934), Luden (1918), Epstein and Lande (1922), and Mason, Hunt and Hurxthal (1930) have shown by clinical or animal experiments, that in hypo-metabolic states, the blood cholesterol is increased whereas in hypermetabolism it is decreased and that the inverse relationship holds true whether brought about by pathology of the thyroid gland or

by administration of dessicated thyroid.

Turner, Present and Bidwell (1937) demonstrated an increase of 19 per cent in blood cholesterol in rabbits, following total thyroidectomy, but the increase was much more marked (137 per cent) in rabbits with experimental hypercholesteraemia previously induced by cholesterol feeding.

Hunt, Paterson and Nicodemus (1938) likewise observed a fall in blood cholesterol following the administration of thyroid extract and a rise to its former level when the thyroid extract was discontinued.

A similar fall in blood cholesterol in hyperthyroidism was described by Boyd and Connell (1936) who also stated that as the cholesterol falls, the fall in the cholesterol esters is more marked than that of the free fraction.

While it is generally agreed that the plasma cholesterol of women and of

other animals increases during pregnancy (Boyd, 1934; Fahrig & Wacker, 1932; Gardner & Gainsborough, 1929; Hermann & Neumann, 1912; Oser & Marr, 1925; Pribram, 1925; Stepp, 1918), Colvin and Bartholomew (1939) describe a greater increase, in women who are liable to develop toxaemia, and a fall in cholesterol during the course of the developing toxaemia. Boyd (1935) observed that the ratio of the total cholesterol to the cholesterol esters was raised in pregnancy complicated by pre-eclamptic toxaemia. There was thus a decrease in cholesterol esters and a further decrease was noted in cases of eclampsia. Indeed, Epstein and Greenspan (1936) found a complete absence of cholesterol esters in the plasma of fatal cases of toxaemia of pregnancy.

It would therefore appear that the correlation between metabolism and cholesterol levels which exists in the

hyperthyroid state is maintained in toxaemia of pregnancy once that condition has become established. The behaviour of the cholesterol fractions, in particular the esters, would seem to correspond with the severity of the condition.

Colvin and Bartholomew (1939) in their study of the behaviour of the basal metabolism in the course of developing toxaemia and the correlation with cholesterol and placental infarction, found that the basal metabolic rate in the first trimester of pregnancy was appreciably lower in the toxaemic group of patients. They also found, however, that without exception, at the onset of clinical symptoms and signs of toxaemia of pregnancy, the basal metabolic rate sharply increased to levels far above those previously noted in the earlier months of gestation or in normal pregnancy at a similar stage in pregnancy. Indeed they observed that the severity of the

toxaemia was proportional to the rise in basal metabolic rate.

The results of the present study as shown in Table VIII indicate a rise of basal metabolic rate above normal in toxaemia of pregnancy, there being a significant difference between the mean values for the two groups.

Further interesting results might have been obtained if the metabolic rate could have been correlated with the amount of oedema present in cases of pre-eclampsia. An inter-relationship between fluid retention; toxaemia of pregnancy (pre-eclampsia and eclampsia) and placental function may well exist. Indeed a placental cause of eclampsia has been suggested by some workers - Browne (1936) Smith and Smith (1948).

That water is retained during pregnancy has been accepted for some time. Studies by Chesley (Chesley, 1943; Chesley & Boog, 1943) by the thiocyanate

method revealed an increase in extracellular fluid in pregnant women too great to be accounted for by the quantities acquired by the reproductive organs, followed by a post-partum reduction thiocyanate space. There is ample evidence that the water retention of pregnancy is exaggerated in pre-eclampsia and eclampsia (Dieckmann & Pottinger, 1955; Chesley, 1951; Browne, 1950).

It has been shown that the human placenta also secretes an anti-diuretic substance which is found in greater amounts both in the placenta and in the urine of toxaemic than in those of normal pregnant women (Ham and Landis, 1942) unlike that hormone derived from the posterior pituitary in that it does not increase excretion of chloride and this substance therefore may act as a cause of retention of water and oedema, directly as an anti-diuretic and indirectly by not

stimulating the renal excretion of salt.

If these facts are correlated with the findings of Dewar (1943) and of Brooksby and Newton (1938) of a precipitate loss of water following loss of the placenta as a result of either parturition, or pseudo-parturition and also the changes in metabolism following pseudo-parturition already referred to (Dewar: 1953), the existence of a possible placenta/metabolism relationship can be readily postulated.

With this postulation in mind it would seem reasonable to support the views expressed by Colvin and Bartholomew (1939) that the sudden elevation in basal metabolism, accompanying the onset and continuing throughout the course of toxaemia of pregnancy, is the result of a sudden increase of thyroid activity brought about by excessive stimulation of the gland by the poisonous autolytic products of acutely infarcted placental tissue and

that the basal metabolic rate as determined in the first trimester of pregnancy bears a direct relation to the incidence of toxaemia in the last trimester of pregnancy.

No attempt was made in the present study to investigate more fully the changes in basal metabolism in toxaemic patients but in the light of the findings of Colvin and Bartholomew (1939) a fuller investigation would seem worth while, as it might offer possibilities in the prevention or at least in the early detection of toxaemia.

Colvin and Bartholomew (1939), although they found a significant fall in the blood cholesterol in the cases which they believed were least likely to develop toxaemia, i.e. those with a high basal metabolic rate early in pregnancy, did not find any significant difference in the groups with a lower metabolism. They suggested that in the

early stages of the pregnancy the degree of hypercholesteraemia was less important as an aetiological factor in toxaemia than the trauma of foetal movements on the unprotected arteries of the surface of the placenta. They believed that the placental infarcts were not necessarily produced by a hypercholesteraemia. The increase in basal metabolic rate is in turn accompanied by a drop of blood cholesterol. This may explain why Slemons and Curtin (1917) did not find hypercholesteraemia constantly present in eclampsia.

