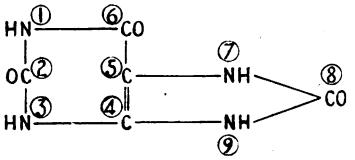
Another interesting story, and one which is only gradually being unfolded, concerns the synthesis of uric acid in the body. This fairly complex compound can be represented by the following structure, with the carbon and nitrogen atoms numbered for reference purposes.



In this case the investigators had to start with relatively few clues, and much of their early work involved the following of hunches. Fortunately, many of the guesses were inspired, and during the past three or four years much has been learned about the way in which uric acid can be built up in man and other animals. In this synthesis, as with those of creatine and the porphyrins, glycine occupies a key position, and it can serve as a source of the C—C—N structure occupying the positions 4, 5, and 7 in the uric-acid molecule. The rest of the picture is not yet complete, but it appears that CO_2 may supply the carbon atom in position 6, and that the carboxyl group of acetate (or some related compound) can furnish the other carbon atoms; the nitrogen atoms in positions 1, 3, and 9 appear to come from the degradation of amino-acids in general. This information about purine synthesis in the animal body should materially advance our knowledge about the metabolism of the biologically important nucleic acids.

Concluding Remarks

The use of isotopic tracers has led to the discarding of the old theory of a dual type of metabolism in the cells of the animal body; an *exogenous* metabolism of energy-bearing food material brought to the cell, and an entirely independent *endogenous* metabolism involving breakdown and repair of tissue cells. We now recognize that in the animal body there is a dynamic equilibrium, with food substances and cell components all forming what has been termed a "metabolic pool." All the tissues are supplied with this pool mixture of relatively simple compounds such as acetate, pyruvate, etc., and these compounds are used for combustion or tissue-building irrespective of their origin. This new concept, for which we are particularly indebted to Schoenheimer and Rittenberg, may be the isotopic tracer technique's finest achievement up to date.

We have used these new tools in my department for the past twelve years, and, as you will have gathered, I am not ashamed to admit my optimism about the future as regards the use of isotopes in medical research. Furthermore, we cannot exclude the possibility, though as yet it is no more than a possibility, that some investigator may one day find a satisfactory general method of using radio-isotopes to get specific irradiation of malignant tissues without damaging normal tissues. Fifty or even twenty-five years hence, the biochemist, the physicist, the clinician, and above all the patient may be able to assess in true perspective the relative gains and losses resulting from the developments which, incidentally or indirectly, produced the atomic bomb. When the balance sheet is drawn up it may well be that the gains will easily exceed the losses.

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SOME OBSERVATIONS ON ENDOGENOUS CORTISONE EXCRETION IN MAN

BY

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Recently (Cope, 1951) a preliminary account was published of a method capable of detecting the presence of cortisone-like activity in urine extracts from human subjects. The method depends on the measurement of the reduction in the number of circulating eosinophil cells in the blood of adrenalectomized mice after the injection of suitably prepared urine extracts. As cortisone and compound F are the only substances at present known which reduce the circulating eosinophil count of adrenalectomized animals, and as both these compounds have been demonstrated in extracts of human urine prepared in a similar manner to our own (Schneider, 1950; Zaffaroni, Burton, and Keutmann, 1950), it is assumed that the test is specific for the presence of these two substances.

The qualitative test can be made roughly quantitative by comparing the eosinophil drop produced by graded doses of cortisone acetate with that produced by the urine extracts. For this comparison to be valid it is essential that both be injected in the same type and volume of solvent, since the magnitude of the eosinophil drop produced by a given amount of cortisone acetate varies considerably with the conditions of the injection. This variation is presumably related to the differing rates of absorption of the compound from the injection site. Using such a quantitative test for small amounts of cortisone, it is possible to make observations on the

behaviour of endogenous cortisone under conditions of varying adrenal activity in man. The main interest of the urinary cortisone excretion lies in the presumption that changes in this excretion reflect similar changes in the blood concentration of the hormone. The amounts present in the circulating blood, with the exception of the adrenal vein, are too small to be detected with certainty, and recourse must therefore be made to such an indirect method for observing changes in adrenal activity. Some observations on the use of this biological method are presented in this paper.

