STUDIES IN THE METABOLISM OF PROGESTERONE*

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THE classical observations of Fraenkel,[1] Loeb[2] and Bouin and Ancel[3] during the period 1903 to 1910 established the corpus luteum as an endocrine gland whose chief function is to prepare the uterus for implantation of the fertilized ovum. Progesterone, the active hormone of the gland, was isolated and chemically characterized in 1934. Within a short time the organic chemist was able to develop synthetic methods which have made available sufficient crystalline progesterone to enable extensive studies to be made of the physiological and pharmacological properties of this hormone under a variety of experimental conditions. Now that the exact physiological rôle of the corpus luteum has been established we are concerned with still another problem which has as its object the elucidation of the chemical changes undergone by the progestational hormone in the course of its inactivation and excretion by the animal body. An understanding of such changes has already resulted in the development of a valuable laboratory method for the study of luteal function and, it is to be hoped, will provide information regarding "the chemical mechanisms involved when these hormones produce their physiological effects in the organs and tissues upon which they act".[4]

It is the purpose of the present communication to review briefly past studies of the intermediary metabolism of progesterone and to describe the progress of such studies which are under investigation in these laboratories in collaboration with Drs. J. S. L. Browne and R. D. H. Heard.

Previous studies designed to follow the metabolism of the corpus luteum hormone by the estimation of progesterone-like material in blood and urine by methods of bio-assay have been singularly unsuccessful. Extracts prepared from as much as 10 litres of urine from various sources failed to exhibit progestational activity.[5, 6, 7] Loewe and Voss,[8] however, did succeed in demonstrating the presence of 1 rabbit unit of progesterone-like substance in 20 litres of human urine collected during pregnancy and the last half of the menstrual cycle. It is to be noted that an equal volume of urine collected during the first half of the menstrual cycle contained no such activity. Even after the administration of relatively large doses of progesterone to women Ehrhardt and Hagena[6] and Hamblen and co-workers[9] were unable to demonstrate the excretion of progesterone-like material in the urine. Likewise Clausberg[5] and Bloch[10] failed to prepare progestationally active extracts from as much as 500 c.c. of blood of pregnant women. One rabbit unit of activity was found however in 12 litres of sow's blood.

The method of bio-assay employed by these authors was that of Corner and Allen[11] or some modification thereof which is dependent upon the capacity of progesterone to transform the endometrium of a suitably treated immature or castrated rabbit into the progestational state. Its sensitivity is such that 0.5 to 1 mgm. of progesterone (1 rabbit unit) is required to obtain a positive response. Recently more sensitive methods of assay have been devised and by their use a progesterone-like substance has been demonstrated in the blood of non-pregnant rhesus monkeys[12] and in pregnant guinea pig blood.[13] Likewise Haskins[12] has reported the presence of approximately 0.13 gamma of progestationally active substance in 1 c.c. of serum of pregnant women. The presence of but a very small amount of progesterone in body fluids is probably due in part to the fact that progesterone in the course of its metabolism is converted into a progestationally inactive compound, pregnanediol-3 (*a*), 20 (*a*).

Pregnanediol-3 (*a*), 20 (*a*), which will hereafter be referred to as pregnanediol, was first isolated from human pregnancy urine in 1929 by Marrian.[14] Later in the same year it was independently isolated from the same source by Laqueur and co-workers[15] and by Butenandt.[16] The latter, in collaboration with Hildebrandt and Brücher[17] succeeded in demonstrating the relationship of this compound to the bile acids

