should not allow Health Service conditions to undermine their independence or their essential relation to patients.

If my analysis of the professional situation to-day is reasonably accurate, a number of things will be necessary; important among these are:

(a) Medical organizations should spend the money allocated by the State to the National Health Service; doctors should be employed by doctor-administered organizations.

(b) Standards of qualification and performance must be defended.

(c) A stand must be made against the lowering of rewards, but public sympathy for such a stand must be developed by sound public relations.

(d) A realization by specialists and hospital doctors of the true importance to the profession of the general practitioner inside the Service: if the G.P. loses caste the public will tend to think of all medical men as mere purveyors of wrapped-up scientific cures, payable at shop clerks' rates.

(e) A realization by all doctors in the Service of the great benefits to be gained by the whole profession from the survival of private practice outside the scheme. It is a sound insurance policy; the profession should do all it can to extend every possible aid to the private practitioner, and fight the State's attempt to penalize him.

(f) The reconciliation of differences between doctors and medical auxiliaries. The medical auxiliaries' status and standards should be raised; and the State given no chance to drive any wedges between the "health professions."

(g) A new approach to administration. Every profession faces here a problem of unexampled urgency. It is foolish to leave the field to lay administrators. There is certainly need for a staff college for the scientific and technical professions; and probably one for the medical profession and all its auxiliaries as well.* How many hospitals have sent doctors to the administrative staff college at Henley meanwhile?

(h) And, finally, the maintenance by every means, personal and propagandist, of the basic ethical relationship between doctor and patient. People basically do not want official doctors, and they might well learn to prefer a less generous Health Service to losing the sort of doctor they traditionally know, like, and trust.

Let us make no mistake, when all professional people are officials there will be no doctors, no lawyers, no artists, and probably no scientists either. There will be no professions; and no life worth living. George Orwell in his *Nineteen Eighty-Four* depicted the sort of life there will be.

One other thing is needful: greater understanding by the professions of each other's problems, and the making of a common stand when this proves practicable. The leadership of this country is now largely professional. The aristocracy is gone; the propertied classes are dying; business is half-professionalized. The bureaucracy is calling in the professions more and more. Should not, then, professional leadership be consciously professional? Professional training and practice gives a man or woman a maturer outlook on affairs than is possessed by any other section of the community; in understanding the professional ideal (largely shaped by generations of doctors) and in seeking to pass it on to the rest of the community—to the business men, to the traders, to the farmers, to the technicians, to the trade union executives, and so to the operatives, supervisory, skilled, and semi-skilled—we have our best chance of restoring balance and vision to our community, which, packed fifty million on this small island, is so sorely beset.

*Cf. *The Times*, November 7, 1951.

HORMONE ASSAYS IN NORMAL AND ABNORMAL PREGNANCIES*

BY

G. I. M. SWYER, D.M., D.Phil., M.R.C.P.

*Consultant Endocrinologist to the Obstetric Department,
University College Hospital, London*

The accompanying list (see Table) of hormones of actual or potential interest in pregnancy is a formidable one, and is not necessarily complete. Assay methods for several of them are still imperfectly developed, so that it will not be possible (or necessary) to devote equal attention to each of them. A word of explanation, though scarcely of apology, is perhaps necessary in the

Table of Hormones in Pregnancy

Oestrogens:	
Oestradiol	
Oestrone	
Oestriol	
Progesterone—Pregnanediol	
Chorionic gonadotrophin	
Pituitary hormones:	
Anterior-lobe hormones	<div style="display: inline-block; vertical-align: middle;"> <div style="display: inline-block; vertical-align: middle;"> Prolactin Growth hormone Adrenocorticotrophic hormone Thyrotrophic hormone </div> </div>
Posterior-lobe hormones	
Adrenocortical hormones:	
" Corticoids "	
17-ketosteroids	
Other cortical metabolites	
Thyroid hormone (serum precipitable iodine)	
(Serum histaminase)	
(Serum pitocinase)	

case of the last two items, the enzymes histaminase and pitocinase, included within parentheses. Hormones and enzymes have a good deal in common, so that their presence in the list is perhaps not so surprising, and their presence in blood only during pregnancy entitles them to some consideration in this paper. The plan to be followed will consist of a description of the findings in normal pregnancy first, followed by a survey of what is known of the hormonal findings in abnormal pregnancies.