For convenience the activity of urine extracts is referred to in terms of cortisone although compound F is probably also present. The relative proportions of these two compounds are, however, as yet unknown, and here the term "cortisone output" is used to denote the combined excretion of the two substances.

Methods

Suitable extracts of complete 24-hour collections of urine were made by the method previously described (Cope, 1951). Creatinine output was measured in all cases to provide some check on the completeness of collection of urine. In all cases hydrolysis was effected, before extraction with chloroform, by acidifying the urine to *p*H 1 with sulphuric acid and allowing it to stand at room temperature for 18 to 24 hours. Final extracts were stored dry in small glass-stoppered phials in the cold until required for assay. The period of such storage was usually about a week, but was occasionally longer. Immediately before injection into the adrenalectomized mice the extracts were dissolved in a small quantity of propylene glycol, which was then diluted with normal saline to a strength of 20%. The amount of propylene glycol used was such that the dose of extract to be injected into each mouse was contained in 0.5 ml. of the final 20% solution.

The sensitivity of the response varies considerably with the volume of the injection and also with the strain of mouse used. Under the conditions we have employed the optimum response is obtained with the equivalent of 50 to 80 μg. of cortisone per mouse, the eosinophil fall with this dose being between 50 and 80%. The size of the urinary aliquots for injection has therefore been so designed that an amount within this range might be expected in each dose. All injections have been made subcutaneously and no toxic symptoms have been noted.

Eosinophil counts were made on each mouse before injection and at four and six hours after. The phloxine-propylene glycol stain of Randolph (1944) was found the most convenient for revealing the eosinophils. No difficulty is encountered in taking sufficient blood from a tail vein if the room is kept warm enough. Maximum eosinophil cell depression may occur at four or six hours, and the lower of these two counts is used to calculate the percentage fall below the starting level.

Results

The Dose Response Curve

A typical dose response curve is shown in the continuous line in Fig. 1. In this figure the black dots represent the responses of individual mice to the injected cortisone acetate. Considerable variation in response occurs with the smaller doses, but this variability becomes less with doses of 50 μg. and over. The greatest constancy of result is found with doses of 50 to 80 μg. of cortisone per mouse.

Accuracy of assay will depend on the number of mice used for each comparison. In these preliminary studies, where greater accuracy was not sought, each unknown extract was injected into three mice and the mean percentage eosinophil drop in the three mice was calculated and used to read off the approximate cortisone equivalent from the calibration curve.

The response curve shown in Fig. 1 cannot be used without confirmation in other laboratories. The interrupted line to the left represents the response when

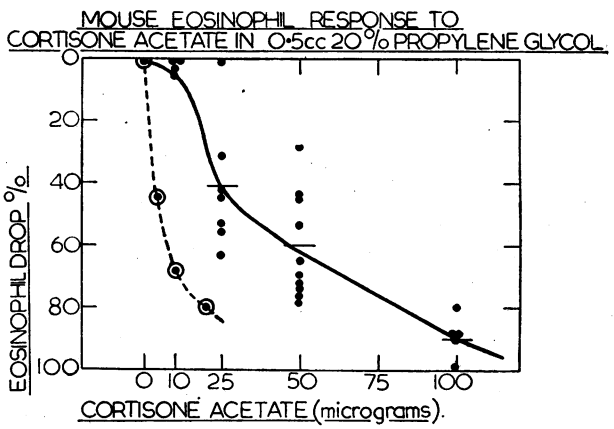

FIG. 1.—Dose response curve for cortisone acetate.

cortisone acetate is injected in a smaller volume in saline suspension into another strain of mice. Under these conditions the mice were nearly five times more sensitive. Nevertheless the white mice we have used were chosen in spite of their relative insensitivity because they were more readily available. Similarly, the constant but relatively large volume used for the injections allowed the uniform handling of urine extracts which varied in bulk and in physical properties.

