BRITISH MEDICAL JOURNAL

LONDON SATURDAY NOVEMBER 28 1959

THE RELIABILITY OF SOME ADRENAL FUNCTION TESTS

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Ever since the hormone-producing role of the adrenal cortex became clearly recognized attempts have been made to obtain, by chemical means, measures of its varying activity under different conditions and in different diseases. The chemical tests developed have in the main attempted to estimate the quantity of adrenocortical metabolites appearing in the urine, though more recently it has become possible to measure directly the concentration of adrenal hormone in the plasma. It has not been possible to measure the total mass of adrenal metabolites in urine because the nature of more than half of these has been, and indeed still is, quite unknown. The only course, therefore, has been to estimate certain types of compounds which represent one group of the metabolites and to deduce the behaviour of the adrenal cortex from the results of such estimates.

Two difficulties were encountered in this approach. First, the complex composition of urine rendered difficult the separation of the chosen group of adrenal metabolites from a wide variety of contaminating substances. Secondly, the extent to which the chemical estimates varied with the true activity of the adrenal cortex was completely unknown, though indirect deductions could sometimes be drawn. Because of these fundamental difficulties the only satisfactory or possible way in which the validity of a test could be assessed was by comparing the chemical results obtained with the results of careful clinical impression. To use such an arbiter of the validity of a test is fraught with danger, for the clinical diagnosis is often limited in accuracy and the essential purpose of the test is to improve this accuracy. The chemical assay gives a quantitative measure, and this the clinical assessment is rarely able to do. Because of lack of other criteria of validity it became usual to regard any test as justified if it gave low figures in Addison's disease and figures well above the normal range in conditions of hyperadrenalism such as Cushing's syndrome or after corticotrophin stimulation. By such relatively crude criteria were most of the earlier tests of adrenal actively justified.

With the great progress which has taken place during the past 10 years in the chemistry and nature of these adrenal hormones and their metabolites, and in their methods of estimation, such crude criteria of validity are no longer sufficient, and a more critical appraisal may justifiably be expected.

Much additional information about these tests can be obtained by deliberately altering the intensity of the adrenal cortical activity and noting the extent to which the various measures follow the changes induced. Thus stimulation of the gland is readily and rapidly achieved with corticotrophin, and inhibition of the gland is effected with equal facility by the administration of suitable synthetic steroids of the types introduced for modern adrenal steroid therapy.

The ordinary techniques of adrenal analysis now usually employed are the urinary 17-ketosteroids and the more recently introduced 17-ketogenic steroids of Norymberski, Stubbs, and West (1953). But other methods are also available, though their clinical use has so far been very inadequately explored. Since one of the major products of the adrenal cortex is cortisol it is logical to attempt to estimate this in plasma or in urine.

The usefulness of estimations of the plasma cortisol has been well explored (Bayliss, 1955), but the results are handicapped by the fact that quite wide natural fluctuations occur and there is a considerable diurnal rhythm. The results are of clinical value in detecting hyperadrenalism, either natural as in Cushing's disease or induced as after corticotrophin stimulation, but they are not so satisfactory for detecting hypoadrenal states because even in normal subjects the plasma cortisol may sink to a low level comparable to that found in Addison's disease.

In contrast to the work done on plasma cortisol levels, very little investigation has been made on the clinical value of urinary cortisol assays. The amount of cortisol appearing in urine is small; it is of the same order as the concentration in blood. But since much larger samples of urine are available, the estimation of urinary cortisol with an accuracy sufficient for clinical purposes is not a difficult procedure. A method for this purpose has been described by Cope and Hurlock (1954) which has an accuracy of about $\pm 20\%$, though Vermeulen (1957) has found he can achieve an accuracy of $\pm 15\%$ with the method.

The estimation of urinary cortisol can, of course, scarcely be justified unless the clinical value to be gained is commensurate with the analytical effort involved.

Another measure which also offers theoretical possibilities is the determination of the amount in the urine of the main cortisol metabolites—tetrahydrocortisone and tetrahydrocortisol. The estimation of these is now a feasible clinical proposition, though the analysis is rather more difficult and takes longer than does the urinary cortisol because a preliminary enzyme

hydrolysis is needed. Because they call for greater technical skill than is ordinarily required for the more routine chemical pathology determinations such analyses could be justified only if they provided information not readily to be obtained by more simple means.