Like Vortzeimer, Fishberg, Langrock & Rappaport (1937), who advocated more watchful care for those patients who presented stigmas of endocrine disturbance and low basal metabolic rate on account of their increased liability to toxaemia, Colvin and Bartholomew (1939) go so far as to suggest that it would seem advisable to determine the basal metabolic rate of

each new patient, early in her pregnancy, in order to determine those cases displaying early evidence of hypometabolism. They further suggest treating such patients with thyroid extract in order to bring the basal metabolic rate to a positive reading.

d) Cardiac Disease.

The importance of heart disease as a complication of pregnancy cannot be overestimated. While everyone concedes that the work of the heart is increased during pregnancy, there is little agreement as to how this increase is brought about. Obviously many factors are involved and all may exert some effect on the heart's action. The most obvious explanation would be that the increase in body weight contributes an added load on the heart. Cases have been recorded, however, in which pregnant cardiac patients were relieved of symptoms of cardiac insufficiency when the foetus had died,

although it was still retained in the uterus. It is noteworthy that under similar circumstances the writer found the basal metabolic rates to be low and below normal.

The effects of mechanical pressure fail to explain the case. Vital capacity, although reduced in cardiac failure in proportion to the degree of failure, remains within the limits for normal pregnancy. Neither do the metabolic demands of the ovum appear sufficient to explain the increase in cardiac work. The minute volume of the heart and the heart rate are however increased and would therefore exert some influence on the heart. There is also a slight retardation of the blood flow Greenstein and Clahr (1937). A further factor causing increased strain on the heart is the fact that the placenta represents a large low resistance shunt which may contain up to one sixth of the

blood volume (Rodbard & Katz, 1944).

The increase in blood volume alone, would require a greater effort on the part of the heart to maintain effective circulation.

An additional factor is the possible association with increased basal metabolic rate the increase of which in pregnancy is suggested by the writer as being related to hyperthyroid activity during pregnancy.

From the results obtained in the present study it would appear that in pregnancy complicated by cardiac disease of mild degree, the basal metabolic rate differs only slightly from that expected in a normal pregnancy. This slight difference in rate is represented by a fall to below the normal levels for uncomplicated pregnancy at a similar stage, but the difference between the groups is not significant.

Rosenkrantz and Marshall (1947)

studied the basal metabolic rate in hypertensive heart disease and found a significant incidence of hyper-metabolism and also noted a decided correlation between basal metabolic rate and both systolic and diastolic blood pressure. On the other hand they did not find any significant association between basal heat production, and the pulse pressure. They also noted a greater incidence of renal dysfunction in hypertensive patients with increased basal metabolic rate than in those with normal or subnormal basal heat production. This they believed to be a result of greater elevation in blood pressure in patients suffering from renal dysfunction. It is of interest to compare their results with the results obtained in the present series where all the cases studied were of valvular disease of the heart. In all of the cases the lesion was either a pure stenosis or a

combination of stenosis and incompetence of the mitral valve. No case showed signs of cardiac failure. The blood pressure, both systolic and diastolic, was within normal limits and therefore the converse effect of a subnormal blood pressure could not be operative in these circumstances.

It is postulated that the behaviour of the basal metabolic rate, at least in pregnancy, bears a relation to the exercise tolerance of the individual. In women with valvular disease, depending on the extent of cardiac damage, a stage may be reached such that if metabolism is raised above a particular level, cardiac compensation will no longer be adequate and signs of cardiac failure will ensue. The clinical improvement which normally takes place in the last few weeks of pregnancy, and believed to be a result of the reduction in blood volume may also be contributed to by the constant level of

basal metabolism noted earlier in the series.

In support of this view, is the close parallel which has been shown by Barwell (1938) between cardiac output and oxygen consumption.

In addition the behaviour of the cardiac output in normal pregnancy as observed by Stander and Cadden (1932), who found an increase in cardiac output up to the ninth lunar month with subsequent decrease prior to labour at term, bears a resemblance to that of the oxygen consumption as observed by the writer.

It is further postulated that, although only two of the patients comprising the series under consideration showed signs of cardiac insufficiency, vital capacity was in fact reduced to below normal in all cases, and that with the reduction in pulmonary ventillation and in carbon dioxide output, general metabolism was reduced as a result.

That the converse of this occurs is suggested by a study of the respiratory changes in myxoedema (Samson Wright, 1952). If this postulation is true, the tendency to lower readings in the Grade II cases as noted in the series would be readily explained.

This does not appear to hold good for the more severe degree of cardiac disease (Grade III) however, since a difference of 4.04 Kcal./Sq.m. per hour was noted between the Basal Metabolic Rate in Grade III cardiac pregnant cases and normal pregnancy.

While this infers that there is a significant rise in the Basal Metabolic Rate in the more severe degrees of cardiac disease it must be remembered that only two cases of Grade III disease were studied and one cannot therefore lay great stress on the findings. A possible explanation might lie in the presence of an increase in body fluid in severe cardiac disease

but obviously further work in this field would be necessary before any real information could be gained from this fact.

Part 3.

Basal Metabolism during the early Puerperium.

When the stage of culmination of normal pregnancy is reached a considerable alteration has taken place in the maternal organism. This alteration has been the result of many gradual and progressive changes in anatomy and physiology over the entire period of gestation of nine months.

