Experimental Results

I can summarize the results of my group by saying that porphobilinogen and δ -aminolaevulinic acid behaved as expected of true intermediates. At the other extreme, added protoporphyrin scarcely affected the radioactivity of the biosynthesized haem at all and had little effect upon the normal protoporphyrin production. Uroporphyrin III and coproporphyrin III occupied intermediate positions, somewhat depressing the haem labelling and significantly diverting radioactivity into their pool. In other words, none of these three porphyrins fulfils the requirement of a true intermediate; simple enzyme inhibition was excluded, but I must repeat the warning that permeability barriers may be playing a part here which it is difficult to assess.

From chemical considerations, it would seem plausible that the first porphyrin formed from porphobilinogen is uroporphyrin, which, by stepwise decarboxylation and, finally, dehydrogenation and iron incorporation, would lead to protoporphyrin and haem, and the enzyme catalysis of this last step has recently been demonstrated by Goldberg. In support of such a mechanism are the observations of porphyrins with from eight to two carboxyl groups in many biological situations. If these porphyrins are not themselves true intermediates they are almost certainly closely related structurally to them. My group has put forward the following scheme (Fig. 8), showing this hypothetical relationship, where X represents the true intermediate and the number

FIG. 8.—Suggested scheme for mechanism of haem biosynthesis from porphobilinogen.

denotes the number of carboxyl groups it carries. We suggested that the X substances might be the porphyrinogens or reduced forms of their respective porphyrins, and within the last few weeks a paper has appeared from Aldrich's group in Portland claiming that reduced uroporphyrin III does in fact behave as a true intermediate. The pathway for handling the series I isomers may differ from the other in that the free porphyrins *do* themselves lie on it.

It has generally been assumed that the presence of a nucleus, as in avian erythrocytes, is essential for porphyrin and haem biosynthesis, since the mature human red cell is unable to synthesize any haem from added glycine. Recent work, still in progress in my laboratory, indicates that this is only partly true. Although mature human red cells cannot utilize glycine, they will form copious amounts of uroporphyrin III and coproporphyrin III from added δ -aminolaevulinic acid. Interestingly enough, however, they cannot alone bring about the further oxidative decarboxylation of coproporphyrin (or 4X) to protoporphyrin, but will do so if a suspension of rat liver mitochondria is also added. High-speed centrifugation of a nucleated red-cell haemolysate—for example, of chicken blood—yields a supernatant similarly requiring a particulate system for the 4X to protoporphyrin conversion, as do also extracts of *Chlorella*.

Conclusion

This is where our knowledge of the normal biosynthesis of haem rests at the present day. I must confess to an oversimplification in what I have told you of some parts of the story, and I have omitted nearly all references to the synthesis of the globin moiety of haemoglobin and to the action of stimulating or inhibiting factors on these processes at the cellular or physiological levels.

Many investigators have contributed to our present knowledge, and work is actively proceeding in the belief that when we know every detail of the normal course of events, pathological deviations and the aberrations of disease will also become intelligible and perhaps amenable to correction.

In the biosynthesis of haem the body uses the simplest of building-stones, glycine and acetate, and yet the discoveries I have traced will have made it clear how many stages, beautifully co-ordinated, are gone through to reach the final product—and may I remind you again that the synthesis of haem is almost certainly one of the earliest achievements of living matter.

Whether chlorophyll preceded haem is a matter for debate, but each is essential, in its setting, for the provision of the energy without which life is impossible: chlorophyll harnesses the sun's rays for the reductive splitting of water; the haem enzymes achieve the release of energy by a recombination to water of metabolically produced hydrogen and the oxygen of the air!

It is not unusual to conclude a memorial lecture such as this with some quotation. Goethe says,

"Was kann der Mensch im Leben mehr gewinnen,
Als dass sich Gott-Natur ihm offenbare,
Wie sie das Feste lässt zu Geist verinnen,
Wie sie das Geisterzeugte fest bewahre!"

which can, I think, be translated,

"What greater end can Man in life attain
Than that, to him, 'God-Nature' should Himself reveal;
Material Substance into Spirit changing,
The Spirit-born to Substance She transforms!"