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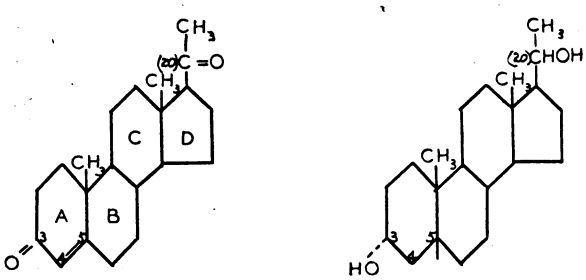
and in 1931 established its structural formula. The significance of the presence of this steroid in pregnancy urine was not realized at this time and the compound, due to its physiological inactivity, received little attention. With the establishment of the structural formula of progesterone by Butenandt and his group[18] and by Fernholz[19] it became clear that these two steroids were closely related chemically. As a matter of fact the proposed formula for progesterone was confirmed by the chemical conversion of pregnanediol into progesterone. This transformation served to emphasize the chemical relationship between the two compounds. Inspection of the formula of these two steroids (Chart 1) makes this clear. It can be seen that pregnanediol differs from progesterone in that the two ketonic groups and the double bond of the latter have been reduced. It was this close similarity that led Butenandt to suspect that pregnanediol arose from the *in vivo* reduction of progesterone and as such represented an excretion product of corpus luteum metabolism.



PROGESTERONE PREGNANEDIOL

Chart 1

The methods then available for the isolation of pregnanediol were not suited for the detection of small quantities of this steroid and by their use it was not possible to demonstrate any physiological significance for the occurrence of this compound in urine. An important step in the development of a more sensitive method was provided by the experiments of Odell and Marrian[20] which showed that pregnanediol is excreted in human pregnancy urine not as a free steroid but for the most part as a water soluble complex from which free pregnanediol can be released by acid hydrolysis. Later in the same year Venning and Browne[21] announced the isolation of this complex and demonstrated it to be a mono-sodium salt of pregnanediol glycuronic acid. The following year Venning[22] published details of her method, which consists of the extraction of the conjugated pregnanediol from urine with butyl alcohol and the subsequent precipitation of the conjugate with acetone. The weight of the precipitate (sodium pregnanediol glucuronide) is converted by means of a factor into an equivalent weight of free pregnanediol. This method of isolation permitted the preparation of pregnanediol in amounts greater than previously reported to have been isolated from such urines and proved to be technically suited for clinical use.

Using this technique Venning and Browne were able to study the excretion of pregnanediol under a variety of circumstances.[23-26] This steroid was shown to be excreted early in pregnancy and in increasing amounts as gestation progresses, disappearing from the urine a few days after parturition. During the menstrual period they found that pregnanediol is excreted in the urine only during the second half of the cycle. In those cases in which it was possible to estimate the time of ovulation it could be shown that pregnanediol appeared about 24 to 48 hours after this event and disappeared from the urine again a few days prior to the onset of the menstrual flow. The excretion of pregnanediol was thus shown to occur at a time when it is well known that a functional corpus luteum is present. These observations have been extensively confirmed by Wilson and associates,[27] Stover and Pratt[28] and others, and support Butenandt's hypothesis that pregnanediol is an urinary excretion product of the corpus luteum hormone.

Conclusive experimental proof of the conversion of progesterone into pregnanediol was provided by the studies of Venning and Browne[26] in which the fate of injected progesterone was determined. Following the administration of 19 to 30 mgm. of progesterone into women who were not excreting pregnanediol they were able to show that 12 to 46% of the injected hormone appeared in the urine as pregnanediol. Attempts to confirm these findings by Hamblen and co-workers[29] and by Stover and Pratt[28] were unsuccessful. This was probably due to the failure of these authors to inject a quantity of progesterone sufficient to yield enough urinary pregnanediol to be detected by the Venning method. It is imperative that adequate precautions be taken to prevent the hydrolysis of the pregnanediol conjugate by the addition of a preservative to the urine. Later work has made it clear that if these precautions are observed the conversion of exogenous progesterone

to pregnanediol can be demonstrated not only in the human female[30, 31] but also in the human male. Thus Westphal and Buxton[32] and more recently Hamblen and co-workers[33] have been able to show that injected progesterone in men is excreted in good yield as pregnanediol glucuronide.