Normal Cortisone Excretion

For the normal group we have selected patients whose adrenal conditions could be regarded as basal. Only those who had not been subjected to a recognizable acute or chronic stress during the preceding three weeks

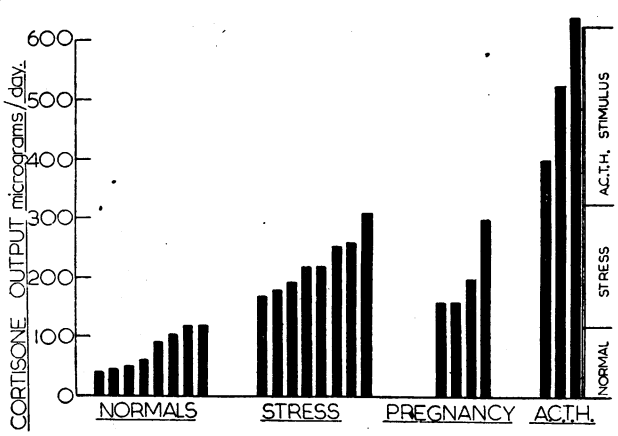

FIG. 2.—Urinary excretion of endogenous cortisone in quiescent normals, stress due to medical disease, late normal pregnancy, and after A.C.T.H. therapy.

were considered eligible, and those chosen consisted of patients in the last week of a routine course of bed rest and diet for duodenal ulcer and certain neurological cases admitted for investigation. Eight such cases, all males, have been studied, and these showed cortisone excretions ranging between 40 and 120 μg. a day (Fig. 2). These normal figures are similar to the normal range found by Venning, Kazmin, and Bell (1946) when using their glycogen-storage method.

Cortisone Excretion in Medical Stress

It is now generally recognized that the adrenal cortex is rapidly stimulated to increased activity by a wide variety of noxious stimuli. To indicate the great variety of such adrenal stimuli to be found in general medical disorders we have deliberately chosen a heterogeneous series of disease states. In all of these the output of cortisone in the urine was raised well above the resting level, and indeed no overlap occurred between the two groups (Fig. 2).

The actual output of cortisone estimated in these cases of medical stress ranged from 180 to 320 μg. a day. The following are brief details of the individual cases included in this stress series. The cortisone excreted each day is indicated in parentheses.

Case 1.—Status asthmaticus. Severe. (260 μg.)

Case 2.—Coronary infarct three weeks previously. Mild. No present symptoms, but still high E.S.R. (195 μg.)

Case 3.—Bronchopneumonia. Mild. Febrile. (220 μg.)

Case 4.—Obstructive jaundice; carcinoma head of pancreas. Serum bilirubin 18 mg. per 100 ml. (170 μg.)

Case 5.—Pneumococcal meningitis. Male aged 56. Three days before death. (220 μg.)

Case 6.—Bronchopneumonia. Moderate. (255 μg.)

Case 7.—Congestive cardiac failure with dyspnoea, mild cyanosis, and slight oedema. (180 μg.)

Case 8.—Diabetic ketosis. Drowsy but not comatose. (320 μg.)

Case 9.—Subacute peritonitis. (250 μg.)

In these cases the increase in cortisone output was not well related to the clinical estimate of the severity of the medical stress. It is of interest that the lowest cortisone excretion of the group was in the case of severe obstructive jaundice. This was surprising in view of Hench's discovery of the beneficial effects of jaundice on the course of rheumatoid arthritis.

Cortisone Excretion in Late Pregnancy

In the eighth month of normal pregnancy the cortisone output in the urine is also raised, and the range found in a series of seven cases of normal pregnancy was the same as that found in cases of medical stress—from 170 to 300 μg. a day (Fig. 2). This increase in excretion of adrenal cortical hormones has previously been reported by Venning (1945), who obtained values similar to our own although she used a different method of bio-assay.