Mighty music! But for the majesty of the full close we must turn, I suggest, to the unknown Hebrew author of Ecclesiastes: "What profit hath he that worketh in that wherein he laboureth? I have seen the travail, which God hath given to the sons of men to be exercised in it. He hath made every thing beautiful in his time; also he hath set the world in their heart, so that no man can find out the work that God maketh from the beginning to the end."

REFERENCES

- Falk, J. E., Dresel, E. I. B., and Rimington, C. (1953). *Nature (Lond.)*, 172, 292.
Rimington, C. (1955a). *Endeavour*, 14, 126.
— (1955b). *Ann. Rep. chem. Soc.*, 51, 295.
Shemin, D., and Wittenberg, J. (1951). *J. Biol. Chem.*, 192, 315.
Wittenberg, J., and Shemin, D. (1950). *Ibid.*, 185, 103.

DIAGNOSTIC USE OF ADRENAL INHIBITION IN CUSHING'S SYNDROME

BY

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In 1955 Cope and Harrison reported in detail the case of a patient with severe Cushing's syndrome due to adrenal cortical hyperplasia in whom it was shown that a temporary reduction in adrenal activity could be produced by the administration of the recently introduced halogen-substituted steroid 9 α -fluorohydrocortisone. They suggested that the response to this drug might prove of diagnostic value in Cushing's syndrome as a means of distinguishing cases with hyperplasia from those due to tumour. That such a distinction can be made in the case of the adrenogenital syndrome by observing the inhibitory effect of cortisone has already been well shown by Lawson Wilkins and his colleagues (1952) and has been more recently confirmed by Jailer, Gold, and Wallace (1954).

In the adrenogenital syndrome the main product of the adrenal gland is an androgen, and the urinary excretion of 17-ketosteroids is increased. Cortisone given orally or intramuscularly causes inhibition of a hyperplastic gland but not of a tumour. In the former the inhibition is demonstrated by a prompt fall in the

excretion of 17-ketosteroids. The administered cortisone during its metabolism produces only small amounts of ketosteroid which do not appreciably interfere with the detection of the inhibition.

In Cushing's syndrome, on the other hand, the main disorder is an excessive production of cortisol (hydrocortisone). Even if administered cortisone also causes an adrenal inhibition in this condition it will not be demonstrable chemically, because any fall in endogenous cortisol production will be obscured by the increased supply derived from the administered cortisone.

By using the steroid 9 α -fluorohydrocortisone instead of cortisone, however, this difficulty can be avoided. A different series of metabolic products is produced, and the effects of this steroid on endogenous cortisol formation can be followed by measuring the urinary output of cortisol, the sole source of which will now be the adrenal cortex.

Observations are presented here on five further subjects, two with Cushing's syndrome due to proved so-called adrenal hyperplasia, one with an adrenal cortical carcinoma, one with a mild and incomplete Cushing's syndrome of as yet unproved aetiology, and a fifth subject with normal adrenal glands. The results support the view previously expressed that the response to 9 α -fluorohydrocortisone will prove of diagnostic value in distinguishing between hyperplasia and adrenal tumour as a cause of Cushing's syndrome.

Methods

Ketogenic steroids have been measured by the method of Norymberski, Stubbs, and West (1953) with the modifications described by Gibson and Norymberski (1954). 17-Ketosteroids have been estimated by the standard Medical Research Council method (M.R.C., 1951).

Cortisol, tetrahydrocortisone, and tetrahydrocortisol have been estimated by the method of Cope and Hurlock (1954), in which the individual steroids are separated by paper chromatography. Cortisol and cortisone were determined on extracts obtained by extracting the urine with chloroform at pH 1. For the other steroids chloroform extracts were made after preliminary hydrolysis of an aliquot of the urine with the enzyme β -glucuronidase in a concentration of 1,000 Fishman units per ml. acting for 48 hours at pH 4.5 and 37° C.

