The layman's ideas of aetiology certainly are practically always of this kind, the classical example being the mentally defective child whose parents attribute its defect to a fall out of a pram. No doubt from the point of view of human self-respect such an attitude is very admirable, but when searching for the truth we must recognize it for what it is—namely, a form of self-conceit. In the case of the feet it has become customary to place the blame for almost all disabilities and deformities (other than those patently congenital) upon footwear. That the form of the foot can be profoundly altered by restricting forces is not denied—the Chinese ladies' feet of a previous generation are sufficient evidence—nor is it proposed to exonerate the shoemaker entirely; but I feel that only when due consideration is given to such evolutionary factors as have here been instanced shall we get a true picture of the origin of many foot troubles or be able to explain their distribution among the population—well shod, badly shod, or even completely unshod. A well-developed foot, judged by evolutionary criteria, may stand up to considerable abuse, failing only when the maltreatment becomes excessive; but a badly adjusted foot may fail under the normal stresses of ordinary locomotion without any misuse whatsoever.

# 17-KETOSTEROID EXCRETION IN ADRENAL VIRILISM

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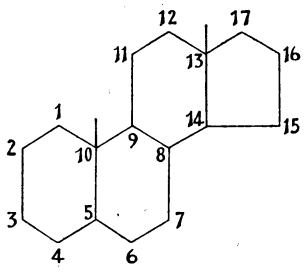
In an earlier publication (Broster *et al.*, 1938) we reported the results of a biochemical study in adrenal virilism and intersexuality. This was mainly concerned with the urinary excretion of androgens, and the qualitative and quantitative findings were based upon the capon method of assay of androgens. Since the completion of that work the introduction of a purely chemical procedure for the estimation of urinary ketosteroids has provided an alternative investigation method of great value in this field, with notable advantages over the biological method for the study of clinical cases, especially in regard to the ease of application and reproducibility. The enhanced facility thus afforded has rendered possible the rapid extension of our knowledge of a subject hitherto studied only with great difficulty. Such knowledge has already established some of the salient




features of adrenal virilism as they appear against a background of normal standards.

In the interest of the general reader it should be explained that the androgens—i.e., substances having male hormone activity—are derivatives of the parent hydrocarbon androstane, which has the skeleton ring structure indicated above. The term "17-ketosteroid" denotes steroid compounds like the two chief androgens of urine, androsterone and transdehydroandrosterone, which have a ketonic group in position 17. Now, it has been found that these two androgens, and certain related compounds of the steroid class all possessing the keto group in position 17, give an intense red colour with meta-dinitrobenzene and potassium hydroxide, such reaction making possible the rapid estimation of the urinary 17-ketosteroids. Because in addition to androgens certain other substances are included in this reaction which are not physiologically active, the colorimetric technique is not capable of giving an exact measure of the male hormone activity of the urine. Nevertheless the assay of the collective 17-ketosteroid has potentially as much interest as has the assay of that fraction which possesses biological activity.

Agreement is reasonably good among those investigators who have attempted to define the normal limits of androgen and ketosteroid output with which to compare findings in pathological cases. Thus Callow *et al.* (1939) give 1.7 to 12.6 mg. as the daily ketosteroid output for normal women, with a mean value of 6.75, and for men 3.5 to 15 mg., with a mean of 9.05. For androgens their values are 2 to 50 I.U. for women and 6.5 to 110 I.U. for men. These same authors review the findings of other investigators, which on the whole do not differ substantially from their own. Friedgood and Whidden (1939) quote 4 to 15 mg. as the daily excretion for normal women, while Chou and Wang (1939) report results in terms of body weight, obtaining values of 1 to 3 I.U. per kg., corresponding to an absolute range of 4.3 to 21 mg. daily. In sharp contrast to these scales, Callow and his fellow workers found outputs varying from 40 to 288 mg. of ketosteroid daily in adrenal tumour cases, while Friedgood and Whidden record figures from 45 to 325 mg., and various isolated tumour cases of which clinical and biochemical details have been published have shown similarly enhanced figures. In general these are of an order which appears to place adrenal tumour cases in a category entirely separate from all other pathological cases. A group of cases classified as "hirsutism, adrenal hyperplasia" investigated by Callow (1938) showed a range of 1 to 33 mg. ketosteroid daily, while in a somewhat similar group which was composed of cases of benign hirsutism and adrenal virilism, studied by Friedgood and Whidden, the range was from 1 to 29 mg.