Although the presence of pregnanediol in the urine of normal non-pregnant women is dependent upon the existence of a functioning corpus luteum it must be pointed out that pregnanediol can be excreted in the absence of this gland. Thus it has been shown that certain patients in whom the corpus luteum of pregnancy has been excised pregnanediol continues to be excreted in the urine.[34] It is generally assumed that under these circumstances pregnanediol arises from the metabolism of progesterone elaborated by the placenta. The occurrence of small quantities of pregnanediol in the urine of ovariectomized non-pregnant women[35] and normal men[36] points to an extra-ovarian source which is most likely the adrenal cortex. The isolation of crystalline progesterone from the adrenal cortex[37] strengthens this view, and may indicate the origin of a part at least of the pregnanediol excreted under these conditions. In addition, pregnanediol of adrenal origin might arise during the metabolism of steroids other than progesterone. In this connection it is of interest that Cuyler and his associates[38] recovered pregnanediol, as the glucuronide, from the urine of men following the administration of desoxycorticosterone acetate, a naturally occurring steroid of the adrenal cortex.[39] The isolation of large amounts of pregnanediol from the urine of women with adrenal cortex hyperplasia or adrenal carcinoma is further evidence that this compound may arise during the metabolism of adrenal cortical steroids.[40]

Pregnanediol assays have proved to be of considerable value in the investigation of various obstetric and endocrine disorders. Since pregnanediol is a metabolite of progesterone, its occurrence in the urine of a non-pregnant woman can generally be considered to be indicative of the presence of an actively functioning corpus luteum and indirectly of the occurrence of ovulation. Its quantitative estimation under these circumstances serves as an index of luteal activity. Pregnanediol determinations are useful in following the course of pregnancy where a diminution of excretion may be indicative of a pathologic change such as threatened abortion or death of the fetus.[41] The excretion of pregnanediol in association with amenorrhœa has been used by Wilson and associates[42] and by Hain and Robertson[43] as an aid in the diagnosis of pregnancy. Some investigators, notably Smith and Smith,[44] are of the opinion that there is a diminished excretion of pregnanediol in the toxæmias of pregnancy. This fact has figured prominently in their explanation of the hormone imbalance which they consider to exist in toxæmias, and pregnanediol assays have been found useful by them in following the course of the toxæmia.

The metabolism of progesterone involves a number of factors which can be studied adequately in the human subject only with great difficulty. It therefore becomes desirable to make available for experimental investigation a laboratory animal which metabolizes progesterone as does the human being. With this object in view the steroid metabolism of a number of the common laboratory animals has been examined.

Although free pregnanediol had been isolated from the urine of pregnant cows,[45] mares[46] and chimpanzees[47] and the urine of bulls[48] prior to the studies herein described, pregnanediol glucuronide had been isolated only from the urine of the human male and female. Thus the urine of normal and pregnant rabbits, cats and monkeys,[49] the urine of pregnant chimpanzees[50] and the urine of male monkeys[49] and bulls[51] was found not to contain sodium pregnanediol glucuronide when these urines were worked up by the Venning method. Nor had the conversion of progesterone to pregnanediol been demonstrated for any species other than the human. Westphal and Buxton[49] were unable to detect sodium pregnanediol glucuronide in the urine of monkeys treated with progesterone. Likewise Fish and others[47] failed to demonstrate pregnanediol glucuronide in the urine of guinea pigs to which progesterone and sodium pregnanediol glucuronide had been administered. Marker and Hartman[52] in a careful examination of the urinary steroids of a pregnant monkey which had received over a gram of progesterone were unable to isolate pregnanediol or any other end-product of progesterone metabolism.

Because of this apparent species difference in the metabolism of progesterone we were interested in investigating further the metabolism

of this compound in laboratory animals. In the course of the present study the metabolism of crystalline progesterone was followed in normal and ovariectomized-hysterectomized adult female rabbits and in normal and castrated male rabbits. The progesterone dissolved in oil was administered in amounts varying from 187 to 550 mgm. either orally or parenterally over a period of 1 to 5 days. In 3 instances α-œstradiol or œstrone was administered concomittantly. In the earlier experiments the pregnanediol was isolated from the acid hydrolyzed urine and fæces as the free steroid by methods previously described by Heard and associates[53] and by Hoffman and Browne,[54] in later experiments it was isolated from the urine as the glucuronide by the method of Venning. The results of these studies are indicated in Table I.