We have explored the relative value of these and some other tests under a variety of clinical circumstances in an effort to determine whether they offer advantages to the clinician.

Adrenal Tests in Hyperadrenalism

One of the best ways to compare the relative clinical value of such tests is to observe the extent to which various measures diverge from the mean normal figure under abnormal clinical conditions.

This has been done in a consecutive series of 12 cases of clinically established Cushing's syndrome. In Fig. 1 are shown the mean results obtained in this series. The biggest divergence from the normal mean is seen to occur with the urinary cortisol, which rises to an average of eight times the normal value, a rise which may be compared with that for the 17-ketogenic steroids, which is on average four times the normal mean. The figures for 17-ketosteroids express the well-known fact that this group of steroids is not significantly raised in Cushing's syndrome, a fact which shows that little relation is to be expected between actual cortisol production and the 17-ketosteroid output. A mean increase for 17-ketosteroids to only 1.4 times the normal mean can scarcely be regarded as a significant rise. It is of interest, too, that the increase in the excretion of the major metabolites, tetrahydrocortisone and tetrahydrocortisol, is also relatively small, suggesting that these indices of adrenocortical activity are comparatively insensitive ones for recording increased adrenal activity.

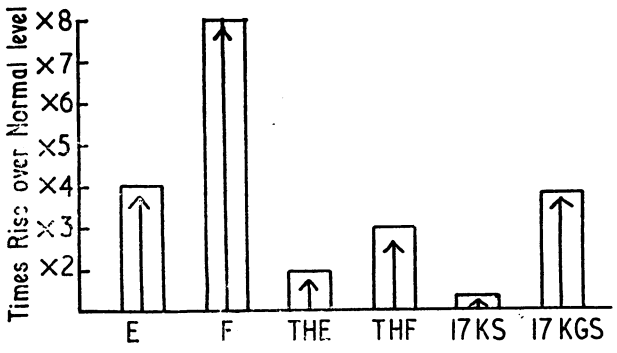

FIG. 1.—Changes in urinary excretion of various steroids in Cushing's syndrome. E=Cortisone. F=Cortisol. THE=Tetrahydrocortisone. THF=Tetrahydrocortisol. 17KS=17-Ketosteroids. 17KGS=17-Ketogenic steroids. Mean of 12 cases.

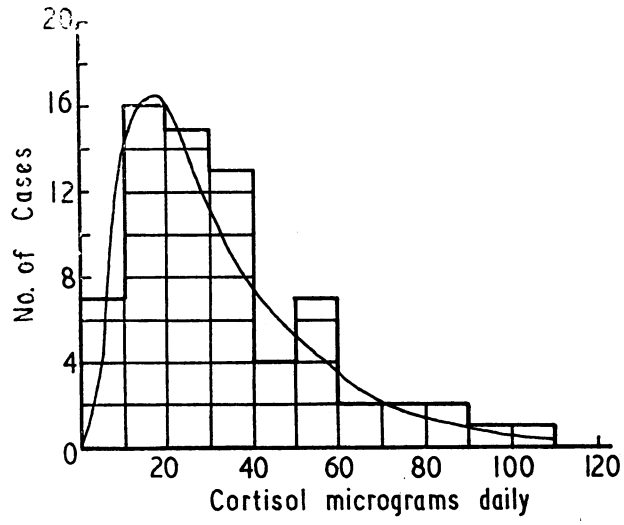

FIG. 2.—Range of urinary cortisol excretion (70 convalescent non-endocrine cases).

Figures such as these are, however, significant only when considered in relation to the normal scatter.

The normal scatter for urinary cortisol concentration is shown in Fig. 2. This distribution is not appreciably affected by ordinary non-endocrine medical disorders. It will be noted that the range is from a small trace up to about 100 μg. a day. The mean for the group is 43 μg. daily. From this curve it is clear that low concentrations of urinary cortisol do not necessarily indicate hypoadrenalism and that therefore the urinary cortisol cannot usefully be employed to detect hypoadrenalism. An excretion of detectable amounts, 40 μg. or more, of cortisol is irrefutable evidence that cortisol production is taking place in that individual provided there is no exogenous source.