Effects of A.C.T.H. on Cortisone Output

An increase in output of cortisone considerably greater than that usually encountered in medical stress can be produced by five or six days' treatment with

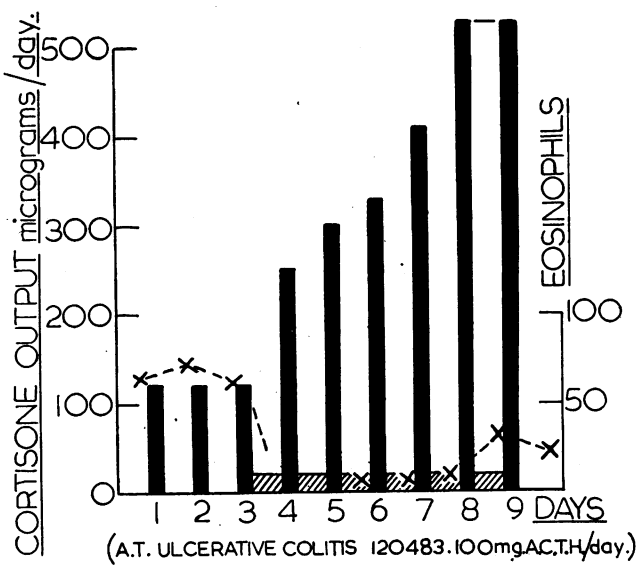

FIG. 3.—Effect of A.C.T.H., 100 mg. daily from the third to the ninth day on cortisone output (black columns) and eosinophil count (crosses) in a patient (A.T.) with ulcerative colitis.

A.C.T.H. The right-hand columns in Fig. 2 indicate the levels achieved after six days' A.C.T.H. therapy in three typical examples. That the rise is progressive over several days is shown by Case A.T. (Fig. 3), a male suffering from mild ulcerative colitis who received 100 mg. of A.C.T.H. daily for six days. Individual variations in adrenal response to A.C.T.H. have, however, been suspected on clinical grounds, and they do indeed seem to occur. Thus Case P. (Fig. 4), who was suffering from scleroderma, was given the same dose of A.C.T.H. for six days; but the response was relatively poor, the cortisone output not rising above 250 μg. daily. In this patient A.C.T.H. therapy was originally delayed because of a mild attack of pneumonia, which responded to antibiotics. At the height of this infection cortisone excretion was raised above normal resting levels by the stress, and the fall to normal output during convalescence is well shown in Fig. 4. In this case the administration of A.C.T.H. for six days produced a scarcely greater cortisone output than had the stress of the pneumonia. This relative insensitivity

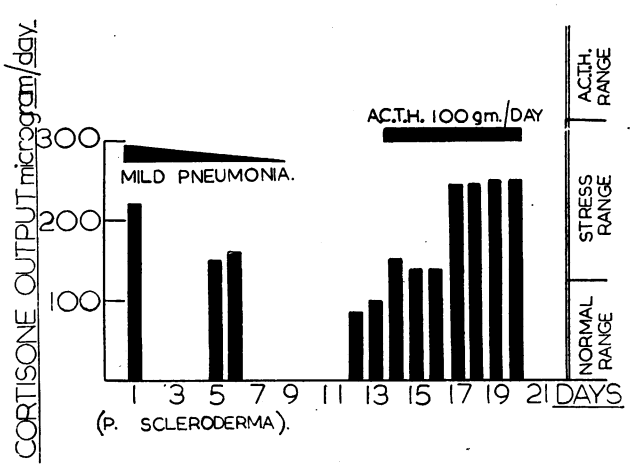

FIG. 4.—Relatively poor response to A.C.T.H. in a case of scleroderma.