Oestrogens

Although wholly satisfactory methods for the assay of oestrogens in body fluids still await development, and estimates of their levels in conditions other than pregnancy must be accepted with great caution, there is no doubt that such a plethora exists in pregnancy that even crude methods have yielded highly significant information. The general pattern of oestrogen excretion in the urine during normal pregnancy is now generally well known and needs little comment. As can be seen in Fig. 1, during the first trimester the levels are low, scarcely differing from those of the menstrual cycle, but thereafter a tremendous increase occurs in the oestriol fraction, and a very much smaller increase in the oestrone and oestradiol fractions. During the last two weeks the oestriol fraction decreases rapidly, reaching early pregnancy values by the onset of labour. The oestrogens are excreted almost exclusively in the combined form, as sulphates or glucuronidates, and as such are biologically relatively inactive.

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FIG. 1.—The average urinary excretion throughout normal pregnancy of chorionic gonadotrophin, pregnanediol, oestriol, oestrone, and oestradiol.

Since the work of Cohen, Marrian, and Watson (1935) it has generally been accepted that at the onset of labour, when the level of combined oestrogens has fallen markedly, free oestrogens suddenly appear in great excess. It has been thought that a causal connexion between the onset of labour and this change in the chemical state of the oestrogens might well exist. On the other hand, not all authors have invariably found such a rise in the free oestrogen at the onset of labour, and some doubt has therefore arisen whether or no such a rise was indeed significant. The recent investigations of Clayton and Marrian (1950) have shown that the explanation of the observed appearance of large amounts of free oestrogen at the onset of labour is contamination of the urine with blood or amniotic fluid. These substances contain large amounts of enzymes— notably glucuronidase—which are able to hydrolyse the conjugated oestrogens. So passes another plausible, but unfortunately incorrect, hypothesis seeking to account for the onset of labour.

The oestrogen content of the blood during pregnancy has been less studied than that of the urine, because it is much more difficult to obtain even remotely plausible results. It seems probable, however, that the blood levels vary similarly to the urinary levels. It is pertinent to point out that most of this work has been done with the use of biological assays; if these are not preceded by fractionation into the three oestrogens, interpretation of the oestrogenic potency of the mixture in terms of a single oestrogen (usually oestrone) is very difficult, since the potencies of the separate oestrogens are different, vary according to the method of assay used, and are not additive. Moreover, there may be present augmenting and inhibiting substances, about which knowledge is meagre. In most published studies little or no attention has been paid to these aspects.

Pregesterone and Pregnanediol

If we take into consideration the difficulties of assaying progesterone—which still await adequate solution—it is surprising how much we know, or think we know, of the role of progesterone during pregnancy (see Kaufmann, Westphal, and Zander, 1951, for a recent review). Virtually none is present in the urine—and there does not seem to be much in the blood either. The corpus luteum during the first trimester, and the placenta in increasing amounts thereafter,

do contain it. Most of our information is derived from studies on the urinary excretion of pregnanediol—a dihydric alcohol first isolated from pregnancy urine in 1929 by Marrian, and, since Venning (1937, 1938) described her gravimetric method for its estimation, the subject of numerous investigations. It has been assumed, more or less tacitly, that the pregnanediol excretion in the urine reflects the metabolism of progesterone (see formulae for the close chemical relationship between the two steroids). Very probably this is in general true, but the complete proof is still lacking, and it is conceivable that, in some circumstances at least, the parallelism is far from close.