We have seen that the mean urinary cortisol in Cushing's syndrome is eight times the normal mean or about 320 μg. daily. In Fig. 3 the range of values encountered in this series of clinically diagnosed cases is shown to have only a small overlap with the normal range. In contrast to this are shown the ranges for ketogenic steroids in normals and the ranges found in small series of cases of Cushing's syndrome derived from three papers taken from the literature. It will be seen that the overlap between normal and abnormal is very much greater in the case of the 17-ketogenic steroids than it is with the urinary cortisol excretion.

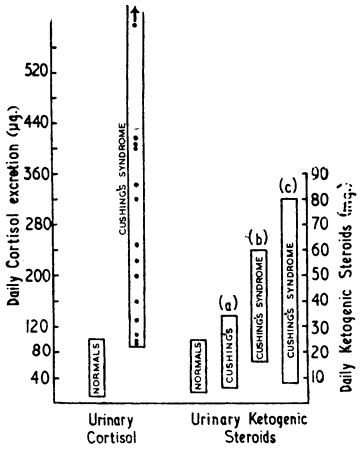

FIG. 3.—Comparison of urinary cortisol and urinary ketogenic steroids in Cushing's syndrome. (*a*) Levell, Mitchell, Paine, and Jordan (1957). (*b*) Moxham and Nabarro (1956). (*c*) Breuer and Nocke (1957).

Essentially similar results are obtained when these tests are compared in the adrenal hyperactivity produced by corticotrophin.

Thus it may be said that estimation of the urinary cortisol is at least twice as sensitive in detecting the hyperadrenalism of Cushing's syndrome as is the 17-ketogenic steroid assay, which is its nearest competitor.

Why this should be so cannot as yet be explained with certainty. But there seems a strong probability that it can be related to the peculiar protein binding that cortisol undergoes in plasma. When plasma cortisol levels are in the normal or low normal range, 90 to 95% of the total is loosely bound to protein. At a concentration of 10 μg. per 100 ml., therefore, only 0.5 to 1 μg. will be free (Daughaday, 1958). If a five-times

rise in plasma cortisol concentration occurs as a result of enhanced adrenocortical activity, then only 75% is bound, so that 12.5 mg. will remain unbound and easily filterable. Thus a five-times rise in concentration can apparently lead readily to a 12 to 25 times rise in filterable cortisol.

Adrenal Tests During Adrenal Inhibition

When adrenal steroids are administered to the human subject suppression of adrenocortical activity rapidly ensues and cortisol production falls rapidly to minimal levels.

If the original adrenal activity before the steroid dose was great enough to lead to an adequate urinary cortisol output, then this inhibition can readily be measured or detected by following the urinary cortisol concentrations daily. This is, of course, only possible if the administered steroid is not either cortisone or cortisol, for both these will be absorbed into the blood-stream as cortisol and will in part appear as such in the urine. Their appearance will naturally mask the changes which are occurring in endogenous cortisol production. But if the administered steroid is one of the modern synthetic ones—prednisone, 9α-fluorocortisol, triamcinolone, etc. the appearance of these in the urine will not interfere appreciably with the estimation of urinary cortisol and the resultant adrenal suppression can therefore be easily followed by measuring the urinary cortisol daily.

It is instructive to measure such an adrenal suppression with the various adrenal tests under consideration. The mean changes which occurred in a group of six cases of Cushing's syndrome are shown in Fig. 4. From this it is apparent that urinary cortisol drops more promptly and more completely than any of the other measures. The tetrahydro metabolites drop rather more slowly, but it will be seen that both 17-ketosteroids and 17 ketogenic steroids fall much more sluggishly and that during the six days of observation neither was reduced by more than 50% of its starting value. It is clear, therefore, that urinary cortisol is very much more sensitive than other indices in general use for detection of adrenal inhibition. This fact has some clinical importance, for the possible value of adrenal-inhibition tests has recently been explored as an indicator of corticotrophin-dependent hyperactivity. It is scarcely justifiable to assess the value of such a test by using methods of analysis which are insensitive. That a mild adrenal inhibition may be missed completely by the use of such