During this period the uterus has increased in weight from 40-50 grammes to 900-1200 grammes, as a result of the hypertrophy of uterine musculature. This hypertrophy not only means an increase in protein but the fat content of the muscle cells is also increased.

Changes principally in the form of hyper-activity occur in almost all of the endocrine glands, many of which play such an important role during pregnancy.

In spite of a positive nitrogen

balance with a reduction of specific dynamic action and a retention of nitrogen far beyond the needs of the growing foetus, the generaly metabolic process in the mother is increased. An increased retention of fat occurs and is accompanied by an increased production of fat. Carbohydrate metabolism also suffers an alteration.

In the light of so many physiological changes it is not surprising to find alteration in the blood of the pregnant woman. Not only is the fluid content of the blood increased but the cellular content is also increased in order to supply the extra needs enforced on the maternal organisms.

These changes which are briefly mentioned have been gradual and have taken place over a period of months. During this period a significant change in basal metabolism has been observed and studied. Suddenly with the birth of the child the

need for all this increased activity is no longer required and in a matter of weeks the maternal organism is expected to revert to its former pre-pregnant state.

This process of reversal, the puerperium, normally takes approximately six to eight weeks to reach completion but probably the most significant and dramatic changes take place within the first week after parturition.

The various physiological processes involved in this reversal, bordering so closely as they do upon the pathological, are referred to collectively as "involution".

The structures undergoing involution include not only the essential parts of the generative tract but also the abdominal wall, the pelvic peritoneum, the supporting structures of the uterus and the lower urinary tract.

The uterus which at the end of labour weighs about 1,000 grammes has by the end of the first week of the puerperium

reduced its weight by one half and within the second week has reduced its mass to around 350 grammes. This reduction in weight is completed by the sixth to eighth week post-partum when the uterus has almost regained its former non-pregnant weight.

The process of involution of the muscular wall of the uterus is believed to be effected mainly by autolytic changes rather than simply by fatty degeneration. This results in a reduction of the protein constituents of muscle fibre to simpler chemical components, which are excreted in the urine. This is shown by an increase in the nitrogen output in the urine. This is confirmed furthermore, in cases of Caesarean hysterectomy, where the characteristic increase in nitrogen output is practically absent, hence its origin in uterine muscle tissue. The uterine vessels similarly undergo a process of involution by a mechanism of thrombosis

followed by degenerative changes.

At the same time as the involutional changes are taking place in uterine muscle, regeneration of the endometrium is taking place. This process originates in the deeper portion of the decidua which remains after separation of the placenta.

The changes occurring in the breasts in the puerperium are those leading to functional activity. Involution of breast tissue never occurs before lactation is established even where lactation has been suppressed.

It is a well accepted fact that mammary development occurs as a result of stimulation by the hormones oestrogen and progesterone and that following parturition the true-milk secretory phase of breast activity is a result of the influence of pituitary hormone; indeed the hypertrophy of the anterior pituitary gland has been shown to persist during lactation.

The breasts at the beginning of the puerperium as a rule undergo little change until the third or fourth day. At this time or even as late as the fifth day true milk secretion or lactation begins.

The behaviour of the basal metabolic rate as a result of the changes mentioned in the puerperium affords an interesting and contraversial study. Several facts however are already apparent as a result of previous study. Firstly, the elevation noted in the ante-natal period which was suggested as being due to both foetal and maternal influence is not likely to be maintained. Indeed a sudden fall should follow delivery of the child, and a less sudden fall might be expected as a result of reduction of thyroid activity. On the other hand even although involutional changes in the maternal organism are essentially catabolic processes, it might be expected that in the early days of the puerperium, when the changes are most

marked, some deflection in the energy metabolism might result from such activity.

Furthermore, since it is an anabolic process, the activity of the breast tissue in preparation for lactation and even lactation itself might result in an elevated metabolism. With these facts in mind the study of basal metabolism in the first seven days of the puerperium was undertaken.

The behaviour of the basal metabolic rate following delivery has been studied by several workers particularly in its relation to the ante-natal increase in metabolism. Those workers who do not believe in thyroid hypertrophy as contributing to the rise have, by adding the energy metabolism of the mother obtained immediately postpartum to that of the foetus, suggested that the sum of the two equals the total pre-delivery energy metabolism of the mother/young combination.

Most workers however, do agree that after delivery the basal metabolic rate falls to reach a normal level some weeks later. Some do however suggest that the heat production is influenced by breast activity.

It was therefore decided that in the present study of the basal metabolic rate in the puerperium particular note would be made of immediate post-delivery readings and the daily observations should be made until the breast activity was fully established.

Method.

The study comprised the observation of the basal metabolic rate during the first seven days of the puerperium in thirty-two normal healthy women all of whom had had normal confinements and had healthy infants who were to be breast fed.

In addition the basal metabolic rate was studied during the first seven days of the puerperium of six normal

women who for various reasons were not breast feeding. In all of these patients lactation was suppressed by the administration of Diethyl Stilboestrol in a dose of 5 milligrammes given three times per day for four days.

The method of study in all of the thirty-eight women was similar. The apparatus used was that described previously. Observations again over a fifteen minute period were made daily for the seven days after delivery. Thereafter it was the custom for the patient to be dismissed home and for the purposes of the present study it was not considered necessary to continue the observations beyond this time.

As the majority of the patients studied had been used as subjects in the earlier experiments carried out in the ante-natal period, they were thoroughly familiar with and unafraid of the apparatus and the test itself. It was

TABLE XI.

Table XI.

Basal Metabolic Rate

in Kcalories per Sq. metres per hour

in

First seven days of Puerperium.

Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
32.03	32.03	28.54	28.23	26.69	28.84	25.37
32.03	33.62	31.72	25.10	28.54	29.18	28.23
32.03	34.25	31.72	29.97	29.62	29.97	30.13
32.35	34.25	32.03	31.72	31.19	31.19	30.71
33.94	34.25	32.03	32.35	31.46	31.72	30.71
34.25	34.57	32.03	32.67	31.72	32.35	31.19
34.25	34.89	32.67	32.98	32.35	32.98	31.19
35.84	34.89	32.98	32.98	32.98	33.30	31.19
36.16	35.52	32.98	33.30	33.30	33.62	32.67
36.16	35.52	33.30	33.62	33.30	33.94	32.67
36.16	35.52	33.30	33.62	33.30	33.94	32.98
36.16	35.84	33.62	34.25	33.94	34.57	33.30
36.47	36.16	33.94	34.25	33.94	34.57	33.62
36.47	36.47	34.57	34.25	33.94	34.89	33.94
36.79	36.79	34.57	35.20	34.57	34.89	33.94
37.42	36.79	35.52	35.52	34.57	34.89	34.25
37.42	37.42	35.52	35.52	34.89	34.89	34.57
37.42	37.42	35.84	35.52	34.89	35.84	34.89
38.69	37.74	35.84	35.84	34.89	36.16	34.89
38.69	38.10	36.16	35.84	35.20	36.79	35.20
38.69	38.10	36.16	36.16	35.52	36.79	35.20
38.69	38.69	36.16	36.47	36.79	37.11	35.52
39.33	38.69	38.10	37.42	37.42	37.11	35.52
39.33	39.01	39.65	37.42	37.42	37.11	36.47
39.65	40.16	39.65	37.74	37.42	37.74	37.74
40.16	41.11	40.16	37.74	37.42	38.06	38.06
40.48	42.50	42.18	37.74	38.06	38.06	39.65
40.48	42.82	42.82	37.74	40.80	41.11	41.11
40.80	43.77	44.09	38.10	41.23	42.18	43.45
42.18	44.72	44.40	38.10	47.91	42.82	47.91
44.09			41.55		44.72	
46.94			42.82		45.99	
47.26			44.72			
Mean: 37.85	37.39	35.74	35.35	34.84	35.85	34.55

therefore considered that duplication of the tests would be unnecessary and each of the daily observations was accepted as the basal rate. No sedation was given in the evening, unless this was indicated for medical reasons.

No patient was disturbed after she had fed her baby at 10 p.m. The babies were left overnight in the nursery, and were cared for and fed by the nursery staff. Again, as previously, patients were studied in pairs and the observations made at 8.30 a.m. In all cases careful notes were made of the time of occurrence of and the degree of breast engorgment.

This was also noted in six cases in whom Diethyl Stilboestrol was administered although in no case did lactation become established.

Results.

Mean values for the Basal Metabolic Rate on each day of the puerperium were calculated as shown in Table XI. These

TABLE XII.

Table XII.

Basal Metabolic Rate

in Kcalories per Sq. metres per Hour

in First Six days of the Puerperium

(Lactation Suppressed)

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
	37.74	34.57	34.25	35.20	33.62	32.67	29.18
	38.69	35.84	35.52	36.47	35.84	35.52	31.72
	39.01	36.47	35.52	36.11	36.16	35.84	32.35
	39.33	37.74	37.42	36.69	37.11	35.84	34.25
	41.11	39.65	37.74	37.15	37.11	36.47	34.57
	41.23				37.74	40.16	35.20
	43.77						
Mean:	40.12	36.85	36.09	36.32	36.26	36.06	32.88

values were plotted as shown in Figure 111. A regression line was fitted to the data giving the equation -

$$B.M.R. = -0.496x + 37.93$$

where x = Number of days after the puerperium. The slope of this line (given by the regression coefficient-0.496) is significantly different from zero, thus showing that there is a significant fall in Basal Metabolic Rate with succeeding days after delivery.

From the results of Basal Metabolic Rate obtained in the non-lactating series of subjects, mean values for the rate on each day of the puerperium from the first to the seventh, were calculated as shown in Table XII. These mean values were also plotted on Figure 111. Although only a relatively small number of subjects were included in non-lactating series it is apparent that the curve obtained follows closely that of the lactating series.

Discussion.

Most authors agree that there is a gradual return to the normal level of basal metabolic rate during the first ten-fourteen days post partum (Hanna, 1938). Plass and Yoakam (1929) found that during the first week after delivery the rate falls from plus 9 per cent in the tenth lunar month of pregnancy to plus one per cent. It was their opinion that by the third week of the puerperium the basal metabolic rate had fallen even further to an average of -7 per cent. Baer (1921) also noted a gradual fall in basal metabolic rate following parturition to plus 1.4 per cent by the eleventh day.

Cornell (1923) on the other hand observed a less marked fall in basal metabolic rate and was unable to show the average return to normal in seven-ten days. He observed that even after ten days the basal metabolic rate had still not returned to normal but

considered this as logical because of the stimulus as a result of milk production. He also suggested that the discrepancy was also contributed to by involution of the generative organs.

Pommerenke, Haney and Meek (1930) studying the basal metabolism in pregnant rabbits found that following parturition there was, at first, a sharp drop and then a gradual return to the normal metabolic level which was reached after about twenty days. They give three possible explanations for the higher post partum rate, the activity of the mammary glands, involution products from the uterus or some unknown chemical product furnished by the foetal tissues and still remaining in the circulation.