While these investigations have provided the broad framework for an understanding of the significance of ketosteroid determinations in respect of adrenal cases, there remains much detail to be fitted into it. In particular the relation of ketosteroid excretion to the various types of adrenogenital virilism which have now been classified clinically calls for a closer study than has hitherto been attempted, and we therefore have endeavoured, with the aid of a considerable mass of clinical material placed at our disposal, to contribute further detail to existing knowledge.

## Methods

For considerations of space only the briefest indication of the technical procedure will be given, as this paper deals essentially with results on clinical cases.

All ketosteroid determinations were made upon twenty-four-hour specimens preserved with either toluene or chloroform, 25 ml. aliquots being taken for an analysis. Hydrolysis was accomplished by boiling with 3% sulphuric acid for thirty minutes; and ether, or a mixture of equal volumes of ether and petroleum ether, was used for extraction. Purification of the ethereal extracts followed the usual lines, and the final product was taken up in 0.5 ml. of alcohol. For the purpose of colorimetric estimation 0.2 ml. of the alcoholic extract was treated

with an equal volume of 2% alcoholic solution of purified *m*-dinitrobenzene and 0.1 ml. 4N potassium hydroxide for one hour at 25° C., readings of the colour intensity being made in a Lovibond tintometer. The ketosteroid value was assessed from a calibration curve constructed from standard solutions of androsterone covering the range 20 to 200 γ (0.02 to 0.2 mg.) per 0.2 ml. In certain adrenal cases it was necessary to use suitable dilutions of the alcoholic extract to bring the colour intensity within the range of the calibration curve.

For the comparative capon assays of androgens four separate twenty-four-hour specimens were used, hydrolysis and extraction being carried out on each day's sample as soon as it became available. With the same acid concentration as for the ketosteroid determination the hydrolysis time was shortened to twenty minutes and ether extraction was again employed.

### Ketosteroid Excretion in Normal Subjects

A series of estimations were made on normal female and male subjects to determine the approximate normal range with which to compare our pathological cases, and also the values obtained by other investigators. The "normals" included not only healthy individuals pursuing their ordinary vocation but also hospital patients convalescent from minor surgical operations. The findings are recorded in Tables I and II.

TABLE I.—*Ketosteroid Excretion in Normal Women*

| Case | Ketosteroid Excretion mg. daily (S) | Creatinine mg. daily (C) | 100 S / C |
|---|---|---|---|
| 1 | 7·0 | | |
| 2 | 5·2, 4·6 | | |
| 3 | 6·3, 5·7, 7·0 | | |
| 4 | 10·0 | | |
| 5 | 3·5 | | |
| 6 | 6·4 | | |
| 7 | 14·6 | 1,670 | 0·88 |
| 8 | 9·4 | 1,088 | 0·86 |
| 9 | 6·3 | 1,123 | 0·56 |
| 10 | 9·1 | 1,274 | 0·71 |
| 11 | 4·5 | 1,235 | 0·36 |
| 12 | 7·1 | 1,122 | 0·64 |

TABLE II.—*Ketosteroid Excretion in Normal Men*

| Case | Ketosteroid Excretion mg. daily (S) | Creatinine mg. daily (C) | 100 S / C |
|---|---|---|---|
| 1 | 13·7, 12·5 (30) | | |
| 2 | 12·5 | | |
| 3 | 9·4 | | |
| 4 | 11·9, 14·8 | | |
| 5 | 9·7, 10·0 (48) | | |
| 6 | 12·6 | 1,706 | 0·74 |
| 7 | 18·6 | 2,293 | 0·82 |
| 8 | 9.4 | 2,043 | 0·45 |
| 9 | 20.9 | 2,560 | 0·82 |

Figures in parentheses denote androgen output expressed in I.U.