TABLE I.
RECOVERY OF PREGNANEDIOL IN THE URINE FOLLOWING THE ADMINISTRATION OF PROGESTERONE TO RABBITS

Test animal		*Hormone administered*			*Urinary pregnanediol isolated*	
No. of animals	*State*	*Route*	*Hormone*	*Quantity Mgm.*	*Mgm.*	*% Conversion**
3	Œstrus	Intraperitoneal	α-Œstradiol Progesterone	360 336	21.2	6.3
2	Œstrus	Subcutaneous	Progesterone	187	13.4	7.2
2	Hysterectomized-Ovariectomized	Subcutaneous	α-Œstradiol Progesterone	350 300	5.7	1.9
2	Œstrus	Subcutaneous	Œstrone Progesterone	300 300	14.2	4.7
2	Normal Male	Oral	Progesterone	500	48.0	9.6
2	Castrated Male	Oral	Progesterone	528	62.6	11.8
2	Castrated Male	Subcutaneous	Progesterone	506	42.4	8.3
2	Normal Male	Oral	Progesterone	550	48.8†	9.0

*Expressed as percentage of the quantity of progesterone administered.
†Isolated as sodium pregnanediol glucuronide (81.3 mgm.)

Both the male and female rabbit convert exogenous progesterone into pregnanediol. The extent of this conversion varies from 4.7 to 11.8% and approximates the degree of recovery demonstrated for similarly treated human subjects. First attempts to isolate the conjugated form of pregnanediol by the Venning method met with failure due to the presence of impurities which interfered with its isolation. It was found that slight modification of this procedure permitted the isolation of sodium pregnanediol glucuronide consistently from the urine of female[55] and male[54] rabbits which had received progesterone. The rabbit then not only metabolizes progesterone as does man but excretes the metabolite in the same conjugated form and thus becomes a suitable test animal upon which to study the factors which influence this metabolic process.

The factors which may be considered to have an influence on the metabolism of progesterone and the subsequent urinary excretion of sodium pregnanediol glucuronide are: (*a*) formation of progesterone, (*b*) conversion of progesterone into pregnanediol, (*c*) conjugation of pregnanediol with glycuronic acid, (*d*) excretion of sodium pregnanediol glucuronide by the kidney, (*e*) excretion of pregnanediol in the fæces, (*f*) excretion of metabolites of progesterone other than pregnanediol. The urinary excretion of pregnanediol glucuronide indicates that the first four factors are functioning properly. The absence of this compound from the urine may indicate the failure of one or more of these factors or the operation of one or both of the last two. An understanding of these factors affecting pregnanediol excretion would enhance considerably its diagnostic value.

Since the present studies are concerned with the metabolism of exogenous progesterone it is not within the scope of this paper to discuss the factors which influence the formation of progesterone.

CONVERSION OF PROGESTERONE INTO PREGNANEDIOL

Originally the endometrium was considered to be essential for the conversion of progesterone into pregnanediol. In a note published in

1938, Venning and Browne[26] stated that two hysterectomized patients each of whom had been injected with 24 mgm. of progesterone failed to excrete pregnanediol. Hamblen and co-workers[29] observed that curettage of the endometrium during the luteal phase of the menstrual cycle resulted in the disappearance of pregnanediol from the urine and therefore concluded that the endometrium was necessary for the metabolism of progesterone. Buxton[56] and Venning and Browne[30] however in recent studies have shown that if sufficiently large doses of progesterone (90 mgm.) are administered to hysterectomized patients pregnanediol can be isolated from the urine. In view of these conflicting reports we investigated the fate of progesterone in the bilaterally salpingo-ovariectomized hysterectomized rabbit. Following the administration of 300 mgm. of progesterone to 2 such rabbits 5.7 mgm. of pure pregnanediol were isolated from the urine. While these studies were in progress Jones and Te Linde[57] confirmed the ability of hysterectomized women to convert crystalline progesterone into pregnanediol. Evidence was also adduced that these patients were capable of metabolizing endogenous progesterone as pregnanediol glucuronide was recovered from their urine at a time when they were estimated to be in the luteal phase of the menstrual cycle. In view of these findings the uterus cannot be considered to be a necessary adjunct to the conversion of progesterone into pregnanediol. This of course does not exclude the possibility that under normal conditions the uterus may play a rôle in this interconversion.