In complete contrast are the views expressed by Sandiford and Wheeler (1924). As a result of study of the basal metabolic rate in a patient for six months after delivery they concluded that lactation in

the human being is not associated with an increase in heat production and that therefore the conversion of the mother's food into milk does not involve a material loss of energy. They further state that the basal metabolic rate is actually lower during the lactating period and suggest that this is caused by the less active life of the mother necessitated by nursing. Hasselbach (1912), and Carpenter and Murlin (1911) as a result of their studies had also concluded that lactation in the human was not associated with an increased heat production.

Garry & Wood (1945-46) in discussing the energy requirements during pregnancy and lactation suggest a daily additional energy requirement during lactation of 600 calories per day in excess of the requirements during pregnancy. This is in agreement with views already expressed by Garry and Stiven (1935-36)

where they suggested the addition of somewhere between 350-700 calories per day during lactation.

Taking the figure of 600 calories as being an average additional daily requirement during lactation and the figure of 2,400 calories per day with a supplement of 600 calories per day for household duties as suggested by the Technical Commission of the Health Committee of the League of Nations (1935-36) for a pregnant woman, we find that the additional caloric requirement during lactation is 20 per cent of the requirements during pregnancy.

The greater part of this increase however represents the calorie content of the milk secreted as according to Garry & Stiven (1935-36) and Sandiford & Wheeler (1924-25) the actual formation of milk is not associated with expenditure of energy, and where there is

restricted muscular activity during lactation there may be a conservation of energy.

Several interesting features regarding the changes in basal metabolic rate during the early days of the puerperium are however suggested by a study of those results obtained in the two series.

a) There appeared to be greater individual variations in the readings than was observed in earlier series.

b) As was anticipated the fall in basal metabolic rate in the first seven days following parturition although considerable was not a return to normal. From a level of 40.24 Kcals./Sq.m. per hour prior to delivery the basal metabolic rate had fallen to a level of 37.85 Kcals./Sq.m. per hour by the first day of the puerperium. This represents a fall in basal metabolic rate of 2.39 Kcals./Sq.m. per hour. Table III and

Figure 11 also show a similar fall in basal metabolic rate, in this case amounting to 4.21 Kcals./Sq.m. per hour. Thus somewhere between 2.39 and 4.21 Kcals./Sq.m. per hour are lost between the day before and the day after delivery. The mean value of those results was found to be 3.3 Kcals./Sq.m. per hour and this expressed as a percentage of the pre-delivery rise in basal metabolic rate shows that 39 per cent of this rise is lost at or around the time of delivery. This would therefore suggest that only 39 per cent of the rise in basal metabolic rate is contributed to by the foetus. This would lend support to the view expressed as a result of earlier experiments, that the pregnancy rise in basal metabolic rate is contributed to, not only by the foetus but also by some other influence presumably a maternal one, probably thyroid hyperfunction.

c) From the trend of the curve it would appear that normal levels are likely to be reached within the first fourteen days of the puerperium, a belief shared by the majority of previous writers.

d) A comparison of the lactating and non-lactating curves suggests a striking similarity between the two. In the light of the results already obtained following the use of oestrogens in the pre-delivery state (Table IX), it would appear that lactation does not affect materially the basal metabolic rate. This is in agreement with the views expressed by Garry and Stiven (1935-36) and Sandiford and Wheeler (1924-25).

Part 4.

Experimental Studies.

The limitation of the study of basal metabolism in pregnancy to that of a purely clinical application necessarily leaves many problems still unanswered.

It was considered that, having studied in the main, the influence of the hypermetabolic state associated with pregnancy, both normal and abnormal, some attempt should be made to study the influence, if any, of a hypometabolic state in pregnancy. In view of the obvious difficulty in obtaining suitable material for the study, it was decided to observe the effects of an induced hypometabolic state in animals. At the same time it would be possible to demonstrate the similarity between the behaviour of the basal metabolic rate in human pregnancy and that in animals.

Such a similarity has already been demonstrated by Pommerenke, Haney and Meek (1930) although they concluded that there was no actual increase in the maternal basal metabolism. They found a close similarity between the basal metabolic rate in the puerperium in animals and in that of women.

As mentioned earlier, hypometabolism in pregnancy, particularly in early pregnancy, was observed by Bloss (1937) and Colvin and Bartholomew (1939), in women who had a particular liability to the development of pre-eclamptic toxaemia later in pregnancy. Litzenberg (1926) among others, suggests that hypo-metabolism is found with unusual frequency in association with infertility and advocates the use of thyroid extract as a form of treatment. Likewise abortion and more especially the tendency to habitual abortion, has been attributed to hypothyroidism and thyroid products have

been given to prevent abortions (King & Herring, 1939; Lerman, 1950).

Experimental studies also, when not confirming the association of infertility, show an increased incidence of abortion and/or foetal resorption in hypothyroidism (Chu, 1944-46; Jones, Delfs & Foote, 1946; Krolin & White, 1949-50).

It was therefore decided to carry out a series of estimations of basal metabolic rate of normal healthy female rabbits during pregnancy. Thereafter in a further series of pregnant rabbits, a state of hypometabolism was artificially produced by the introduction of methyl thiouracil in a dosage sufficient to depress thyroid activity and the basal metabolism was again studied.

The choice of the use of methyl thiouracil lay in the fact that here was a simple method of inhibiting the action of the thyroid gland, a method whose

accuracy could be confirmed by examination of the thyroid gland at the end of the experiment and one not necessitating any surgical interference with the animal.

Method.

The female rabbit was chosen as the experimental animal because of the convenient length of its period of gestation. The animals were easily obtainable and they readily became pregnant.

Six adult female rabbits whose weight varied from two to three kilogrammes, were used in each series. The animals were housed under similar conditions and feeding was arranged such that at least twelve hours elapsed from the time of the last feed until the estimation of the metabolic rate.