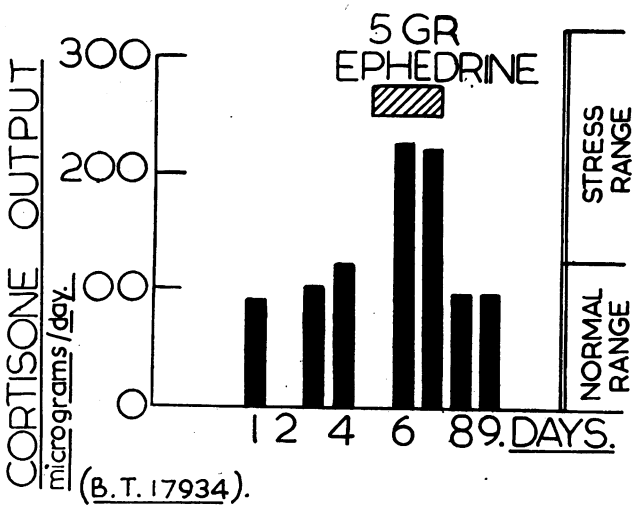

FIG. 5.—Effect of oral ephedrine on endogenous cortisone output.

of the adrenal cortex may have been due to the preceding infection, but such a conclusion should not be drawn from a single case.

Effect of Ephedrine

It is now well recognized, from experimental evidence in animals and from indirect evidence in man, that adrenaline acts as a potent stimulant to adrenal cortical function. Whether this is a specific effect or whether adrenaline merely represents another type of noxious stimulus or stress is at present undecided. Elsewhere (Cope and Bain, 1951) we have shown that continued adrenaline injection provokes an increase in the chemically determined neutral reducing steroids in the urine. Ephedrine acts similarly as an adrenal cortical stimulant. It can be used as an alternative to adrenaline in the eosinophil depression test in man (Abelson and Moyes, 1950). That it can also increase the actual output of cortisone in the urine is shown in the chart of B.T. (Fig. 5). This patient, who complained of anxiety type symptoms, was given 1 gr. (65 mg.) of ephedrine orally three times a day for five doses, after which he complained of symptoms suggesting overdosage, and the drug had to be stopped. A doubling of the cortisone output was observed during the period of administration, and there was a prompt return to normal on withdrawal of the ephedrine.

In view of this stimulant action of ephedrine it was of interest to determine whether this drug could be used to maintain in hyperactive state an adrenal cortex which had previously been stimulated to hyperactivity by A.C.T.H. Fig. 6 shows the result of such an experiment. The patient (N.S.) was suffering from fairly severe ulcerative colitis and received 100 mg. of A.C.T.H. daily for six days. There was a big increase in the cortisone output, which on the sixth day was estimated to be more than 650 μg.—a figure more than ten times the initial level of output. A.C.T.H. was stopped at this point, and ephedrine, ½ gr. (32 mg.) three times a day, was continued by mouth for the next 12 days. At the end of this time a fresh determination showed that cortisone output had again fallen to normal levels. Ephedrine therefore failed to maintain the intense adrenal stimulation induced by A.C.T.H. Three weeks later a non-specific stress arose when peritonitis developed, and this provoked an increase in cortisone output greater than ephedrine had achieved.

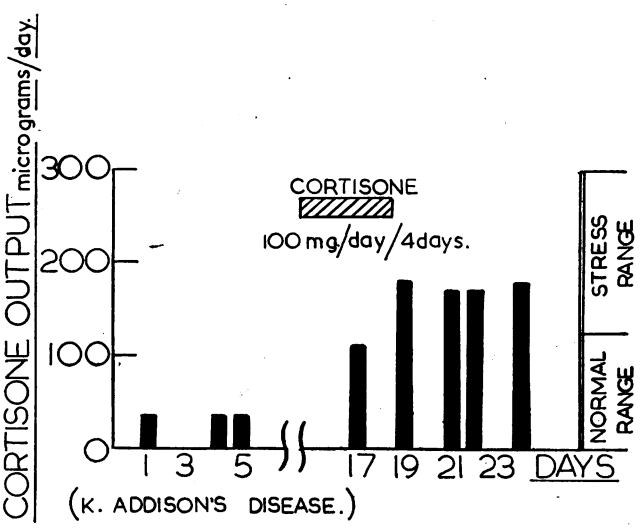

FIG. 7.—Effect of cortisone acetate injection on excretion of urinary cortisone.