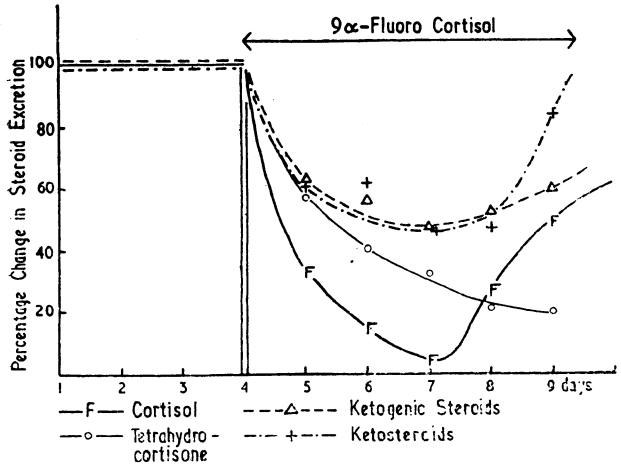

FIG. 4.—Urinary steroids as indices of adrenal inhibition. Mean of six cases.

methods was shown by Cope and Harrison (1955), who reported a case in which adrenal inhibition was revealed by urinary cortisol fall, but in which no change was observed in the urinary 17-ketogenic steroids.

This high sensitivity of the urinary cortisol as an index of reduction of adrenal activity probably has its explanation also in protein-binding, for as a result of this binding the amount of free diffusible cortisol in plasma will fall much more rapidly than does the total plasma cortisol concentration.

Why the 17-ketogenic steroids should drop so slowly and imperfectly when the adrenal cortex is inhibited by steroid therapy is not entirely clear. A major factor is likely to be the need to eliminate all these metabolites by renal excretion in contrast to the cortisol, which has a very short half-life in the blood-stream and disappears rapidly by decomposition. Another factor no doubt will be the fact that if the administered inhibiting steroid appears in the urine it may be estimated as 17-ketogenic steroid, thus in part disguising the true fall.

Function Tests in Adrenal Hypofunction

From the distribution curve of normal, or non-endocrine, urinary cortisol values (Fig. 2) it is apparent that a concentration near the lower limit of detection of the method—that is, below 15 μg. a day—may be encountered in normal subjects. It follows, therefore, that a low urinary cortisol output is not evidence of the presence of a pathological degree of hypoadrenalism. But for obtaining such evidence the urinary output of tetrahydrocortisone, or of tetrahydrocortisol, or of the two combined, is a much more valuable measure. In this respect its value stands in sharp contrast to its failure to indicate well an increasing adrenal activity.

The situation may perhaps best be explained by an analogy. The intensity of burning of a fire is generally best measured by the heat produced, but to determine whether the fire has been extinguished it is often preferable to observe whether or not smoke is still being produced. In the adrenal the smoke is represented by the metabolites, the tetrahydro compounds.

The distribution curve for tetrahydrocortisone or tetrahydrocortisol excretion under ordinary circumstances is a broad one. For the former steroid it ranges from about 1,000 μg. daily to 4,000 μg., and occasionally more.

The great advantage of this measurement over other measures, such as the 17-ketosteroids or the 17 ketogenic steroids, is that the determination of tetrahydrocortisone is a specific one which is not subject to appreciable interference by non-specific chromogens or, as a rule, by other interfering steroids. As a result the estimation can be carried out with an accuracy quite sufficient for clinical purposes even when the tetrahydrocortisone excretion is reduced to one-tenth or less of the minimum value for the normal range. Such sensitivity is scarcely feasible with either 17-ketogenic steroid or 17-ketosteroid assays.

The lowest degrees of adrenal cortisol production are found in hypopituitarism rather than in Addison's disease. For in the latter the factor commonly determining the onset of symptoms is the aldosterone deficiency rather than the cortisol shortage, and the former may be serious before the latter has reached extreme degrees. In both conditions the tetrahydrocortisone excretion is much reduced, often below 250

μg. a day. The mean figures we have observed for a group of 12 cases of hypoadrenalism due to these causes was for hypopituitarism (six cases) 200 μg. and for Addison's disease (six cases) 390 μg. In severe cases of either condition the tetrahydrocortisone output may fall to less than 5% of the normal mean.

But a diminished output of tetrahydrocortisone may be due to impaired hepatic function, with resultant impaired metabolism of a normal quantity of cortisol formed. This is especially likely to occur in advanced hepatic cirrhosis.