The apparatus used was a modification of the Benedict-Roth recording spirometer which had been used throughout the entire

human series. A circulating pump was introduced into the closed circuit thus ensuring an adequate rate of flow of about five litres of oxygen per minute in the circuit. The animal was put into a large bell jar with both inlet and outlet connections through which the air was being circulated by the pump. A soda-lime absorber was incorporated in the circuit. Before each test the apparatus was tested to ensure that the circuit was air-tight. For two-three minutes prior to the commencement of each test and before completing the closure of the circuit, the apparatus inside was perfused with pure oxygen in order to ensure that at the start of the test no carbon dioxide was present in the atmosphere of the circuit. The test animal had already been placed in the bell jar which was sealed with vaseline.

The apparatus was then connected

up as a closed circuit and the supply of oxygen was cut off. Each observation was maintained for a fifteen minute period. Three such consecutive observations were made on each occasion and the third reading was taken as representing the basal reading. It was found that by the third test the animals had settled down completely and seldom moved during the experiment. The animals were weighed after each occasion and the barometric pressure and temperature were also noted.

In all series, the experiments were conducted personally at regular weekly intervals and at the same time of day using the same technique.

Series I constituted a study of the basal metabolic rate as observed in six normal adult female rabbits whose weights varied between two and three kilogrammes. It was necessary to carry out the investigation in order to have the results for comparison with those

obtained during pregnancy. The rabbits used in this series were left apart from the male for at least four weeks before estimations were made in order to exclude the possibility of the existence of pregnancy.

Series II comprised the estimation of the basal metabolic rate of each of six normal pregnant rabbits at weekly intervals throughout the entire pregnancy and in the puerperium.

Series III consisted of a study of the effect of the hypothyroid state, induced by the administration of anti-thyroid drug on the pregnant state and also on the basal metabolism. The drug chosen was methyl thiouracil and again as previously, six pregnant rabbits of similar weights were the subjects of the investigations. In this instance pregnancy was confirmed radiologically in each case before the commencement of the drug.

A dosage of 100 milligrammes of methyl thiouracil daily was calculated to be a dose adequate for the inhibition of thyroid function. The drug was administered in the form of a solution, by intra-peritoneal injection over a period of seven days and on the morning of the seventh day, three consecutive fifteen minute observations of oxygen consumption were made.

In suitable control animals, intra-peritoneal injections of a similar volume of sterile water were made over a similar period.

That the drug was having the desired effect on the thyroid gland was confirmed by histological examination of the thyroid glands of control animals before and after the administration of methyl thiouracil.

Calculation of Results.

As has already been stated, it has been established under experimental

conditions that the calorific value of one litre of oxygen, assuming a Respiratory Quotient of 0.82, is 4.825 calories. If one makes the assumption that in a rabbit the Respiratory Quotient is of the same order, one can assume that the calorific value for oxygen in the rabbit is in the region of 4.825 calories per litre.

The basal metabolic rate of the rabbit was calculated on each occasion from the oxygen consumption as measured during the test. The surface area of each animal was calculated using Meeh's formula for surface area - $S = KW^{\frac{2}{3}}$ where S is the surface area, K is a constant and W the weight in kilogrammes. The constant for rabbits is 0.128 (Stewart & Menne, 1933).

The oxygen consumption in millilitres per minute, as observed in each case, was corrected to the volume which would have been consumed at normal

temperature and pressure in one hour. The heat output of the rabbit was then calculated using the figure for the calorific value of oxygen as described. In this way the basal metabolic rates of the rabbits were obtained.

Results.

Series I. - Basal metabolic rate of normal female rabbits.

In order to have a basis for comparison for the results obtained in the two pregnant series (Series II and III) it was necessary to determine the average basal metabolism of normal rabbits.

An average of the estimations of basal metabolism made on the six rabbits forming this series and obtained under like conditions was calculated and was found to be 31.6 calories per square metre of body surface per hour.

This figure compares favourably with the average rate of 32.73 calories

TABLE XIII.

Table XIII.

		Average calories per square metre of body surface per hour (Six rabbits)	Percentage increase in basal metabolic rate.
Stage of Pregnancy in Weeks	1	34.13	9
	2	37.42	19
	3	38.36	22
	4	42.15	32
Days of Puer-perium	3	36.20	12
	10	33.47	6

Table XIII showing increase in basal metabolic rate in normal pregnancy in rabbits. Percentage increase calculated from average normal figure of 31.6 calories per square metre per hour for normal non-pregnant rabbits.

per square metre in rabbits observed by Pommerenke et al (1930). The figure obtained lies within the range of those for other laboratory animals as well as that for women (Robertson & Reid, 1952), and is very close to that obtained in the present human non-pregnant series.

Series II. - Basal metabolic rate in normal pregnant rabbits.

The basal metabolism of six rabbits during pregnancy was determined. Observations were made at weekly intervals throughout the pregnancy and on two occasions in the puerperium, one within the first three days and the second around the tenth day of the puerperium.

The results obtained are shown in Table XIII and it becomes apparent that a rise in basal metabolic rate towards the end of pregnancy occurs in the rabbit as in humans. This rise is detectable before the end of the first half of pregnancy. Similarly the metabolic rate

falls after delivery in a similar manner to that in humans. In the series it was not possible to show a correlation between the number of foetuses in each litter with the basal metabolic rate.

Series III. - The effects of hypothyroidism on pregnancy in rabbits.

(a) Effect on the basal metabolic rate.

Six pregnant rabbits were again studied in this series. As mentioned earlier, pregnancy in all cases was confirmed radiologically and basal metabolic rate estimations were carried out in each rabbit.