Pregnanediol is excreted in the form of sodium pregnanediol glucuronide, and in the original Venning method is measured as such. Most of the more recent assay methods have combined hydrolysis with extraction and thus determine free and combined pregnanediol together. This is advantageous, since partial hydrolysis may take place in the voided urine, thus causing variable losses of pregnanediol glucuronide. It would be out of place to discuss in detail the various assay methods which have been developed in recent years, but, disregarding the older techniques, it may be said that they fall into two main groups—"rapid" methods, intended for clinical application, and quite unsuitable for dealing with the small amounts of pregnanediol found during the luteal phase of the menstrual cycle; and longer methods, intended for careful research and applicable to small amounts. In the first group comes the Guterman method (1944) and, distinctly preferable, the method of Sommerville, Marrian, and Kellar (1948). In the second group come the method of Sommerville, Gough, and Marrian (1948) and the ingenious technique of Huber (1947) and de Watteville *et al.* (1948), which employs adsorption chromatography with alumina for purifying the pregnanediol.

As can be seen in Fig. 1, the pregnanediol excretion in normal pregnancies shows a slow rise during the first 20 weeks, reaching a level of 20–30 mg. per 24 hours. Thereafter the rise is increasingly rapid, a peak, in the region of 90 mg. being attained about the 37th–38th week. The excretion then drops rapidly, disappearing altogether a few days after delivery. It must be emphasized that variations from this mean curve are considerable even in apparently normal pregnancies, so that the interpretation of isolated determinations may be difficult or impossible.

A number of attempts have been made to use pregnanediol assay as a method of pregnancy diagnosis, since it is obvious that an accurate and relatively simple chemical method would have distinct advantages over biological procedures (Guterman, 1944, 1945; McCormack, 1946; Reinhart and Barnes, 1946; Merivale, 1948; Henderson *et al.*, 1949; Swyer, 1949; de Watteville, 1951; *etc.*). The reliability of the results has varied markedly in different reports, and a considerable literature has developed, arguing the case for and against. It is unnecessary to enter into the controversy here, but one conclusion is inescapable: the amounts of pregnanediol excreted during the first few weeks of pregnancy—that is, after the period has been missed—may be no different from those during the luteal phase of the normal cycle, so that on these grounds alone the theoretical basis for the test becomes invalid. The exclusion of all cases in which bleeding has occurred after the suspected onset of pregnancy, as Guterman (1945) considers essential, clearly limits the value of the test considerably. It seems fair to state that, although some authors have found the test as reliable as the Friedman test, since many others—for example, Reinhart and Barnes (1946), Merivale (1948), and

Swyer (1949)—have reported very different findings, pregnanediol assay is not to be recommended as a worth-while substitute for the established biological methods of pregnancy diagnosis.

Chorionic Gonadotrophin

The "pregnancy hormone" *par excellence* of the human (though apparently not necessarily of most other species) is chorionic gonadotrophin (C.G.) (also known as "anterior-pituitary-like hormone" and prolan) since it occurs only during pregnancy—if we except certain relatively rare teratoid tumours of so-called chorion epitheliomatous type. Curiously enough, it cannot be said that we are at all certain of its function during pregnancy; and there is no doubt that its peculiar curve of production (Fig. 1) remains unexplained. It is the substance responsible for the reactions which provide the basis of biological pregnancy diagnosis tests, causing ovulation in immature mice (Aschheim-Zondek test), in mature rabbits (Friedman test), and in the South African clawed toad (*Xenopus laevis*); and causing the appearance of spermatozoa in the cloacal urine of the male South American toad (*Bufo arenarum* Hensel) and in the North American leopard frog (*Rana pipiens*). Probably the most satisfactory quantitative method for its assay is that developed by Loraine (1950) employing the weight of the immature rat's prostate.

C.G. first appears as soon as the fertilized ovum has become embedded, and is believed to be formed by the trophoblast. It has been detected as early as the 25th day after the beginning of the previous period (based on a 28-day cycle) and therefore before the next period has been "missed." Its excretion in the urine rises rapidly, reaching values between 20,000 and 40,000 i.u./24 hours between the 40th and 80th days of pregnancy. By the 100th day the peak period is over and a relatively steady level is maintained until the end of pregnancy. Loraine regards the normal range for this level as between 4,000 and 11,000 i.u./24 hours. A slight but apparently significant rise occurs about the 37th week of pregnancy, and after parturition the hormone rapidly disappears from the urine, none usually being detectable by the fourth day after delivery.