Where creatinine output has been determined it has been included in these tables, for such figures in relation to the ketosteroid output have a certain interest when compared with the corresponding findings in the series of secondary virilism cases which are to be considered later.

The range for women is 3.5 to 14.6 mg. daily, with a mean value of 7.4 mg. In calculating this mean we have used the average figure for those individuals whose output has been determined more than once. For men the range is 9.4 to 20.9 mg., with a mean value of 13.3 mg. Though the point has not been closely investigated, there seems, broadly, to be some relation between body size and ketosteroid excretion. The highest value in the female series, which greatly exceeded the next highest in the list, related to the biggest individual; while in the case of the men, too, the highest figures were encountered in the two biggest subjects. This observation derives some support from the creatinine figures, it having been long established that creatinine excretion has a certain parallelism with body weight.

In relation to the normal values it became of interest to ascertain whether in the adult female there were any appreciable changes during the menstrual cycle. In one subject on whom determinations were made throughout a complete cycle the ketosteroid output, as shown in Fig. 1,

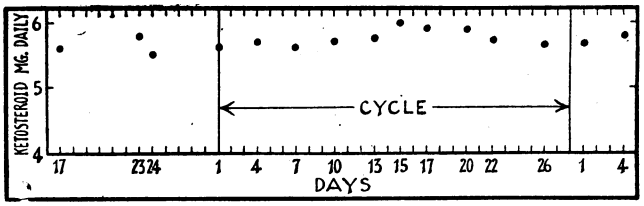



FIG. 1.—The ketosteroid output during the menstrual cycle of the normal adult female.

was found to keep at a fairly steady level. A slight peak occurs in the middle and a slight depression at the end of the cycle, but from this particular case at any rate there is no indication that any special day or time should be chosen in the determining of ketosteroid excretion in subjects of normal ovarian function. On the whole the ketosteroid excretion for any individual has been found to maintain a fairly even level from day to day, the occasional wide discrepancies occurring in the daily output having in most cases been traced to inaccurate collections of urine. The creatinine output has been found in such cases to be variable in the same direction and in much the same degree.

### Ketosteroid Excretion in Adrenal Cases

By far the largest number of the cases examined were those of female subjects belonging to the clinical group of adrenal virilism. These have been arranged according to the following classification, previously adopted by Broster and Vines (1933): Group I, primary or pre-pubertal virilism; Group II, secondary or post-pubertal virilism; Group III, Achard-Thiers syndrome. Cases of adrenal tumour have been separately grouped, and the results in this class will be dealt with first. The findings are recorded in Table III.

TABLE III.—*Adrenal Tumour Cases*

| Case | Sex | Age | Ketosteroid mg. daily | Androgen I.U. daily | Clinical Type |
|---|---|---|---|---|---|
| 1* | M | 1 | 28† | 90† | Isosexual precocity |
| 2 | M | 5 | 27 | " | " |
| 3 | F | | 170 | 800‡ | Cushing's syndrome |
| 4 | F | 34 | 270 | " | " |

* Case published by Fraser (1940). † These values are per litre. ‡ Assay by inunction method.