Subsequently methyl thiouracil, in a solution, was injected intraperitoneally, as described earlier, into each of the six rabbits. This was continued daily, a dose of one hundred milligrammes being given at each injection daily, for seven days. On the seventh day the basal metabolic rate was again measured.

TABLE XIV.

Table XIV.

	Basal Metabolic Rate in Calories per square metre per hour. Pregnancy.		Percentage decrease of Basal Metabolic Rate.
	Before Thiouracil	After Thiouracil	
	37.51	31.27	20
	32.29	28.02	14
	40.81	35.00	14
	38.62	36.61	6
	37.16	29.85	27
	39.10	30.92	26
Mean	37.58	31.94	18
Mean Decrease		5.64	

Table XIV showing the effect of the administration of methyl thiouracil on the basal metabolic rate of pregnant rabbits.

The results of the estimations in this series are shown in Table XIV. It is clearly evident from those results that, as was expected, methyl thiouracil had depressed thyroid function and consequently caused a lowering of the basal metabolic rate, the difference between the means of the two sets of results being statistically significant ($P < 0.01$).

(b) Effect on the pregnancy.

None of the rabbits appeared to show signs of any upset as a result of administration of the thiouracil. All appeared healthy and showed no marked alteration in the amount of food taken, nor did they appear to have suffered from loss of appetite.

Abortion occurred in four of the pregnant rabbits at varying intervals of from six to ten days subsequent to the commencement of thiouracil. In all of those the foetuses were born dead. Of

the remaining two rabbits, one gave birth to its young on the sixth day of the course of thiouracil, six foetuses were born and all were alive. They survived only two days, the mother having made no attempt to suckle them. The other rabbit gave birth to one live rabbit out of a litter of five, but again the sole survivor only lived for one day, the mother having made no attempt to care for it. In one of the abortion group the mother consumed one of the dead foetuses.

Discussion.

Estimations of the basal metabolism of normal rabbits have been carried out by various workers and have been expressed both in relation to surface area and to body weight. Pommerenke et al (1930) with whose results those of the present series compared favourably, although disagreeing with Webster, Clawson and Chesney (1928), that surface area might

be ignored and that the results might be expressed on the basis of weight alone, did find however that the average number of calories per kilogramme per hour was constant for rabbits in the various weight groups studied. They therefore found that their results for the metabolism of normal rabbits agreed with those of Marine (1922) and also with those of Webster, Clawson and Chesney (1928).

In the present study it was possible, having obtained a standard for comparison, to study the results obtained during pregnancy and the puerperium. The increase in basal metabolic rate was observed to simulate the rise as observed in the human series reaching its peak just before parturition. Following parturition the rate similarly fell and approached normal levels by the end of the first week of the puerperium. It is presumed that the factors responsible for the increase in basal metabolic rate

are similar to those present in humans. The results obtained in the present series again compare favourably with those of Pommerenke et al (1930) and also with those described by Stewart and Menne (1933).

Hypometabolism, in the form of myxoedema, in association with pregnancy is a rare occurrence (Lister & Ashe, 1955). This is not surprising in view of the alterations in menstrual function, impairment of fertility and the occurrence of repeated abortions which have been noted in association with human hypothyroidism for years (Litzenberg & Carey, 1929). Nevertheless it is probable that milder degrees of hypometabolism exist in greater numbers, but because of their mild nature and lack of definite signs and symptoms evade detection. Indeed there have been many observations in sterility and on the outcome of conception in patients with

hypothyroidism. As a result many conflicting opinions persist. However, it is impressive that animal experimentation, when not confirming the association of sterility does depict a strikingly increased incidence of abortion with hypothyroidism (Chu, 1944-46; Jones et al, 1946; Krolin & White, 1949-50).

The production of hypothyroidism in the present series of rabbits by the use of methyl thiouracil resulted in the same effects on the pregnant state as did thyroidectomy in the series of pregnant rats studied by Chu (1944-46). In both series abortion occurred frequently. The mothers showed no interest in any of the young, whether born alive or dead. Some were observed to eat their young.

It might be argued that in the writer's series abortion and foetal death may have been contributed to by a depressant effect of methyl thiouracil on the foetal thyroids. However this

is most unlikely in view of the extreme rarity of the occurrence of abortion in pregnant women who are being treated by anti-thyroid drugs. In a total of eighty-three cases reviewed by Piper and Rosen (1954) only one case of abortion (Hone & Margarey, 1948), and one case of stillbirth (Saye, Watt, Foushee & Palmer, 1952) were found.

Similarly it might be said that the fall in basal metabolic rate as observed in the mother following the administration of the drug might also be contributed to in part by a depression of function of foetal thyroid tissue.

That the foetal thyroid plays no significant part in causing the increase in basal metabolic rate in pregnancy is suggested by the fact that Lister and Ashe (1955) could find no evidence either clinically or historically that the thyroid tissue of the growing foetus supplied thyroid hormone in sufficient quantities

to increase the metabolism of the myxoedematous mother.

Furthermore, Petersen and Young (1952) found that the maternal thyrotrophic hormone does not pass the placental barrier in the guinea-pig and therefore the foetal thyroid, in that animal at least, is not stimulated by the maternal hormone.

This is contrary to an earlier belief of Baird (1951) that there is evidence of a two-way traffic in the transfer of thyroid hormone through the placental circulation in the human and that as a result, a myxoedematous mother might tend to improve during pregnancy and relapse again after delivery. Even if such was the case, the contribution by the foetus is likely to be small and the clinical improvement in the mother is more likely to be a result of the normal hyperplasia which occurs in the thyroid gland in pregnancy.