Some simple arithmetic applied to these values gives interesting results. It is probable that 15 i.u. or more of C.G. is required to produce ovulation in the rabbit—that is, to give a positive Friedman test—and, since 10 ml. of urine is usually injected, it follows that not less than 1.5 i.u./ml. must be present. Assuming the first morning specimen to have twice the concentration of the total 24-hour specimen, and assuming a 24-hour volume of 1,500 ml., this implies that, in general, the 24-hour excretion must exceed 1,125 i.u. in order that a positive Friedman test may be obtained—and, clearly, this value will usually be greatly exceeded. But it is easy to see how this lower limit may occasionally have to be raised three to four times in order that a positive result may be obtained, thus accounting for the occasional false negative tests early in pregnancy—especially before the sixth week—and later on after the peak has been passed. Similar calculations applied to the peak period show that a positive result at 1:10 dilution—that is, with 1 ml. of urine—will generally be obtained, and occasionally the result may be positive at 1:100 dilution—that is, with 0.1 ml. of urine. Between the 40th and 80th days, therefore, a positive Friedman test at 1:100 dilution may be physiological and not indicative of hydatidiform mole.

The distribution of C.G. in mother and foetus has been studied by Bruner (1951), who found the concentration always to be highest in the chorionic placenta, thus supporting the view that the hormone originates in the trophoblast. In the mother, the highest concentration was found in the blood, the endometrium coming next and being richer in the hormone than any other tissue. The concentration in the foetus is very low, being about 1/10 to 1/20 that in maternal muscle; nevertheless it was thought that the total amount of C.G. reaching the foetus might be of physio-

logical significance. Evidently, therefore, the hormone is released by the chorion into the maternal blood stream, from which a small amount passes the "placental barrier" to enter the foetal blood stream.

Anterior-pituitary Hormones

The substances of potential interest under this heading are prolactin, growth hormone, adrenocorticotrophic hormone and thyrotrophic hormone. No simple methods for the assay of any of these are available and knowledge of their behaviour during pregnancy is slight. The fact that the pituitary enlarges during pregnancy has led many to suppose that it becomes more active at that time. Direct evidence supporting this view is very scanty. Prolactin is probably produced in small amounts during pregnancy, but apparently (Lyons and Page, 1935; Meites and Turner, 1941) in considerably larger amounts *post partum* (not altogether confirmed by Coppedge and Segaloff, 1951). The possibility of increased growth hormone production during pregnancy, particularly in the diabetic and pre-diabetic woman, and of its implication in the foetal complications in those conditions (Barns and Morgans, 1948; Gilbert, 1949; Barns *et al.*, 1950), is an interesting speculation not yet susceptible of proof. Recent investigations seem to indicate an increased production of A.C.T.H. during pregnancy (Parrott, unpublished); the increased secretion of some adrenocortical steroids (see below) certainly suggests the probability of such an augmentation. Swelling and hyperplasia are often observed in the thyroid gland during pregnancy and suggest increased thyrotrophic hormone production, but no accurate studies have lent support to this view.

Thyroid Hormone

It is now usual to regard the serum precipitable (or protein-bound) iodine (S.P.I.) as giving a measure of the amount of thyroid hormone present in the blood. In normal non-pregnant women this value varies between 4 and 8 μ g. per 100 ml. of serum. Peters *et al.* (1948) found that from the second month the level rose to a mean of 8.3 μ g., the range being 6.2 to 11.2 μ g. They observed that this rise in S.P.I. occurred much earlier in pregnancy than that in the B.M.R., which begins only after the fourth month.

Adrenocortical Hormones

Venning (1946) has studied the output of adrenal steroids during pregnancy and has shown that the glycogenic corticoids—that is, those able to cause deposition of glycogen in the livers of adrenalectomized mice—increase in a complex fashion (Fig. 2). There is a rise to about twice the normal value, coinciding with the gonadotrophin peak, followed by a fall, with a subsequent rise to about four times the normal value during the third trimester. Using chemical methods, other workers (Heard *et al.*, 1946; Tobian 1949) have shown similar rises in the neutral lipid-soluble reducing fractions of the urine during pregnancy, though the increases are less than those found by the biological method. There is as yet no means of separately estimating the so-called glucocorticoids and the mineralocorticoids; indeed, the validity of such a differentiation is doubted by some. It should also be remembered that there is an increasing awareness of the defects and limitations of all hitherto proposed methods for determining the excretion of adrenocortical metabolites (cf. Marrian, 1951).