The tumour cases comprise two distinct types: (*a*) two cases in young male children in which the tumour has given rise to isosexual precocity; and (*b*) two cases in women in which the clinical manifestations simulated those of Cushing's syndrome. The former gave much lower figures than the latter, which yielded the highest values for ketosteroid obtained in the investigation, with a correspondingly high value in the androgen excretion in one of these patients, the other not having been examined in this respect. Relative to the appropriate normal standards, however, the younger patients have quite as high an excretion as the adults. The only adequate control case we have had for comparison with the infant was a child, aged 20 months, whose excretion was so low that it could not be accurately

determined, but was less than 0.6 mg. per litre ; from which it was evident that Case 1 in this tumour group was excreting at least 45 times the normal amount of ketosteroid. Since normal children in the age group 5 to 7 excrete only about 0.5 mg. daily (cf. Nathanson, Towne, and Aub, 1939), the older child in the tumour group was excreting about 50 times the normal amount. Against these ratios the outputs of the adult members exceeded the average normal by 25 to 35 times.

*Primary or Pre-pubertal Virilism.*—The next group comprises 7 cases of primary or pre-pubertal virilism, the experimental findings being summarized in Table IV. The cases in this group, of which 4 have been submitted to unilateral adrenalectomy and the diagnosis of adrenal hyperplasia fully established, constitute the most interesting of all the virilism subjects in that in them the adrenogenital syndrome is present in its most complete form. The age range is from 7 to 18, those of a post-pubertal

TABLE IV.—*Primary or Pre-pubertal Virilism*

| Case | Age | Ketosteroid mg. daily | Androgen I.U. daily | Remarks |
|---|---|---|---|---|
| 1 | 9 | 52 | 109 | |
| 2 | 18 | 56 | | 2 years' post-adrenalectomy |
| 3 | 17 | 35 | 80 | |
| 4 | 7 | 37, 34 | .88 | |
| 5 | 18 | 54 | | 1 year „ „ |
| 6 | 13 | 64 | 101 | |
| 7 | 9 | 50 | 101 | |

age having histories of virilism dating back to childhood. Ketosteroid excretion lies in the range 34 to 64 mg. daily, a range which might appear, on the basis of previously published results on adrenal cases, as characteristic only of adrenal tumour cases. Like the younger members of the previous group, the younger patients of this series exhibit a very striking enhancement of ketosteroid output in relation to the appropriate normal standards. Actually the youngest (Case 4, Table IV) shows about 70 times the normal excretion, those slightly older but still below puberty at least 20 to 25 times, which ratio falls to the level of about 6 to 8 in those examined at a post-pubertal age. However, it should be noted that two of these latter patients had previously been operated upon and one adrenal removed before we began examining ketosteroid excretion. One other case which cannot strictly be included in this group has, however, a close connexion with it, and indeed also with the previous group. The 9-years-old brother of Case 4 was found to be a fairly well marked case of isosexual precocity, thus resembling two of the earlier cases that have been mentioned. Clinical evidence and investigation could not confirm the presence of a tumour, but strongly suggested that his condition, like that of his sister, was due to pronouncedly hyperplastic adrenals. Three estimations of his daily ketosteroid output gave values of 60, 55, and 53 mg. From a consideration of the data just presented, it must be accepted that it is impossible in the pre-pubertal stage to differentiate between adrenal tumour on the one hand and adreno-cortical hyperplasia on the other solely on the basis of the urinary ketosteroid level.

*Secondary or Post-pubertal Virilism.*—The remainder of our cases of clinical virilism, with one exception, fall into by far the largest group of the whole series, that of secondary or post-pubertal virilism. In all, 67 such cases have been investigated. As representative of the class as a whole, details of 21 consecutive cases examined about the mid-period of the investigation are furnished in Table V. The relation to normal of the whole of the ketosteroid findings obtained in this group is illustrated in the distribution diagram (Fig. 2). It will be seen that these cases cover a fairly wide range—from 6.4 mg. daily at the lowest to 33.4 mg. at the highest. Rather less than half the cases show findings clearly in excess of the normal female range. In the present state of our knowledge it is impossible to make any really satisfactory classification within this series. The only manifestation common to all is some degree of