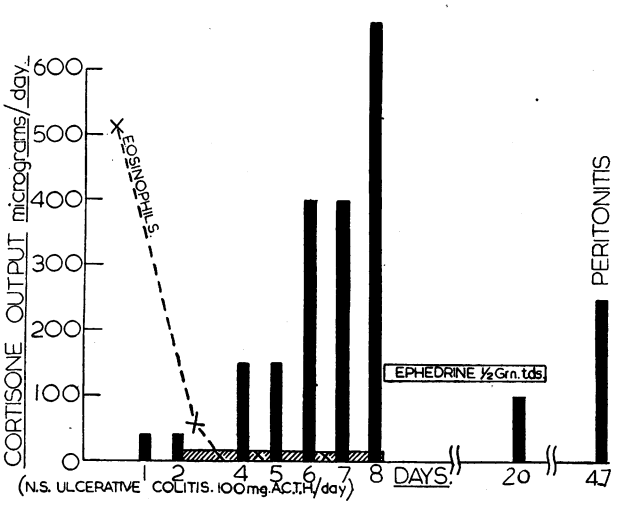

FIG. 6.—Good response to A.C.T.H. and failure of ephedrine to maintain the raised cortisone output.

Effects of Cortisone Therapy

With the mouse bio-assay method a rise in cortisone output in the urine can readily be detected in the 24 hours following a single intramuscular injection of cortisone acetate (Fig. 7). The excretion is very small compared with the dose given and does not represent more than 0.2%. The accompanying Table shows some typical

Table Showing Some Typical Rises in Cortisone Output in Cases of Adrenal Insufficiency after Cortisone Therapy

Case	Cortisone Output (μg./daily)			
	Output Before Treatment	Dose of Injected Cortisone (mg.)	Output After Last Injection	
			Days After	Amount
F. Hypopituitarism	<30	200 I.M.	1	180
			7	125
C. Hypopituitarism	50	50 (oral)	1	190
H. Addison's disease	70	50 × 10 I.M.	1	290
K. Addison's disease	<30	100 × 4 I.M.	1	180
			6	180

rises in cortisone output observed after cortisone therapy in varying dosage to persons with adrenal insufficiency. Three main points emerge from these figures. First, the rise in cortisone output after average therapeutic doses is in general less than occurs after similar therapeutic doses of A.C.T.H. This may not always be so, however, for all the cases included in this table were suffering from adrenal insufficiency. It is possible that higher outputs may be found when cortisone therapy is added to the production of a normal adrenal cortex in normal persons. Secondly, in two instances the rise in cortisone output persisted with little diminution for six or seven days after the last injection. This effect is presumably to be attributed to the slow absorption of this relatively insoluble substance from the depot produced at the injection sites. Thirdly, a prompt rise in cortisone excretion was observed in one case in the 24 hours following a small oral dose of cortisone acetate, thus providing objective confirmation of the clinical impression that cortisone is well absorbed when given by mouth.

Cortisone Output in Adrenal Insufficiency

A lowered output of cortisone in the urine is to be expected in Addison's disease and in hypopituitarism, and is usually but not invariably found. Seven cases of Addison's disease have been investigated. Cortisone could not be detected in the urine of three. In three other cases traces of activity were found, estimated as not exceeding 40 μg. daily, and in the seventh case a normal output of 70 μg. a day was assayed. Four cases of panhypopituitarism of varying severity have also been studied. In the urine of three of these no cortisone activity could be detected, but the fourth case excreted about 50 μg. a day.