By contrast, the 17-ketosteroids (representing roughly the "androgenic" activity of the adrenal cortex), when measured by the Pincus reaction (which uses antimony trichloride), shows practically no change throughout pregnancy. On the other hand, with the Zimmerman reaction (using *m*-dinitrobenzene in alcoholic potassium hydroxide), a progressive rise is found during the second half of pregnancy. Now the Zimmerman reaction is also given by 20-ketosteroids (such as pregnanolones), so that

FIG. 2.—The urinary excretion throughout normal pregnancy of "corticoids," 17-ketosteroids, and the suggested excretion of pregnanolones

Venning (1946) has suggested that this discrepancy between the two methods might be due to the excretion of increasing amounts of pregnanolones, and, since these give only about one-eighth the colour of 17-ketosteroids in the test, it would follow that their excretion would apparently rise to something like 80 mg. per 24 hours at full term (Fig. 2).

If the increased secretion of corticoids—that is, compounds related to corticosterone—during pregnancy is due to increased stimulation by A.C.T.H., it must be concluded that the activity of the adrenal cortex is modified during pregnancy, since in the non-pregnant state the typical response of the adrenal to A.C.T.H. involves the 17-ketosteroids as well as the corticoids (the latter, however, to the greater extent).

Posterior Pituitary Hormones—Pitocinase

There have been no convincing studies of the production of posterior-lobe principles during pregnancy. Page (1947), however, has shown that there is a remarkable increase in the pitocinase activity of plasma during pregnancy, the level near term being several thousand times that at conception. Indeed, during the first 16 weeks of pregnancy the increase in activity follows a linear function and can be made the basis of a test for determining the duration of pregnancy. Though the significance of this enzyme is still far from clear, it would seem that its increased production serves to prevent the stimulating action of "pitocin" on the uterus, and its sudden disappearance at term would have an obvious association with the onset of labour.

Serum Histaminase.—Another enzyme characteristic of pregnancy is histaminase, which arises in the placenta and appears in the plasma only during gestation. Numerous methods for its assay, some chemical, some biological, have been proposed from time to time, but hitherto all have had their drawbacks. A very recent method described by Kapeller-Adler (1951) seems much more promising and has the great advantage of simplicity. It depends upon the fact that during the action of histaminase on histamine in the presence of indigo carmine one molecule of H_2O_2 is formed for each molecule of histamine oxidized, so that the amount of unoxidized indigo can be estimated by titration with $KMnO_4$, thereby giving a measure of the histaminase activity.

The histaminase content of the plasma bears a close relationship to the functional capacity of the placenta and shows a sharp rise from about the 14th week of pregnancy, reaching a peak value near the 26th week which is about eight times that found before the 14th week. Thereafter it falls slowly until term, disappearing altogether within four to five days of parturition.

Hormonal Findings in Abnormal Pregnancies

Toxaemia of Pregnancy

Since this condition (the "disease of theories") is one of the two outstanding unsolved problems of obstetrics (the other being uterine inertia), it deserves consideration first. A very able review of the subject has been given by Smith and Smith (1948), who summarize the findings as follows: in eclamptogenic toxæmia there appears to be (1) excessive antidiuretic substance in the urine and placenta; (2) a melanophore-expanding principle (perhaps from the intermediate lobe of the pituitary gland) in the blood and placenta; (3) a hypersensitivity to the injection of posterior pituitary secretions (this probably indicates deficient production of pitocinase); (4) high titres of C.G. in a large percentage of cases; (5) decreased excretion of oestrogens and pregnanediol; and (6) histological and histochemical changes in the placenta similar to but more marked than those of the normal placenta at term and primarily involving degeneration of the syncytial cells which probably secrete the steroid hormones.