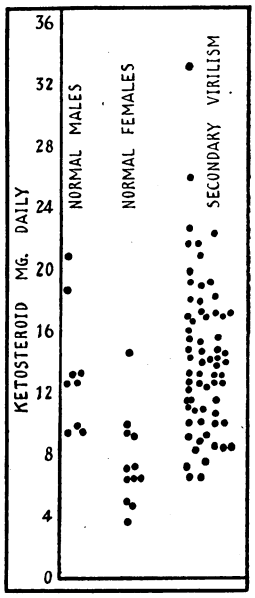



FIG. 2.—The ketosteroid findings in a group of 67 cases of secondary virilism compared with those of normal subjects.

hirsutism of male distribution. Among them are several very mild cases, and doubt must exist as to whether some of these are really adrenal cases at all. Others show one or more additional features belonging to the full adrenogenital syndrome. On the evidence so far available it is

TABLE V.—*Secondary or Post-pubertal Virilism*

| Case | Age | Ketosteroid mg. daily (S) | Androgen I.U. daily | Creatinine mg. daily (C) | 100 S/C | Clinical Notes |
|---|---|---|---|---|---|---|
| *1 | 32 | 10·8 | 80 | | | Moderate hirsuties, scanty menses (A) |
| 2 | 18 | 21·0 | 62 | 1,100 | 1·86 | Mild hirsuties, irregular menses |
| | | 19·4 | | | | |
| | | 20·5 | | | | |
| | | 25·2 | | | | |
| | | 23·8 | | 1,147 | 2·07 | |
| 3 | 25 | 19·4 | 82 | | | Moderate hirsuties, amenorrhoea (A) |
| | | 25·9 | | | | |
| 4 | 31 | 15·6 | | 1,358 | 1·21 | Marked hirsuties, obesity of Cushing type, normal menses |
| | | 16·4 | | | | |
| 5 | 21 | 14·2 | 36 | | | Moderate hirsuties, irregular menses (A) |
| | | 13·2 | | | | |
| 6 | 26 | 19·2 | | 1,333 | 1·44 | Very marked hirsuties, irregular menses (A) |
| | | 18·8 | | | | |
| 7 | 22 | 15·7 | | 1,122 | 1·40 | Mild hirsuties, irregular menses, family history of hirsutism |
| 8 | 24 | 11·5 | 33 | 1,187 | 0·97 | Moderate hirsuties, normal menses, severe headaches (A) |
| | | 11·6 | | | | |
| 9 | 21 | 22·3 | | 1,589 | 1·40 | Mild hirsuties, irregular menses |
| 10 | 18 | 14·8 | | 1,094 | 1·33 | Moderate hirsuties, normal menses |
| 11 | 24 | 13·3 | | 1,140 | 1·16 | Mild hirsuties, scanty menses |
| 12 | 22 | 13·9 | | 1,650 | 0·84 | Marked hirsuties, normal menses |
| 13 | 21 | 18·0 | 80 | 1,565 | 1·15 | Moderate hirsuties, irregular menses (A) |
| | | 19·0 | | 1,411 | 1·35 | |
| 14 | 29 | 11·1 | | 1,300 | 0·85 | Mild hirsuties, irregular menses |
| †15 | 27 | 33·4 | | 1,522 | 2·19 | Mild hirsuties, irregular menses, obesity of Cushing type (A) |
| | | 28·6 | | | | |
| 16 | 34 | 9·0 | | 1,580 | 0·57 | Mild hirsuties, irregular menses, obesity of Cushing type |
| 17 | 18 | 12·1 | | 1,150 | 1·05 | Moderate hirsuties, irregular menses |
| 18 | 25 | 10·5 | | 1,327 | 0·79 | Mild hirsuties, irregular menses, family history of hirsutism |
| 19 | 20 | 14·8 | | 1,394 | 1·06 | Very marked hirsuties, normal menses |
| | | 14·7 | | | | |
| 20 | | 13·3 | | 1,080 | 1·23 | Mild hirsuties, irregular menses, obesity of Cushing type |
| 21 | | 16·7 | | 1,549 | 1·08 | Moderate hirsuties, irregular menses |