Though clinical confusion between hepatic cirrhosis and hypoadrenalism is likely to be a rare problem, it could arise, for instance, in some cases of haemochromatosis. The severer forms of each can, however, usually be distinguished without great difficulty by means of the tetrahydrocortisone assay.

In a group of seven cases of advanced hepatic cirrhosis with severe impairment of liver function, the range of tetrahydrocortisone excretion was found to be from 220 μg. to 1,300 μg. daily, with a mean of 670 μg. The distribution of these cases is shown in Fig. 5, and from this it is apparent that any clinical

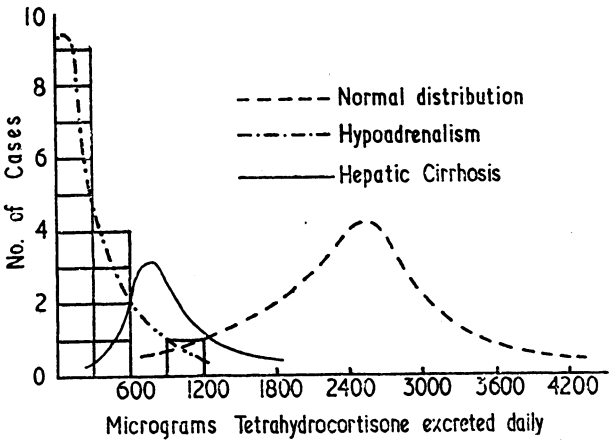

FIG. 5.—Urinary excretion of tetrahydrocortisone in hypoadrenal states and in hepatic cirrhosis.

confusion between hypoadrenalism and severe hepatic cirrhosis could usually be resolved satisfactorily by means of this test.

Illustrative Difficult Cases

But though tetrahydrocortisone excretion provides a valuable method of recognizing hypoadrenalism, useful information may sometimes be obtained in difficult clinical circumstances by the demonstration of cortisol in the urine. While no certain conclusions about adrenal function can be drawn from the finding of only a trace of cortisol in the urine, yet the demonstration of an adequate or generous normal quantity of cortisol in the urine is positive proof that cortisol is being produced in the body in appreciable quantity. This seems to exclude hypopituitarism of any severity, and excludes also severe degrees of Addison's disease, but it does not exclude Addison's disease of moderate degree, in which aldosterone formation may be damaged much more than cortisol production. The recognition of urinary cortisol may be particularly valuable in the difficult clinical case, and has the great advantage that the reducing steroid spot on the toluene/propylene glycol chromatogram at the appropriate point is not subject to contamination or confusion by interfering substances and may be accepted as cortisol with reasonable certainty. In a large series of chromatographic analyses of urine extracts obtained from a wide variety of clinical subjects we have never recognized a reducing contaminant at the cortisol spot. This is not true in our experience of most other reducing steroid spots on the chromatograms of urine extracts.

Two cases may be quoted which illustrate well the value of urinary cortisol estimations.

Case 1.—The patient was a large muscular healthy-looking man aged 45. He had been diagnosed as suffering from Addison's disease in 1938. He joined a Guards Regiment in the last war and served satisfactorily until he was recognized by a medical officer who had treated him for Addison's disease in civil life five years previously. After resultant discharge from the Army he took to playing water-polo for a crack team. He was seen in 1955 because of reduction of exercise tolerance below his previously exceptionally good performance. He had a fine muscular physique, no pigmentation, and normal blood-pressure. Serum sodium and chloride were normal. Water-excretion test gave 94% output in 4 hours. The 17-ketosteroids were 6 mg. Both adrenals were very intensely calcified and 5 cm. in diameter. An intravenous corticotrophin-stimulation test caused no change in function as judged by 17-ketosteroid excretion or urinary or plasma cortisol (4 μg. per 100 ml.).

The diagnostic ambiguity in this patient was in large measure resolved by the demonstration of 20 μg. a day of cortisol in the urine together with 1,600 μg. of tetrahydrocortisone and 380 μg. of tetrahydrocortisol. This provided proof that he was indeed producing good supplies of cortisol. It was later possible to show, by the use of ^{14}C-cortisol, that his daily cortisol production was 19 mg. daily, an amount adequate for most purposes.