Some further comment in relation to the oestrogens in toxæmia is pertinent. The Smiths, impressed by the apparent reciprocal relationships of oestrogens and C.G., believe that the latter is utilized by the placenta for the production of oestrogen and progesterone. In many cases of toxæmia they observed a rise in C.G. coinciding with a fall in oestrogen and pregnanediol excretion. This they have interpreted as being due to failing utilization of C.G. because of degeneration of the syncytial cells. In those cases of toxæmia in which C.G. was found to be present in normal amounts they further postulate decreased production of C.G. as a secondary result of placental damage. Their studies of the excreted oestrogen fractions and oxidation products have led to the formulation of a scheme of oestrogen metabolism in which progesterone facilitates the conversion of oestradiol to oestrone, which is then further transformed to oestriol as follows:

They believe that the oxidation products stimulate the production of oestrogen and progesterone through the increased utilization of C.G.; and, further, that stilboestrol behaves in this respect like the oxidation products in causing a fall in serum C.G. and an increase in pregnanediol excretion in pregnant women. The fall in serum C.G. has been confirmed by Loraine (1949), who has shown, however, that it is transient, the C.G. level rising again even though stilboestrol administration be continued. The increased excretion of pregnanediol has not been confirmed. Indeed, Sommerville, Marrian, and Clayton (1949) have found that stilboestrol regularly decreases the excretion of pregnanediol, which rises to the normal level again on stopping the stilboestrol. These authors suggest that the Smiths' findings on pregnanediol excretion might be explained by the fact that, having used the Venning method which determines sodium pregnanediol glucuronide, they would probably also be measuring at the same time some conjugated excretory product of stilboestrol. The Smiths are not satisfied with this explanation, and the controversy still is unsettled.

Some older observations—for example, those of Fauvet and Münzner (1937)—seemed to indicate decreased adrenocortical activity in toxæmia of pregnancy, but more recent studies point in the direction of increased activity, particularly with respect to the corticoids. Thus Tobian (1949) found that whereas during the last trimester in normal pregnancies twice as much corticoid is excreted as by non-pregnant women, a still higher corticoid excretion was seen in women with excessive oedema (46% more, which is statistically significant). Twin pregnancies were also associated with increased corticoids. There was no correlation between the elevation of the blood pressure in toxæmia and the corticoid excretion, but in essential hypertension in pregnancy no abnormal changes in the corticoids were seen. In addition to the rise in corticoid excretion, Devis and Eeckhoudt (1949) claim to have found abnormally low 17-ketosteroid outputs and seek to ascribe to this alleged hormonal imbalance an aetiological role in toxæmia of pregnancy. It seems fair, however, to point out that the hormonal findings might just as well represent the reaction of the adrenal cortex to the stress imposed by the disease. There is general agreement that the histaminase content of the plasma is significantly reduced in toxæmia of pregnancy, the degree of reduction being related to the disturbance in functional capacity of the placenta. The new simple method of Kapeller-Adler already mentioned may prove to be of real clinical value in helping the obstetrician to decide when, because of the failing placenta, the pregnancy should be terminated to avoid intrauterine death of the foetus.

In *hyperemesis gravidarum* there is reason to believe that C.G. levels are sometimes abnormally high. A plausible explanation of the condition is that it represents a hypersensitivity response to what is essentially a foreign protein. Clearly, therefore, excess of C.G. is not indispensable for the production of the condition, and such an excess is not always found.

Hydatidiform mole, on the other hand, is almost invariably accompanied by a greatly increased output of C.G., so that usually as little as 0.1 ml. of urine will give a positive Friedman test—that is, 1:100 dilution. A similar positive response (though usually in a lower dilution) can be obtained with cerebrospinal fluid. It has already been pointed out that, at the peak of C.G. excretion—that is, about the 60th–70th day of pregnancy—positive Friedman tests are sometimes obtained at similar dilutions in normal pregnancies, and particularly in multiple pregnancies. It is therefore easy to be misled by such a finding, at about the 10th week, if there is some vaginal bleeding together with a twin pregnancy—so that the uterus would seem larger than the expected size. The fact that pregnanediol excretion has been reported as zero in hydatidiform mole (Guterman, 1945; McCormack, 1946; Swyer, 1949) engendered the hope that its measurement might help to disentangle such a problem, but there is now no doubt that the absence of pregnanediol in cases of hydatidiform mole is not invariable, and its assay will not therefore serve as a differential test in these cases (Bender, quoted by Swyer, 1949; de Watteville, 1951).