(A) denotes a patient selected for adrenalectomy.
* Case published by Allen *et al.* (1939).
† Case published by Broster (1940).

a reasonable presumption that those exhibiting a greater output than 15 mg. of ketosteroid daily, and having a greater ketosteroid/creatinine ratio (i.e., 100 S/C) than 1, are cases in which there is an underlying adrenal element. Certainly the six cases of this kind which have been subjected to unilateral adrenalectomy have all shown evidence of adrenal abnormality, some in a degree that was recognizable on macroscopic examination. In others the abnormality was demonstrable by the special histological technique used by Vines. Three cases in the next lower range of excretion (i.e., between 10 and 14.9 mg.) have likewise shown histological evidence of abnormality, so that in the upper part of the normal range one cannot rule out the possibility of mild adrenal involvements where clinical signs suggestive of virilism are present. In fact, it would seem justifiable under these circumstances to suspect slight cortical hyperactivity where the ketosteroid/creatinine ratio is greater than 1. Lower still in the scale there has been only a single case in which adrenalectomy was performed. This was done on the ground that the case in question closely resembled clinically a type which had been found to benefit by the operation. The examination of the removed gland, however, revealed no abnormality, a finding which accords with the view that adrenal involvement is unlikely where the ketosteroid excretion falls below 10 mg.

*The Achard-Thiers Syndrome.*—A third group of virilism exists in the form known as the Achard-Thiers syndrome, a pluriglandular syndrome in which adrenal hyperfunction is one element. Patients show not only obvious signs of virilism but also well-marked diabetes and hypertension. Only one case conforming to this type has become available to us for investigation; it gave a value of 11·1 mg. for the daily ketosteroid excretion.

*Other Types of Sexual Dysfunction.*—While engaged in this study of adrenal cases we have from time to time encountered other cases, representing different forms of sexual dysfunction, which were of interest from the point of view of making comparisons with adrenal cases. The results are classified in Table VI.

TABLE VI.—*Other Types of Sexual Dysfunction*

| | |
|---|---|
| (A) Feminized males; ? pituitary infantilism: | |
| *1 | 7·8, 6·4, 8·5, 6·9, 8·5, 7·1, 8·8 mg. ketosteroid daily |
| 2 | 7·0 |
| 3 (aged 14) | 1·0 |
| (B) Hypogonadism; male subjects: | |
| 1 | 11·1 |
| 2 | 9·6 |
| 3 | 15·6 |
| (C) Homosexuals; female subjects: | |
| 1 | 15·6 |
| 2 | 12·0 |
| 3 | 6·7 |
| (D) Hypopituitarism (Simmonds's disease): | |
| 1 | 4·2 |

* Case published by Broster (1941).

The feminism group has considerable interest in that at once it is suggestive of being the clinical counterpart in males of the adrenal virilism of females. It would, however, be going beyond the evidence so far available to regard the condition as being primarily due to the influence of feminizing adrenals. A primary dyspituitarism may equally well be its basis. In all three cases the ketosteroid excretion is low, but that in itself would not distinguish between adrenal feminism and hypopituitarism.

There is nothing in the ketosteroid figures to reflect the clinically obvious hypogonadism of the cases (B) selected for investigation, nor in the next set of figures is there any definite indication of a possible ketosteroid imbalance in homosexuality.