Case 2.—A man aged 53 of gipsy origin, was known to be suffering from a carcinoma of the bronchus. He was heavily pigmented, especially in the flexures. There was extensive buccal pigmentation. His blood-pressure was 100/55. 17-Ketosteroid excretion was 1 mg. daily. A water-excretion test gave an output in four hours of only 25% of the dose. After 50 mg. of cortisone acetate this was increased to 41% and after 100 mg. diuresis rose to 93% of the dose. The serum sodium was 122 mEq and chloride 96 mEq. An intravenous corticotrophin-stimulation test produced an ambiguous result. The suspicion was strong that Addison's disease had arisen as a complication due probably to metastatic invasion of the adrenal glands. Chromatography of a simple *p*H 1 extract ($CHCl_3$) of the urine revealed a high normal (103 μg.) output of cortisol, and this practically excluded even mild hypoadrenalism. At subsequent necropsy the adrenal glands showed no metastatic or other involvement and the cortices were mildly hypertrophied.

A similar clinical problem arises not infrequently in advanced tuberculosis not responding to modern antituberculous therapy. In such persons the combination of pigmentation, low blood-pressure, asthenia, low serum sodium, and low serum chloride inevitably raises the question of a complicating Addison's disease due to adrenal involvement by the tuberculous process. The finding of a low 17-ketosteroid output, which is usual in wasting disorders, will enhance the suspicion.

Yet such subjects usually excrete high normal amounts (>60 μg.) of cortisol in the urine, and the demonstration of more than 500 μg. of tetrahydro-

cortisone daily in the urine will afford additional proof that cortisol production is continuing.

Relation of Adrenal Tests to Cortisol Production Rate

It is thus apparent that these various measures of adrenal activity differ greatly in their suitability for use under differing clinical conditions. It is now possible to obtain a useful estimate of the actual daily cortisol production from the human adrenal cortex by making use of radioactive cortisol labelled with ^{14}C. With this it becomes feasible to compare these various tests with the actual daily cortisol production and to determine the extent to which they actually reflect the true production rates of cortisol (Cope and Black, 1958).

In Fig. 6 is plotted the daily cortisol production rate against the daily elimination of cortisol in the urine. It will be seen that the amount appearing in the urine

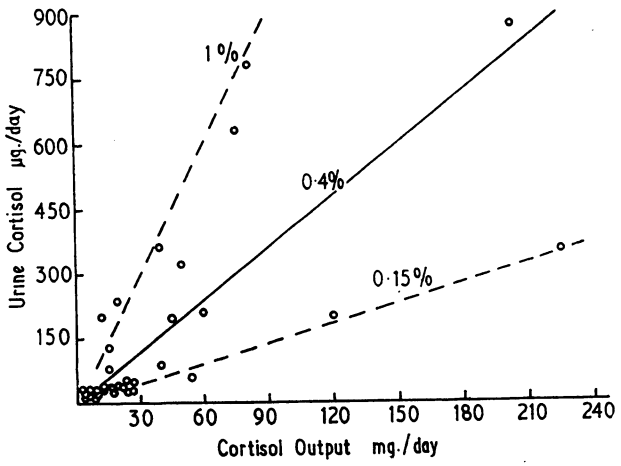

FIG. 6.—Comparison of cortisol production rate with urinary cortisol excretion.

represents from 0.15 to 2% of the actual daily production. The extent of the scatter is such that quantitative conclusions about the absolute rate of cortisol production cannot be drawn from knowledge of the urinary cortisol. Thus a urinary cortisol excretion of 75 µg. may be associated with a cortisol production of 15 to 50 mg. daily, and one of 340 µg. with production rates of from 40 to 225 mg. a day. This lack of correlation is likely to be due far more to individual variations in the percentage of cortisol bound to protein than to any variations in renal function.

A rather better agreement with the production rate of cortisol is seen in the urinary excretion of tetrahydrocortisone or of tetrahydrocortisol. At low and normal levels of activity about 20% of the total cortisol produced appears in the urine in the form of these metabolites. But as the activity of the adrenal increases and cortisol production is raised, the percentage of the total appearing in the urine in the form of the tetrahydrocortisone or tetrahydrocortisol tends to fall until at high productions it may be as low as 5%. To some extent this fall may explain the relative insensitivity of urinary tetrahydrocortisone as an index of raised adrenocortical activity.