In *chorion epithelioma* the output of C.G. increases to still higher levels, the daily excretion reaching the order of millions of international units.

Abortion

It was claimed by Guterman (1946) that by the use of his semiquantitative test for pregnanediol the fate of cases of threatened abortion was correctly predicted in 93% of 73 cases, a "positive" test being correlated with continuation of the pregnancy. Other workers have not found so close a correlation, though there is no doubt that the mean excretion for those cases in which the pregnancy continues is significantly higher than in those in which abortion occurs (Swyer, 1949; de Watteville, 1951). It is, of course, clear that some patients will abort even though the pregnanediol excretion is normal, because some cause other than pro-

gesterone deficiency is operating. Bender (1948) has produced evidence that, by using the Guterman test to differentiate cases of threatened abortion with high pregnanediol excretion from those with low outputs, and reserving treatment with progesterone for the latter only, a statistically significant increase in the salvage rate can be obtained; on the other hand, progesterone given to patients with threatened abortion but with positive Guterman tests increased the likelihood of abortion.

The pregnanediol excretion in the early months of pregnancy in patients who have had two or more consecutive early abortions does not differ significantly from randomly selected antenatal patients at comparable stages of pregnancy (Swyer, unpublished observations). This evidence therefore does not lend support to the view that deficiency of progesterone may be a cause of so-called habitual abortion. Further discussion of this problem would be out of place here.

The serum histaminase level is usually low in threatened abortion (Kapeller-Adler, 1951). It seems that the serum precipitable iodine may also be low in threatened abortion; thus Peters, Man, and Heinemann (1948) found that in 8 of 12 S.P.I. determinations in such cases the value was less than 6.2 $\mu\text{g.}$, the lowest amount found in normal pregnancy. None of these patients, it should be noted, showed any stigmata of hypothyroidism.

In *incomplete abortion* it is not uncommon to find fluctuating pregnanediol levels in serial determinations, while pregnancy diagnosis tests depending upon the detection of C.G., such as the Friedman test, may give irregularly positive and negative results. This is due to the survival of portions of placenta. In *missed abortion*, however, where placental separation is usually complete, consistently negative results are the rule.

In *multiple pregnancy* the excretion of C.G. and the serum histaminase levels are usually high, but these estimations are not of diagnostic value.

The diagnosis of *ectopic pregnancy* is often difficult, and assistance is usually sought from a pregnancy diagnosis test. The value of a rapid test, especially in cases of suspected ruptured ectopic pregnancy, needs no comment. In practice, however, all tests may prove misleading because the abnormal implantation usually results in a deficient production both of C.G. and of progesterone. Consequently, the Friedman and Aschheim-Zondek tests may be negative and the pregnanediol excretion too low to allow of the confident diagnosis of pregnancy.

So far as other commonly encountered complications of pregnancy are concerned, studies of the hormone levels have not been sufficient to permit any generalizations. It is obvious, therefore, that much work on this subject remains to be done, and the time is still a long way off when the clinical pathologist, working in a routine laboratory, can hope to be able to give the perplexed obstetrician much assistance by means of hormone assays.

Summary

The list of hormones of actual or potential interest in pregnancy is a formidable one, and assay methods for several of them are still imperfect. In normal pregnancies the oestriol fraction and, to a lesser extent, the oestrone and oestradiol fractions show marked increases during the last two trimesters, but fall rapidly during the last fortnight; progesterone production, as judged by pregnanediol excretion, follows a somewhat similar pattern; chorionic gonadotrophin secretion begins as soon as implantation of the ovum has been established, rises to a striking peak between the 60th and 80th days, and then falls to a more or less steady level; complex changes occur in the adrenocortical metabolites, the precise nature and significance of which are but little understood; ill-defined and uncertain changes occur in the

various pituitary hormones; and the histaminase and pitocinase contents of the plasma rise in characteristic fashions.