## Discussion

A general survey of the results which have been recorded shows that when the maximal obtainable values for the daily ketosteroid excretion are taken into account the various groups of subjects can be arranged in ascending order as follows: normal women, normal men, secondary virilism, primary virilism, adrenal tumour cases. When the full limits of each group variation are considered there is seen to be much overlapping among the respective groups. Certain individuals in the tumour group yield figures far in excess of those obtained in any other group, and when such findings appear they are in themselves of absolute diagnostic significance. No clear idea has yet been formulated as to the minimum level which if exceeded must definitely establish the case as one of adrenal tumour. Crooke and Callow (1939) on this point find that, in view of the results which they cite in other adrenal cases, it is impossible to consider any value up to 35 mg. daily as by itself diagnostic of adrenal tumour. As a result of our work, which embraces a class of case not separately distinguished by these authors from other types of adrenal virilism, the figure quoted above must be raised to at least 70 mg., for the primary virilism group ranges practically up to that height. It is most unlikely that our cases have covered the complete range, so that setting the demarcation line at 70 mg. does not allow of a sufficient safety margin when considering the ketosteroid assay as an absolute diagnostic test for adrenal tumour. One would probably not be erring on the side of caution in suggesting that values clearly and consistently above 100 mg. would be required in order that this significance could be attached to them. On the other hand two of the established tumour cases have had lower ketosteroid excretion than any hitherto recorded. Both patients were young children, one an infant. In both, however, the ketosteroid excretion rates relative to the normal of the corresponding age were actually higher than in many of the tumour cases, the values for which have already been published. Even so, the high relative value does not distinguish them from certain non-tumour cases in children, for it is found that those with markedly hyperfunctioning glands which give rise to primary virilism in females and isosexual precocity in males yield excretion figures quite comparable to those of tumour cases.

There is only very slight overlapping between the cases of secondary virilism and those of the other two groups just considered. However, in the lower part of the secondary virilism range are to be found many figures which come well within the normal female range. It has been established that a number of cases in which reliable clinical evidence clearly points to adrenal hyperfunction lie within normal limits. Seeing that ketosteroid determination *per se* fails in such instances to detect any abnormality, it has been suggested in an earlier section that it might have more significance when considered in relation to the creatinine output, for a proportion of cases which are not outside the normal limits of variation of ketosteroid have a higher ketosteroid/creatinine ratio than normal. Added weight is given to this suggestion by the fact that, where it has been possible to make a pathological examination of the adrenals from cases falling into this category, the findings characteristic of adrenal virilism have been observed. This ratio may thus provide an aid to the diagnosis of secondary virilism in those cases in which the ketosteroid figure lies in the upper part of the normal range.

The androgen (expressed in I.U.)/ketosteroid (expressed in mg.) ratio has varied from 1.6 to 7.4 in the cases taken as a whole. Taking the separate groups, the variations in the ratio are as follows: adrenal tumour, 3.2 and 4.7

(two cases only, and in the second the androgen was obtained by a technique that differed from the standard procedure); primary virilism, 1.6 to 2.5, mean 2.1; secondary virilism, 2.5 to 7.4, mean 4.2. The literature on this subject shows figures which cover the range 0.4 to 7.0, which is slightly wider than, but very similar to, the total range given above. In primary virilism it would appear that there is proportionally rather less biologically active material in the total ketosteroid than is encountered in the other two groups. Considering both sets of values —those for androgens and ketosteroid—in relation to their respective normal ranges, we find only one case (Case 1, Table V) in which the ketosteroid was well within normal limits while the corresponding androgens were definitely above normal. Here the ketosteroid determination failed to reveal the degree of abnormality present in the urine. Except for this, a somewhat unusual case clinically, the results of the investigation uphold the view that the ketosteroid determination alone can be relied upon to give adequate expression of the degree of abnormality in respect of cortical hyperfunction in adrenal cases of the type forming the subject of this study.

## Summary

Ketosteroid output has been estimated in the following groups of cases: adrenal tumour, primary virilism, and secondary virilism.

Both primary virilism and adrenal tumour groups show very high excretion rates. At a pre-pubertal age it is impossible, solely on the basis of the ketosteroid output, to differentiate between adrenal hyperplasia and adrenal tumour.