It has already been stated that the basal metabolic rate bears a relationship to the plasma cholesterol levels. Changes in cholesterol metabolism, particularly in the esterified portion, have been described in severe pre-eclamptic toxaemia and in this disease stillbirth is a very common outcome of the pregnancy. While it would be unjustifiable to claim that stillbirth in toxaemia of pregnancy is entirely or always due to changes in function of the maternal thyroid gland it is possible that it is a contributory factor and the alteration in cholesterol levels may well be associated with degenerative changes in the placenta.

It is also known that cholesterol metabolism and fat metabolism in general is upset in diabetes, a complication of pregnancy which is likewise associated with a high foetal loss. Although it has not been possible to pursue metabolic studies in diabetic pregnant patients

it is obvious that some investigation is necessary in this field since the foetal salvage has not been improved by any of the modern methods of treatment and does not appear to depend directly upon the insulin requirements of the mother.

Summary and Conclusions.

A study was made of the basal metabolic rates of sixty normal pregnant women at various stages in pregnancy.

The merits of the various methods which have been employed in measuring the basal metabolic rate have been discussed and the method used is described in detail. It was found that satisfactory results (as suggested by the quiet and regular respiratory movements) could be obtained from the third of three consecutive tests without the use of sedative drugs.

The influence of the stage of pregnancy, age and parity on the basal metabolic rate was observed.

It was found that there was a progressive rise in basal metabolic rate from the third to the eighth lunar month of pregnancy when a level of 40.26 Kcals./Sq./m. per hour was reached. This

represents an increase of 24% over the normal non-pregnant rate. Thereafter from the eighth lunar month to delivery the rate remained at an almost constant level.

The results obtained compared favourably with those of other workers although it was apparent from a study of the literature that there was a considerable variation in the results obtained by various workers.

The possible reasons for the rise in basal metabolic rate associated with pregnancy were considered and the relative literature has been discussed.

It is suggested that both foetal and maternal factors contribute to the increase.

It is postulated that a hormonal influence, possibly arising in the placenta causes stimulation of the thyroid gland which results in an increase in the basal metabolic rate.

Neither age nor parity have any significant influence on the basal metabolic rate during the reproductive years.

An attempt was made to observe closely the behaviour of the basal metabolic rate prior to the onset of labour. No significant fluctuations in the rate were noted.

A study of the basal metabolic rate in other than normal pregnancy was made. This included observations in multiple pregnancy, in pregnancy where intra-uterine death of the foetus had occurred, in pregnancy complicated by pre-eclamptic toxaemia and cardiac disease. The relevant literature was perused and the results compared with those of other workers.

The basal metabolic rate in multiple (twin) pregnancy as studied in six subjects showed a considerable increase over the rate pertaining where a single foetus existed but the increase was not

proportional to the number of foetuses present. This further substantiates the suggestion that the increase in basal metabolic rate in normal pregnancy is not entirely due to foetal influence.

Six subjects in whom intra-uterine death of the foetus had occurred were studied. The basal metabolic rate was found to be significantly reduced to almost pre-pregnancy levels. This suggested that the estimation of basal metabolic rate in such cases might be used as an aid to the diagnosis of intra-uterine foetal death.

The influence of pre-eclamptic toxaemia on the basal metabolic rate was investigated in ten patients. It was found that in the established condition a significant rise in basal metabolic rate occurred. The results of other workers in this field have been discussed and the significance of a reduction in basal metabolic rate as a precursor of

toxaemia of pregnancy, as suggested by some workers, commented upon.

Estimations of basal metabolic rate was carried out in twelve pregnant women who suffered from cardiac disease, but in whom cardiac failure was not a marked feature. It was found that the basal metabolic rate bore a resemblance to the rate in normal pregnancy although a slight average fall in rate was observed. A relationship between the basal metabolic rate and exercise tolerance is suggested but further work in this field is indicated.

The effect of oestrogen on the basal metabolic rate has been studied in four pregnant women and the relevant literature dealing with the hormonal influence on the basal metabolic rate discussed. A significant reduction in basal metabolic rate appeared to follow the administration of oestrogens. This has also been the experience of other

investigators.

In a study of basal metabolic rate following parturition in thirty-two women a considerable decrease was noted. From a level of 40.24 Kcals./Sq.m. per hour at the end of pregnancy the rate fell to an average level of 37.85 Kcals./Sq.m. per hour in the first day of the puerperium. Thereafter a steady fall in basal metabolic rate occurred to reach a level of 34.55 Kcals./Sq.m. per hour by the seventh day. It is suggested that this indicates that the rise in basal metabolic rate which occurs in normal pregnancy is not accounted for by the presence of foetal tissues alone.

Lactation did not appear to affect the basal metabolic rate.

A series of experimental studies was conducted on pregnant rabbits, in which the basal metabolic rate was observed at weekly intervals. It was found to show a similar increase during

pregnancy to that in pregnancy in human females. A corresponding decrease was noted following parturition.

The effect of hypothyroidism, induced experimentally by the administration of methyl thiouracil, was also studied in the pregnant rabbit. In a series of six rabbits studied an average decrease of basal metabolic rate of 18 per cent was observed following administration of the drug. It was also found that abortion and stillbirth occurred frequently. In cases where the foetus was born alive, the mother displayed a lack of maternal feelings towards the young and made no attempt to suckle. In one case the mother actually consumed one of the foetuses.

The results obtained in this study were found to be in agreement with the literature on the subject of hypothyroidism in pregnancy.

It is evident from the study that

the basal metabolic rate suffers considerable fluctuations as a result of various altered and abnormal states of pregnancy.

In the light of the results which have been obtained it would seem reasonable to suggest that the scope of the investigations could be extended to other fields.

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