Medical Stress in Adrenal Insufficiency

In one case of hypopituitarism the opportunity arose of observing cortisone output during a period of stress. The patient was suffering from the typical syndrome of post-partum pituitary necrosis. She was admitted to hospital in deep hypoglycaemic coma. In the 48 hours following recovery of consciousness the cortisone output did not exceed 40 μg. daily—a figure less than 25% of what might be expected after a comparable stress in a person with normally reacting adrenals. During a quiescent period ten days later no cortisone activity could be detected. Subsequently, after adrenal stimulation by 150 mg. of A.C.T.H. a cortisone output of about 150 μg. was observed, and a similar raised output resulted when cortisone was injected intramuscularly, showing that the low outputs at rest and during stress were not due to any inability of the kidney to excrete the hormone.

Discussion

It is concluded that the method of bio-assay of cortisone and compound F in urine which we have developed is sufficiently reliable, even when only three mice are used for each assay, to reveal the more gross variations in cortisone output in man. With larger numbers of mice in each group a higher accuracy would no doubt be obtained, but larger quantities of urine would be required for each assay. The technique we have used has necessitated for each assay urine collected over from 12 to 48 hours, according to the cortisone concentration present.

Four main ranges of cortisone excretion can be defined :

1. A low output, from 0 to 50 μg. a day, is usually found in conditions of adrenal inadequacy due either to Addison's disease or to panhypopituitarism.

2. The normal resting range lies, in our small series, between 40 and 120 μg., and these figures are very similar to those found earlier by Venning (1945).

3. A higher output is encountered in states of medical and probably other stress. The range then lies between 170 and 320 μg. a day. Outputs in this stress range are also found in the eighth month of normal pregnancy, and they can also be produced by oral ephedrine, or by intramuscular or oral cortisone acetate.

4. Finally, artificial stimulation of the adrenal cortex by intramuscular A.C.T.H. will, in suitably reactive subjects, lead to excessive outputs of cortisone—from 300 to 650 μg. a day, and probably even higher. Such outputs appear to be well above those encountered in medical stress. This range of high outputs of cortisone may therefore be called the "A.C.T.H. range."

An assay of the type here discussed has two main advantages over a study of the circulating eosinophils of the human subject. First, a moderate rise in cortisone excretion such as occurs in the first day of A.C.T.H. therapy is often sufficient to send the circulating eosinophils down to zero. Thereafter, further increases in cortisone excretion cannot be revealed by the eosinophils. Secondly, there is evidence that the changes in the circulating eosinophil cells do not necessarily reflect the cortisone output. Thus eosinophils reappeared in the blood of patient A.T. (Fig. 3) on the sixth day of A.C.T.H. therapy, when his observed cortisone excretion was at its maximum. We have also recently observed a patient with ulcerative colitis whose cortisone output rose under A.C.T.H. therapy to over 300 μg. a day, but whose eosinophil cells never fell below 100 per c.mm. and were often much higher. This lack of reliability of the eosinophil depression as an indicator of adrenal cortical stimulation in the human subject has also been noted by Posey, Mathieson, Mason, and Bargen (1950) in similar cases of ulcerative colitis. In their patients there was no satisfactory relation between adrenal corticoid output determined by a chemical method and the eosinophil drop.

Another method of following changes in adrenal cortical function now widely used is the chemical measurement of the daily output in the urine of the so-called adrenal corticoids. These are extracted by varying procedures in different laboratories and are usually estimated either by their reducing power towards sugar reagents or by their ability to produce formaldehyde on suitable oxidation. We have determined the reducing power towards Nelson's sugar reagent of a few extracts which had also been assayed for cortisone in adrenalectomized mice, and no parallelism between the two results has been apparent except after gross stimulation of the adrenal cortex by A.C.T.H. In late normal pregnancy, for instance, the cortisone output has always been found to be above normal although the total neutral reducing steroids determined chemically remain within normal limits. At least 90% of the total neutral reducing steroid present in such pregnancy urine is biologically inactive. Wick, Pecka, and Medz (1950) have come to a similar conclusion.