The relationship between urinary 17-ketosteroid output measured by the classical routine method and the cortisol production rate is shown in Fig. 7. The lack of any useful correlation is in conformity with clinical impressions and with the well-recognized fact that 17-ketosteroid output is not necessarily raised in Cushing's syndrome. From Fig. 7 it will be seen that a 17-ketosteroid output of 25 mg. may occur with a cortisol production of 10 mg. daily and that an output of 30 mg. occurred in a patient with cortisol production of 225 mg. a day. It is clear that no useful conclusions about the actual daily cortisol production can be drawn from the 17-ketosteroid excretion.

With the 17-ketogenic steroids of Norymberski *et al.* (1953) the relationship is a good deal more encouraging (Fig. 8). It is evident that, though considerable scatter occurs, the points lie about a line which represents an excretion of 50% of the total cortisol production in the form of analysable 17-ketogenic steroids. But the degree of scatter is not appreciably reduced at the lower levels of cortisol production. The normal range of cortisol production is up to about 25 mg. daily, and none of the patients with florid Cushing's syndrome whom we have so far examined have had cortisol production

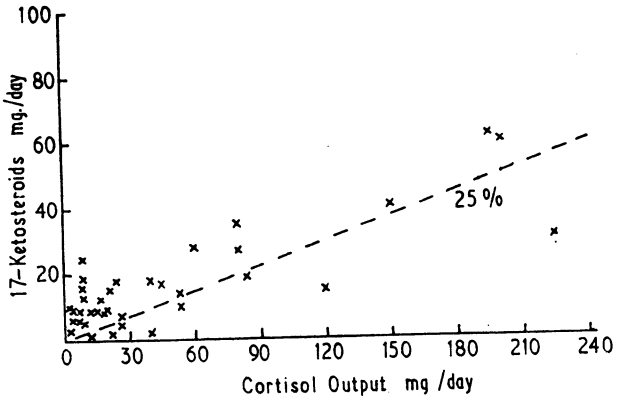

FIG. 7.—Comparison of cortisol production rate with urinary 17-ketosteroid excretion. (Broken line represents 25% of cortisol produced, not the line of best fit.)

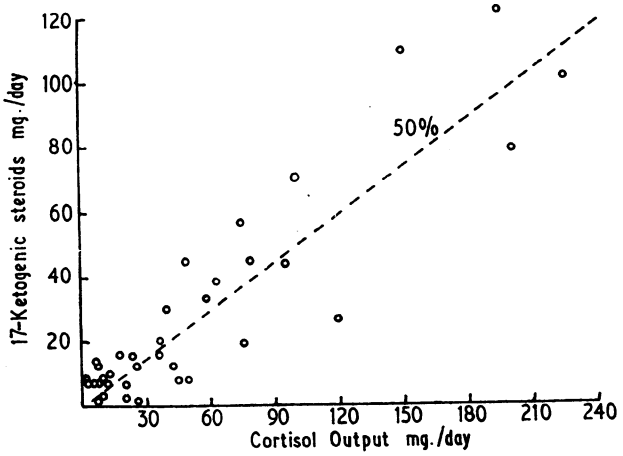

FIG. 8.—Comparison of cortisol production rate with urinary 17-ketogenic steroid excretion. (Broken line represents 50% of cortisol produced.)

rates above 90 mg. daily. In this range, where laboratory guidance for the clinical problem is most needed, it will be seen that there is a relatively poor relation between cortisol production and observed urinary ketogenic steroid excretion. To some extent no doubt this scatter is attributable to experimental errors in carrying out the 17-ketogenic steroid

estimations, for by its nature the 17-ketogenic steroid method is subject to increasing percentage errors at its lower range of values, whereas the isotope method of measuring the cortisol production rate is not subject to such limitations at low outputs.