Case 1. Adrenal Hyperplasia

A woman aged 46, with history and signs of typical Cushing's syndrome of moderate degree. The condition had developed progressively over six years. On admission she had an obese trunk, a plethoric face, facial hirsuties, and she bruised easily on arms and legs. She was mentally depressed. Her abdomen was protuberant but there were no striae. The blood pressure was labile from 130/70 to 200/110. The diabetic sugar curve showed figures of 148, 390, 381, 287, and 230 at half-hourly intervals. X-ray examination was suggestive of lumbar osteoporosis. 17-Ketosteroid excretion averaged 25 mg. daily. Administration of 100 mg. of cortisone daily by mouth caused no fall in excretion of 17-ketosteroids. Subtotal adrenalectomy was performed (Mr. Selwyn Taylor), and all the right gland (9 g.) and five-sixths of the left gland (8 g.) were removed. Histology of adrenal tissue: "Both glands show thickening of zona fasciculata with depletion of lipid in the inner part. No irregular nodularity of outer fasciculata such as is often found in Cushing's syndrome. Appearances suggest raised cortical activity."

Preliminary urinary estimations on two successive days showed an average daily output of 232 μ g. of cortisone and 183 μ g. of cortisol. There was an average daily excretion, measured on three days, of 2,630 μ g. of tetrahydro-

cortisone and tetrahydrocortisol combined. The excretion of these metabolites is well within normal limits; the excretions of cortisone and cortisol are in the high normal range. Mean 17-ketosteroid excretion was 25 mg. a day and ketogenic steroids 24 mg. daily.

After this period of observation, 10 mg. of 9 α -fluorohydrocortisone was given daily in four divided doses by mouth for five days. In Table I the outputs of several

TABLE I.—Case 1

Day	Dose 9 α -Fl-F (mg.)	17-Ketosteroid	17-Ketogenic Steroid	Cortisone	Cortisol	Tetrahydro E + F
1	0	101	136	111	120	104
2	0	89	74	89	79	82
3	0	111	89	Lost	Lost	113
4	10	58	95	27	24	82
5	10	38	48	4.7	3.6	63
6	10	26	21	4.2	2.9	36
7	10	33	67	13	9.3	20
8	10	59	45	15	40	26
9	0	91	65	55	41	73

All figures are expressed as percentages of the mean excretion rate of each steroid before the drug was given.

relevant steroids in the urine during administration of the drug are expressed as percentages of the average starting figure for each steroid. A prompt reduction of cortisone excretion to 4.2% of the initial rate occurred while cortisol excretion fell by the third day to below 3% of the initial output. In spite of continued administration of the drug, the output of both these steroids started to recover, suggesting a partial escape of the adrenal from the influence of the drug. The excretion of the combined tetrahydro compounds—important metabolites of cortisol—also fell, but rather more slowly and to a less extent, the lowest being 20% of the average initial figure. Falls of equal degree occurred in the excretion of ketosteroids and of ketogenic steroids. A sharp and almost complete inhibition of adrenal activity is indicated by these results, the strongest effect being reached on the third day.

Case 2. Cushing's Syndrome with Proved Hyperplasia

A man aged 39 had had a gradual increase of weight over ten years. During the past year easy bruising, mooning of face, and plethora started. Dorsal kyphosis and bright abdominal striae developed. B.P. 160/110. Hb 15.7 g. Negative calcium balance. 17-Ketosteroids 20 mg. daily, and ketogenic steroids 43 mg. Plasma corticosteroids 21 mg. rising to 80 mg. after intravenous corticotrophin drip. Subtotal adrenalectomy was performed. Adrenal weight 17.5 g. "Section showed a cortex wider than usual, the increase being due to a hypertrophied fasciculata. All layers of cortex contain lipid, especially the fasciculata. The appearances were those of cortical hyperplasia."

In the pre-operative period this patient was given 5 mg. of 9 α -fluorohydrocortisone daily for five days. On the third day the output of cortisone and of cortisol had fallen to 30% of the initial figure (Table II). That the adrenal

TABLE II.—Case 2

Day	Dose 9 α -Fl-F (mg.)	17-Ketosteroid	Cortisone	Cortisol
1	0	102	—	—
2	0	98	100	100
3	5	—	—	—
4	5	—	—	—
5	5	44	31	29
6	5	55	53	60
7	5	80	96	101
8	0	—	—	—
9	0	—	146	233

inhibition was incomplete in this case may have been in part due to the fact that a smaller dose of 9 α -fluorohydrocortisone was used than in Case 1. There was in this case an even greater tendency than in Case 1 to escape from the effect of the drug during the fourth and fifth days. This tendency to escape from the influence of the drug is not

confined to severe cases. Case 3 also showed it, although the extent of the Cushing-like features was mild and the clinical picture was incomplete.