That the uterus may have some influence on the metabolism of progesterone is indicated by a comparison of the percentage yield of pregnanediol from a given quantity of progesterone in women whose endometria are in different stages of development. Following the administration of progesterone to 3 patients with amenorrhœa with hypoplastic endometria Venning and Browne[30] noted the excretion of only a trace of pregnanediol. However when the progesterone was administered following pretreatment with œstrogens 12 to 18% of the injected hormone was recovered as pregnanediol, and the endometrium underwent progestational changes which it had failed to do when progesterone was administered without œstrogenic pretreatment. No correlation however was shown to exist between the amount of pregnanediol recovered and the degree of progestational effect. Still higher recoveries (20 to 55%) of pregnanediol following injections of progesterone were obtained by these workers when the hormone was administered in the luteal phase of the menstrual cycle or in early pregnancy. It should be noted that in these particular cases pregnanediol was already being excreted from the metabolism of endogenous progesterone so that only an approximate estimate can be made of the increased excretion of pregnanediol due to the injection of progesterone. The available evidence, although still incomplete, indicates that the presence of a normal proliferated endometrium facilitates the conversion of progesterone to pregnanediol.

Marker and co-workers[58] have demonstrated that the bull excretes twice as much pregnanediol as the pregnant cow. However the urine of steers castrated in infancy did not contain any pregnanediol.[59] This observation has given rise to the suggestion that the testis may in some way be involved in the conversion of progesterone into pregnanediol. To test this hypothesis progesterone was administered to male rabbits prior to and after castration. There was no significant difference in the amount of pregnanediol recovered, 9.6% of the administered progesterone was isolated as pregnanediol from the normal male rabbit and 11.8% after castration. The testis then does not appear to be essential for the metabolism of progesterone.

CONJUGATION OF PREGNANEDIOL WITH GLYCURONIC ACID

That the method of conjugation might not be the same in all species is indicated by the failure to isolate sodium pregnanediol glucuronide from the urine of various animals which are known to excrete pregnanediol. Up to the present only the human being and the rabbit have been shown to excrete pregnanediol as the glucuronide.

The method of Venning estimates sodium pregnanediol glucuronide only. Free pregnanediol or pregnanediol conjugated with a detoxifying agent other than glycuronic acid would not be detected in urine processed by this procedure. Although it is very unlikely that more than a trace of free pregnanediol is excreted normally the possibility that pregnanediol might be present in urine, in part at least, in a form other than the glucuronide has

not been excluded. For the glucuronide estimations to have quantitative significance in relation to progesterone metabolism it must be shown that it is the major form in which pregnanediol is excreted by the kidney. The presence of pregnanediol in human urine in a form other than the glucuronide has not been established. Studies upon the rabbit indicate that there is no significant difference in the amount of free pregnanediol isolated from acid hydrolyzed urine of progesterone treated animals from that isolated as the glucuronide. As the conditions of acid hydrolysis employed were such that pregnanediol would be expected to be freed from any conjugated form in which it is likely to be excreted it would appear that in the rabbit at least pregnanediol is excreted for the most part if not entirely as the glucuronide.

It is generally assumed that the conjugation of pregnanediol takes place in the liver. Is it not possible that in some forms of liver damage the glycuronic acid conjugating mechanism might be impaired and under these circumstances pregnanediol, if it is excreted at all, might appear in the urine in a form other than the glucuronide, perhaps as the sulphate in which form it is known that œstrone[60] and androsterone[61] are excreted? The effect of partial hepatectomy and liver damage on the excretion of pregnanediol by the rabbit is now under investigation in these laboratories.