All our ketogenic steroid estimations were carried out in duplicate, and in many of the instances where an unexpected result was obtained a check was made with the results of an independent routine laboratory analysis. There is little doubt, therefore, that much of the scatter is a real discrepancy between the ketogenic steroid output and the estimated cortisol production. In a few instances the apparent excretion of 17-ketogenic steroids actually exceeds the estimate of the cortisol produced. But all these occur at cortisol production rates below 10 mg. daily and with ketogenic steroids below 15 mg. a day. It is likely in these either that interfering substances have inflated the true 17-ketogenic steroid figure or that small amounts of ketogenic steroids are derived from sources other than cortisol metabolism. But from the relatively small number of comparisons made here and plotted in Fig. 8 the following general conclusions may be made. (1) A 17-ketogenic steroid output in excess of 25 mg. indicates a cortisol output raised well above the normal upper limit and generally in excess of 35 mg. daily. (2) The higher the 17-ketogenic steroid output the more this tends to approach 50% of the actual cortisol production. (3) With 17-ketogenic steroid outputs in the normal or low range—that is, below about 20 mg. a day—the relation to actual cortisol production rate is so indefinite, and the scatter is so wide, that no conclusions about the cortisol production rate can be drawn save that it is probably not greatly raised above normal. But it may be observed that in one instance a cortisol production of 75 mg. daily was associated with a 17-ketogenic steroid output in the urine of only 20 mg.

General Conclusions

It is thus apparent that the 17-ketogenic steroid determination has its limitations in precisely the range of borderline degrees of hyperfunction of the adrenal where its help is most needed. But of all the tests which have been considered here the urinary 17-ketogenic steroid output correlates better than any other with the actual cortisol production as estimated by the isotope technique. Maybe with the borohydride method results will be still better (Appleby, Gibson, Norymberski, and Stubbs, 1955).

The other tests, too, have their shortcomings. The urinary cortisol, most sensitive in the detection of increased adrenal activity or of inhibition of hyperactivity, is quite unsatisfactory for the detection of hypofunction. The urinary 17-ketosteroid output bears no relation to actual cortisol production, and the tetrahydrocortisone excretion, very valuable for providing evidence of gross hypoadrenalism, is not a good index of increased adrenal activity.

It follows, therefore, that ideally the test used should be adapted to the problem at hand. For routine clinical purposes the 17-ketogenic steroid estimation is probably the best general test, but its limitations should be recognized. For research purposes it may not be sensitive enough to detect the changes which are being sought, and more specific steroid analyses may then be necessary. The use of radioactive cortisol offers the best ultimate prospects of solving this problem, but at present its great expense and the shortage of supplies preclude its use except for special research purposes; but in the absence of this the relatively simple urinary cortisol assay can often produce evidence of great clinical value in the ambiguous case.

Summary

Adrenal-function tests vary widely in their sensitivity to different conditions, and therefore in their suitability for various purposes.

Urinary cortisol excretion is more than twice as sensitive as ketogenic steroid excretion for demonstration of adrenal hyperactivity and for detecting inhibition of such hyperactivity.

Urinary cortisol excretion is unsuitable for detecting adrenal hypofunction, but this is sensitively revealed by measuring the main cortisol metabolites—tetrahydrocortisol and tetrahydrocortisone — in the urine. Excretions as low as 5% of normal can still be measured with sufficient accuracy..

The excretion of various steroids and steroid groups has been compared with the daily cortisol production rate measured by isotopic means.

There is no relation between 17-ketosteroid excretion and the daily cortisol production.

There is a poor correlation between daily cortisol production and urinary cortisol excretion.

At high rates of adrenal activity the urinary excretion of 17-ketogenic steroids is approximately half the daily cortisol production.

In low, normal, or moderately raised adrenal activity the correlation between cortisol production rate and 17-ketogenic steroid excretion is poor, and no conclusion is justified about the former from the magnitude of the latter.

Adrenal function tests need to be carefully selected for their suitability for the purpose intended.

Our thanks are due to the Medical Research Council for a grant to one of us (E.G.B.), and to the United States National Institute of Health, Division of Research Grants, for a generous gift of ^{14}C-labelled cortisol. We are grateful to Miss Sylvia Hughes for valued technical assistance.

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In a foreword to the Annual Report of the Royal National Institute for the Blind for the year ended March 31, 1959, Mr. GODFREY ROBINSON, Chairman of the Institute's Executive Committee, draws attention to the fact that the R.N.I.B. has, in one year, spent over £1m. on services to the blind, produced nearly 600,000 Braille volumes, periodicals, and leaflets, and succeeded in placing in industry and commerce nearly one trained blind man or woman for each working day. The report says that about 12,000 new names a year are added to the register of blind persons in this country.