Rather more than 50% of cases of secondary virilism give ketosteroid values that are within the normal female range. Some of these have ketosteroid/creatinine ratios that are higher than normal, for which reason this ratio is believed to have a diagnostic significance.

Three cases diagnosed as "feminism" (representing in males a near clinical counterpart of adrenal virilism in females) have shown a low ketosteroid excretion rate.

Comparative androgen and ketosteroid determinations in all groups support the view that the latter assay furnishes a reliable index of the cortical hyperfunction associated with virilism.

We are particularly indebted to Mr. L. R. Broster of Charing Cross Hospital, whose cases have constituted our main clinical material, and our warmest thanks are due to him for his close co-operation throughout. We also express our gratitude to Dr. E. C. Warner, Mr. Ian Fraser, Dr. H. W. Barber, and Dr. T. N. MacGregor for presenting us with interesting cases; to Dr. H. W. C. Vines for kindly communicating to us the results of his histological investigations; and to Dr. J. Adler for valuable assistance in compiling clinical notes.

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# FLUOROSCOPIC CONTROL IN THE REDUCTION OF FRACTURES

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Although fluoroscopic control in the reduction of fractures has been practised for many years the principles of protection from the risks of radiation promulgated at the second International Congress of Radiology in 1928 have not been generally accepted by the surgeons. Radiologists have always viewed the practice with misgiving and have discouraged it. In recent years, however, new impetus has been given to this type of work by the development of small, efficient, and cheap portable *x*-ray sets free from danger of electrical shock. These machines are often controlled and operated by surgeons without technical assistance and seldom under the direct supervision of a radiologist.

Some surgeons now maintain that the use of *x* rays for this purpose is of such assistance that it is essential in certain types of fracture, and actually manipulate fractures into position under the *x*-ray screen. Others use *x*-ray observation to see the result of their manipulation, while others are content with films.

It is for the radiologist to show how *x* rays may be applied to the greatest advantage without harm. His first duty is to point out the dangers involved from misuse; for *x* rays are essentially dangerous, and no warnings or precautions can render the use of them fool-proof. The surgeon who, in spite of all warnings, actually manipulates under *x* rays, exposing his hands to the direct beam, will suffer sooner or later from the cumulative effect of such exposures, even though no one of them has been sufficient to produce any noticeable change in the skin.

Recent experience in this country has prompted the Ministry of Health to issue a timely warning against the dangers of setting fractures and removing foreign bodies under the *x*-ray screen (E.M.S. Circular, 1941, Supp. 6, Sect. III).

That the dangers involved are real is well shown in an article by Leddy and Rigos (1941) from the Mayo Clinic, quoted by Jupe (1941), on 135 cases of severe radiodermatitis among physicians. In the period 1919-34 there were 55 cases, and from 1934 to 1939 a further 80 cases. All these had injuries to the skin manifesting as severe telangiectasis, keratosis, acute or chronic ulceration, or epithelioma (39 produced cancers in themselves). Cases with early changes such as erythema, fissured nails, rough skin, slight telangiectasis or mild pigmentary changes, atrophy of the fat pads, and hangnail were excluded. Out of the 135 cases 91 sustained injury during the fluoroscopy they had employed in the reduction of fractures or the localization of foreign bodies, 6 others from taking films, and 13 admitted that they "did a little *x*-ray work." The authors found that in general the injuries were due either to a lack of proper equipment or to deficient knowledge; possibly, in some cases, they were the result of inexperience or carelessness. The use of the *x*-ray screen in the reduction of fractures was strongly condemned unless the operator carefully measured the dose he received or was under the direct supervision of an experienced radiologist, or unless he used the recommended protective devices.

All this harm is unnecessary, for with knowledge and intelligent appreciation of the dangers involved the risks may be reduced to such proportions as to be negligible and quite justifiable if fluoroscopic control leads to better surgical results.

In response to a request from the surgical staff of the Accident Service in the Radcliffe Infirmary for advice on