EXCRETION OF SODIUM PREGNANEDIOL GLUCURONIDE BY THE KIDNEY

Little is known of the effects of renal efficiency on the excretion of pregnanediol. Hamblen and his collaborators[29] have suggested that the temporary interruption of pregnanediol excretion occasionally observed by them during the luteal phase of the menstrual cycle might be the result of changes in renal activity. Cope[31] compared the hourly excretion rates of pregnanediol with those of creatine and creatinine during labour and concluded that changes in renal activity affect pregnanediol excretion to approximately the same extent as they affect the excretion of creatine and creatinine. The abnormally small amounts of pregnanediol glucuronide excreted by pregnant women with eclampsia has been shown by Bachman and co-workers[62] to occur simultaneously with the onset of proteinuria and to be associated with this phenomenon during the remainder of gestation. They are of the opinion that this depression in excretion need not necessarily be due to defective renal action, and suggest that it is more likely an expression of faulty synthesis or conjugation of pregnanediol to form the glucuronide. That impairment of renal function can have a marked effect on the excretion of pregnanediol is indicated by the failure of Cope[31] to isolate pregnanediol glucuronide from the urine of late pregnancy of two women with chronic nephritis. Before any determining rôle can be ascribed to the abnormally low excretion of pregnanediol in the pathogenesis of the toxæmias of pregnancy it must be satisfactorally demonstrated that such low excretion is not the result of impairment of renal function but of deficient secretion or faulty metabolism of progesterone.

As a preliminary to an investigation of the effects of various forms of kidney damage on the urinary excretion of pregnanediol we determined the curve of urinary elimination of this compound following the administration of progesterone and sodium pregnanediol glucuronide to normal rabbits. The progesterone as an oily solution and the sodium pregnanediol glucuronide dissolved in water were given at a single injection and the urinary excretion of pregnanediol glucuronide determined at 24-hour intervals. Following the administration of progesterone intramuscularly or subcutaneously the curve of excretion of pregnanediol assumed a characteristic form shown in curves A and B of Chart 2. The time required for the complete elimination of the pregnanediol complex was found to be three days. Only a trace of pregnanediol glucuronide was excreted in the first 24 hours following the injection; the major portion appeared in the second 24-hour collection of urine followed again by a trace in the third 24-hour specimen. A similar time lag in the excretion of this compound has been observed by Venning and Browne[30] following the administration of progesterone to patients with amenorrhœa and metropathia hæmorrhagica, and by Hamblen and co-workers following the injection of progesterone to normal men. When progesterone was injected by the former authors during the luteal phase of the menstrual cycle or in early pregnancy it was observed that the increased excretion of pregnanediol occurred immediately. This led them to suggest that it takes some time for the mechanisms leading to the excretion of preg-

nanediol to become effective if they are not already operative prior to the injection, as in the case of the luteal phase of the menstrual cycle or in early pregnancy.

To gain further insight into the explanation of this 24-hour lag in excretion a single dose of sodium pregnanediol glucuronide was administered subcutaneously and intravenously and the rate of pregnanediol excretion determined (Chart 2, curves C and D). Although the time required for complete elimination of the pregnanediol by the kidney was still two to three days these curves of elimination differ from those following progesterone administration in that the excretion of pregnanediol was immediate, one-third to one-half of the total excreted pregnanediol appearing in the first 24-hour specimen of urine. It would seem then that the time lag is not the result of delayed excretion of sodium pregnanediol glucuronide by the kidney but is concerned with either (*a*) the rate of absorption of progesterone, (*b*) the rate of conversion of progesterone into pregnanediol, or (*c*) the rate of conjugation of pregnanediol with glycuronic acid. Which of these factors is responsible could be ascertained by determining the curve of excretion following the administration of progesterone and pregnanediol intravenously.