Case 3. Incomplete Mild Cushing's Syndrome, Undetermined Aetiology

A man aged 25 had a rapid increase in weight of 80 lb. (36.3 kg.) in one year. B.P. 150/90. Marked moonface. Many bright red striae on thighs and abdomen. Sugar tolerance curve, 80, 170, 180, 170, and 115 at half-hourly intervals. Urinary steroid excretions were within normal limits, the mean daily outputs being 17-ketosteroids, 13 mg.; ketogenic steroids, 19.7 mg.; cortisone, 29 μ g.; cortisol, 25 μ g.; tetrahydrocortisone, 1,225 μ g.; and tetrahydrocortisol, 360 μ g.

After four days' observation to establish these mean steroid excretions a course of five days on 10 mg. daily of 9 α -fluorohydrocortisone was given. A prompt inhibition of steroid output occurred, this being complete by the second day. The percentage changes in steroid output are recorded in Table III.

TABLE III.—Case 3

Day	Dose 9 α -Fl-F (mg.)	17-Keto-steroid	17-Keto-genic Steroid	Corti-sone	Corti-sol	Tetra-hydro E	Tetra-hydro F
1	0	127	118	—	—	—	—
2	0	—	—	130	80	121	90
3	0	74	84	59	108	95	74
4	0	102	115	117	132	123	99
5	0	98	84	96	84	61	137
6	10	85	42	24	44	51	62
7	10	50	25	0	0	11	5
8	10	67	22	0	0	15	19
9	10	50	21	0	34	11	10
10	10	64	76	85	47	130	124
11	0	76	65	76	108	165	195

Such an inhibition of the adrenal cortical activity is in no sense peculiar to adrenal hyperplasia, although its occurrence in this disorder is of great theoretical interest. The response of the normal adrenal is precisely similar.

A typical response by a normal adrenal is given by Case 4.

Case 4. Normal Adrenal

This patient, a man aged 56, was convalescent from pulmonary embolus and mild left-sided heart failure. He was normotensive, and had no adrenal or other endocrine abnormality.

The mean daily excretions of steroids during a four-day observation period were cortisone, 148 μ g.; cortisol, 20 μ g.; tetrahydrocortisone, 2,460 μ g.; and tetrahydrocortisol, 998 μ g. After this four-day period of preliminary observation daily doses of 10 mg. of 9 α -fluorohydrocortisone were given for seven days. The small amount of cortisol in his urine resulted in a big experimental error in the analyses and as a result the percentage changes were irregular. In Table IV the changes in the combined cortisone + cortisol

TABLE IV.—Case 4

Day	Dose 9 α -Fl-F (mg.)	Cortisone + Cortisol	Tetrahydro E	Tetrahydro F
1	0	87	113	165
2	0	135	124	96
3	0	81	87	35
4	0	96	76	104
5	10	5	74	116
6	10	9.5	24	31
7	10	3	25	33
8	10	40	24	32
9	10	11	14	17
10	10	Lost	30	44
11	10	„	22	27

output have therefore been recorded; the former steroid in this patient comprised about 90% of the total. An almost complete disappearance of cortisone and cortisol from the urine occurred promptly, whilst the excretion rate of the major metabolites tetrahydrocortisone and tetrahydro-

cortisol fell more slowly to 14 and 17% respectively of the initial average levels. The changes are almost identical with those occurring in patients with adrenal cortical hyperplasia, although the tendency to escape from the influence of the drug was not so evident in this man.