In abnormal pregnancies comparatively few hormone studies have been made except in toxæmia and abortion. In the former it seems that most, but not all, cases show an increase in chorionic gonadotrophin and a decrease in oestrogens and pregnanediol; probably the adrenal corticoids are also increased, though the 17-ketosteroids are decreased. In threatened abortion there is usually, but certainly not always, a low pregnanediol excretion and a low serum precipitable iodine (representing circulating thyroid hormone) and histaminase content. The chorionic gonadotrophin is greatly increased in hydatidiform mole and in chorion epithelioma. Less well-defined hormone changes may be found in various other abnormalities of pregnancy.

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The international conference on blood transfusion, recently held at the British Standards Institution in London, reached agreement on several fundamental proposals, the objectives of which are to get standardization and interchangeability of the equipment involved both in obtaining blood from donors and in giving transfusion to patients. Among the proposals agreed, and which it is expected will be the subject of International Organization for Standardization recommendations for national standards, are such important items as: overall sizes of glass containers, including sizes of the necks of the bottles; properties to be possessed by the stoppers of the bottles; the dimensions of the mounts for flexible tubing and piercing needles; identification of the piercing positions in the stoppers separately for collecting and for transfusion of blood; minimum rate of filter and drip chamber flow. Items for future study include: standard sizes of the most used bottle; type of mount for hypodermic needle; simple label identification of the blood group of the contents of the bottle, and performance standards for the glass bottles.

CHANGES IN BASAL METABOLISM, SERUM-PROTEIN-BOUND IODINE, AND CHOLESTEROL DURING TREATMENT OF HYPOTHYROIDISM WITH ORAL THYROID AND L-THYROXINE SODIUM

BY

J. DOUGLAS ROBERTSON, M.D., D.Sc., F.R.C.P.
F.R.I.C., D.P.H.

Director

AND

H. F. W. KIRKPATRICK, Ph.D., B.Sc., F.R.I.C.

Chemical Pathologist

Department of Clinical Investigation, the London Clinic

It has been generally established that in patients with untreated hypothyroidism the serum-protein-bound iodine (P.B.I.) is consistently below the normal range of 4 to 8 $\mu\text{g.}$ per 100 ml., and the literature has been reviewed by Rapport and Curtis (1950). Further, Winkler, Riggs, and Man (1945) claimed that serum iodine is not only a valuable aid in the diagnosis of hypothyroidism but a useful criterion of the adequacy of treatment with thyroid substance, for its return to within the normal range with adequate treatment is a better indication of the thyroid status of the patient than the basal metabolic rate (B.M.R.), the latter becoming stabilized at a slower rate than the serum iodine.

In support of this statement Winkler *et al.* described their findings, first, in a case of post-operative hypothyroidism, after thyroidectomy for thyrotoxicosis: "Forty days after operation the serum iodine had already fallen to 1 $\mu\text{g.}$ per 100 ml., yet the metabolic rate was still + 3%; and, secondly, their observations in controlled hypothyroidism after withholding thyroid: "Indeed, in the entire series of patients at the time of the initial iodine determination, metabolic rates as low as -30% or less need not appear unless the patient had remained untreated for several years." They also quoted the case of a patient with hypothyroidism whose initial (untreated) B.M.R. was -34, and who after more than a year of adequate thyroid therapy maintained a normal B.M.R. of -6, despite a period of over eight months without thyroid, and a serum iodine of 2.6 $\mu\text{g.}$ per 100 ml. It has also been stated that the latter is less subject than the B.M.R. to fluctuations in serial determination (Riggs, 1947). Hypercholesterolaemia is usually another characteristic feature of hypothyroidism, but it is not apparently an obligatory accompaniment (Winkler, Riggs, and Man, 1945).

The treatment of hypothyroidism with synthetic thyroxine has been described by Hart and MacLagan (1950), who conclude that L-thyroxine sodium is as satisfactory for the purpose as thyroid extract, and suggest that it has an advantage in reliability in that it is a synthetic substance and requires no biological or chemical standardization.

In order to compare the results of treatment of hypothyroidism with L-thyroxine sodium and with whole dried thyroid we have made serial examinations of five established cases. The patients voluntarily agreed to stop treatment for a period of some two months, after