EXCRETION OF PREGNANEDIOL IN THE FÆCES

For urinary sodium pregnanediol glucuronide assays to have quantitative significance in relation to progesterone metabolism it must be demonstrated that little if any pregnanediol is excreted by other routes. Since it is known that œstrogens[63] and androgens[64] are excreted in the fæces it was considered not at all improbable that pregnanediol might be similarly excreted. To investigate this possibility acid hydrolyzed fæces of progesterone treated rabbits were examined to determine the presence of pregnanediol by a method developed in these laboratories.[54]

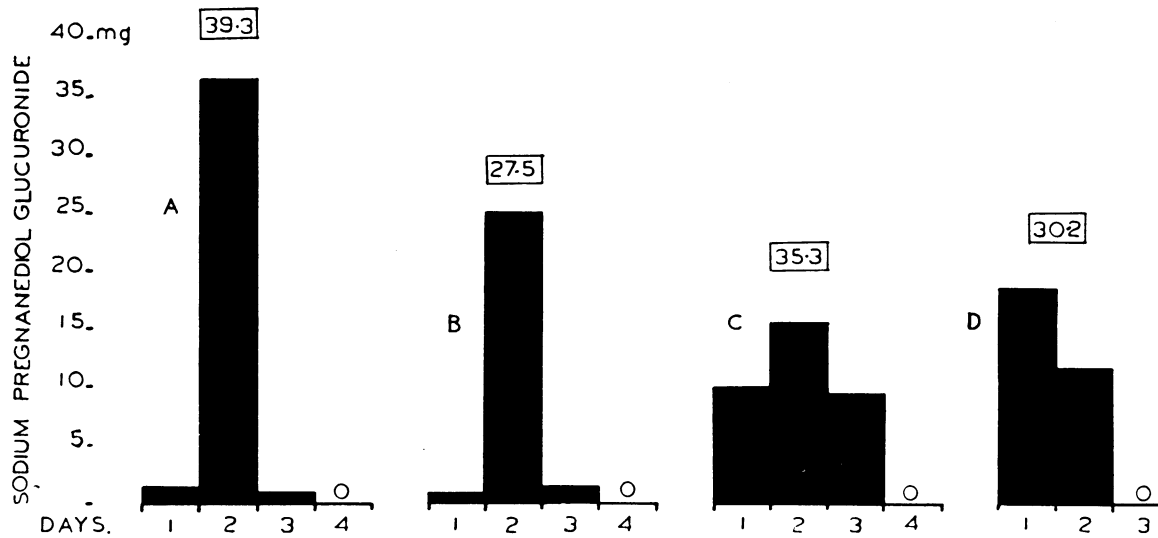


Chart 2.—The urinary excretion of the pregnanediol complex following the administration of progesterone and sodium pregnanediol glucuronide to rabbits.

Numerals in square signify the total excretion of sodium pregnanediol glucuronide.

Curves A and B.—Following the administration of progesterone intramuscularly (300 mgm.) and subcutaneously (275 mgm.) respectively.

Curves C and D.—Following the administration of sodium pregnanediol glucuronide subcutaneously (150 mgm.) and intravenously (135 mgm.) respectively.

It was found that when progesterone was injected subcutaneously in the quantities indicated in Table II it was not possible to demonstrate pregnanediol in the fæces. However 5 to 7.1% of the progesterone given by gavage could be recovered as pregnanediol from the fæces. A possible explanation of the occurrence of pregnanediol in the fæces under these conditions is that it arose from the reduction, perhaps through bacterial action, of unabsorbed progesterone in the gastrointestinal tract. In view of the failure of parenterally administered progesterone to be excreted as pregnanediol in the fæces it seems improbable that under normal conditions endogenous pro-

gesterone could be so excreted. To settle this point it is proposed to determine the steroid content of the fæces of pregnant women.