The cortisone excretions we have observed may not represent the whole amounts originally present in the urines, as some may well be lost or destroyed in the process of extraction (Paterson, Cox, and Marrian, 1950). Nevertheless, until more reliable methods of extraction are developed we believe that much useful information can be obtained by the bio-assay of such extracts.

Summary

The combined cortisone and compound F content of human urine has been measured by bio-assay. In resting normals the output ranges from 40 to 120 μg. daily.

In many types of stress due to medical disease the output is raised. The stress output ranges from 160 to 320 μg. a day. The output of cortisone-like hormone is raised in late normal pregnancy. A progressive rise in output occurs during A.C.T.H. therapy, when maximum outputs of over 600 μg. daily have been observed. The response to A.C.T.H. varies in different persons.

Ephedrine increases the output of cortisone-like hormone in the urine. It is unable to maintain adrenaline stimulation induced by A.C.T.H.

After cortisone, either injected or by mouth, a rise in output in the urine occurs, and may persist for at least a week after the last injection.

Excretion of cortisone-like hormone is usually reduced in Addison's disease and in panhypopituitarism.

The increased output of cortisone which medical stress normally provokes did not occur in a case of panhypopituitarism subjected to stress.

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TRIALS OF ORAL STREPTOMYCIN FOR INFANTS WITH NON-SPECIFIC GASTROENTERITIS

Previous papers concerning the treatment of infantile gastroenteritis by streptomycin have reported contradictory results. James, Kramer, and Armitage (1948), recording the treatment of 30 infants, concluded that the course of the disease was materially shortened by streptomycin given by mouth; they used a total dosage of 2 g. over a period of seven days. They qualified this conclusion by the observation that many of their cases were infected with *Proteus vulgaris* and that it was not expected that all types of gastroenteritis would respond so well. Pulaski and Seeley (1948), and Leisti (1947) have also reported favourable results from treatment with oral streptomycin, and Goettsch, Cobley, and Mulloy (1948) from combined treatment by the oral and intramuscular routes. None of these authors had a comparable series of control cases under observation during the period of their investigations.

On the other hand, Holzel, Martyn, and Apter (1949), in a carefully controlled study of the value of streptomycin in non-specific infantile diarrhoea and vomiting, were unable to demonstrate that the drug was an effective therapeutic agent. They gave some cases oral and some cases intramuscular streptomycin in similar amounts to those used by James *et al.* They record an impression that certain of their patients appeared to benefit, judged by the rate of clinical improvement. However, clinical and bacteriological observations failed to give either statistical evidence that the drug was of value or indications for its use.

The following papers report two independent clinical trials of the oral administration of streptomycin to infants suffering from non-specific gastroenteritis in which similar results have been obtained. They were carried out in centres in Edinburgh and London respectively.

I. TRIAL AT THE CITY HOSPITAL, EDINBURGH

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In the gastroenteritis unit at the City Hospital in Edinburgh a trial of streptomycin therapy in non-specific gastroenteritis has been carried out by treating 24 cases with streptomycin and comparing the results with a concurrent control series.

The 48 cases here reported represent about half the cases treated in the unit during the period November, 1948, to January, 1950; very mild cases and cases treated with other oral antibiotics were excluded. In other respects the streptomycin-treated cases were "unselected." They were, in fact, nominated for streptomycin treatment on admission in rotation with control cases and cases treated with other antibiotics. The control cases were in the same way originally "unselected," but the 24 controls here presented are chosen from the larger group of control cases, so that each trial case is balanced by a control case of approximately the same age, date of admission, and clinical severity of enteritis.

As no epidemic of gastroenteritis occurred during the period of the trial, all the cases were of endemic type. Most of the babies were admitted from their own homes, where the social conditions were poor; two cases were transferred from maternity units, and 15 came from institutions.