EXCRETION OF METABOLITES OF PROGESTERONE OTHER THAN PREGNANEDIOL

As the conversion of progesterone into pregnanediol involves the addition of hydrogen to the three reducible groups of the former compound many partly reduced intermediary compounds are theoretically possible in the course of this reduction. Several of these have already been isolated from human pregnancy urine by Marker and his collaborators.[64] It is generally assumed that these compounds are progesterone metabolites and since they are present in human pregnancy urine in an amount not exceeding 2% of the pregnanediol excretion they have generally been ignored in considerations of progesterone metabolism. To determine if such compounds arise in the rabbit during the course of progesterone metabolism the neutral urinary steroids excreted following the administration of approximately 800 mgm. of progesterone to normal female rabbits were examined. Pregnanediol was the only compound isolated. Neither the partly reduced intermediates or isomers of pregnanediol were detected. We must therefore conclude that pregnanediol is the major end-product of progesterone metabolism in the rabbit.

SUMMARY

1. The conversion of progesterone into pregnanediol by the male and female rabbit has been demonstrated.

2. The pregnanediol is excreted as the glucuronide in this species.

3. It has been shown that the uterus and the testis are not essential for the interconversion of progesterone into pregnanediol.

4. Pregnanediol is excreted in the fæces of rabbits receiving progesterone orally but not when the hormone is administered parenterally.

5. The factors affecting the metabolism of progesterone and the subsequent excretion of sodium pregnanediol glucuronide are discussed.

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TABLE II.

RECOVERY OF PREGNANEDIOL IN THE FÆCES AFTER THE ADMINISTRATION OF PROGESTERONE TO RABBITS

Test animal		*Progesterone administered*		*Fæcal pregnanediol isolated*	
No. of animals	*State*	*Route*	*Mgm.*	*Mgm.*	*% Conversion**
1; R_9	Normal♂	40 mgm. pregnanediol added to fæces		25	62.5
2; R_7R_8	Castrated♂	Subcutaneous	506	0	0
2; R_9R_{10}	Normal♂	Subcutaneous	400	0	0
2; $R_{30}R_{31}$	Normal♂	Oral	550	39	7.1†
1; R_{13}	Normal♀	Oral	300	15	5.0

*Expressed as percentage of progesterone administered.
†Total conversion, including urinary pregnanediol, is 16.1%.

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PSYCHONEUROSIS IN THE CANADIAN ARMY OVERSEAS

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THE prolonged sojourn of the Canadian Army in Britain, without being engaged in active warfare, has led to a unique situation from the standpoint of the mental health of the soldiers. True war neuroses associated with the mental stress of violence, excessive fatigue and fear of injury are few, yet neurotic disorders constitute an important problem because of the presence of a large number of predisposed individuals in the army, and also because of certain disturbing elements in military life, such as separation from families, boredom, inactivity and indefinite waiting.

This report is a survey of our experiences at No. 1 Neurological Hospital, R.C.A.M.C., where a large proportion of the psychoneurotic disorders of the Canadian Army have been sent for investigation, treatment and disposal. The figures given are based on admissions to hospital and do not include the large number of cases seen in the out-patient clinic. An attempt has been made to determine the factors predisposing to these disorders and to discuss the common, immediate precipitating conditions. Certain general conceptions of neurosis are outlined, principles of disposal and treatment are considered in some detail, and results are reviewed. The special problem of alcoholism as related to neurosis is being considered in a separate paper which is now being prepared for publication. The aims of this report are to record our experiences in the hope of providing some information of general value, to present data that may be of use to medical boards in Canada, and to provide medical officers with some basic principles that may be of practical value in dealing with personality disorders.

GENERAL CONSIDERATIONS OF SYMPTOMS OF NEUROSIS

A tendency still prevails to look upon neurotic symptoms in a vague, mystical light, or to consider them as a product of the imagination or of wilful simulation. With the latter attitude, the neurotic tends to be regarded, and even openly called, a "lead-swinger", "bloody-minded", or other similar epithets. Not uncommonly he is left with the impression that his medical officer considers him a criminal of despicable type. The true psychoneurotic patient then becomes resentful and determined; he may exaggerate his symptoms to prove his case and probably will be reticent and uncooperative in later attempts at treatment. This is not a plea for excessive sympathy and gentleness, but merely for a careful, informed approach to neuroses. The necessity for diagnosing and dealing firmly with the actual