Case 5. Adrenal Carcinoma

A boy of 9 years had had obesity of feminine distribution with gynaecomastia for six months. Hirsuties on back and legs. Pubic hair well developed but of feminine distribution. Penis and testes normal. B.P. 135/80. No striae or plethora. Skeletal precocity with bone age 12 years. Large adrenal tumour easily palpable in left hypochondrium. When removed this measured 15 by 11 by 3 in. (38 by 28 by 7.5 cm.). Section showed an anaplastic carcinoma of adrenal cortex with many large cells of varying size and many multinucleated giant cells. During a preliminary period 17-ketosteroid output averaged 21 mg. (four determinations) and ketogenic steroids 30.7 mg. (three determinations). Cortisone excretion was 97 μ g. and cortisol 60 μ g. daily (two determinations each).

A five-day course of 7.5 mg. daily of 9 α -fluorohydrocortisone in three divided oral doses was given and the effects on the excretion rates of the various steroids were observed. The results are collected in Table V, in which the figures for each steroid are again expressed as percentages of the average excretion rate during the preliminary period. It will be seen that no diminution in the excretion rate of any of the steroids estimated occurred during the five days of the test; indeed, the excretion of ketogenic steroids, of cortisone, and of cortisol showed a steady and uninterrupted rise throughout the period. It is of interest, however, that in spite of the steady rises in these steroids there was no equivalent rise in the output of tetrahydrocortisone and of tetrahydrocortisol, the mean excretion of these during the period of drug administration being 104 and 94% respectively of the initial level.

TABLE V.—Case 5

Day	Dose 9 α -Fl-F (mg.)	17-Keto-steroid	17-Keto-genic Steroid	Corti-sone	Corti-sol	Tetra-hydro E	Tetra-hydro F
1	0	135	108	122	132	113	115
2	0	65	90	77	68	58	69
3	0	100	102	Lost	Lost	132	117
4	7.5	108	139	111	123	142	122
5	7.5	120	187	135	142	85	79
6	7.5	165	207	201	178	107	74
7	7.5	155	236	260	200	116	113
8	7.5	132	284	265	225	71	83

All figures are expressed as percentages of the mean excretion rate of each steroid before the drug was given.

Discussion

It is apparent from the data obtained in these cases that the activity of the normal adrenal cortex can be almost completely inhibited by 9 α -fluorohydrocortisone, and that similar inhibition may be produced, at least temporarily, in Cushing's syndrome associated with adrenal hyperplasia. Four cases of Cushing's syndrome have now been tested, three being due to proved hyperplasia and the fourth of as yet undetermined aetiology. All have shown a significant degree of inhibition of cortisone and hydrocortisone excretion under the influence of the drug 9 α -fluorohydrocortisone. In sharp contrast to these is the proved case of adrenal carcinoma in which no trace of interruption in the steadily increasing output of cortisone and hydrocortisone occurred.

The difference in behaviour between the two types of adrenal hyperfunction is well shown in the Chart (see next page). The results in these cases support the view, previously expressed, that an inhibitory test with the drug 9 α -fluorohydrocortisone may be of diagnostic value in Cushing's syndrome as a means of distinguishing between hyperplasia and tumour. Many more trials will need to be undertaken, however, before the reliability of such a test can be fully evaluated.

It is recognized that few laboratories will possess either the facilities or the time to determine the urinary outputs of cortisone and of cortisol which appear to be the most sensitive indices of changing adrenal function. Few also will be prepared to estimate the plasma corticosteroids, which are probably almost as sensitive.

Other criteria of adrenal functional inhibition will be needed for routine clinical use.

The estimation of the major metabolites tetrahydrocortisone and tetrahydrocortisol is as laborious as that of

Inhibition of adrenal hyperplasia and failure to inhibit adrenal carcinoma. Numbers 1 to 5 refer to cases reported in the text. Number 6 refers to the case of Cope and Harrison (1955). All changes are expressed as percentages of initial output in each patient.

cortisone and is not justified for clinical purposes, since changes in excretion of these products reflect the changing adrenal function much less reliably than does cortisol. This is well shown in Case 5, where the output of these steroid metabolites remained essentially constant although the activity of the adrenal tissue, as judged by the excretions of cortisone, of cortisol, or of the ketogenic steroids, was steadily increasing.

In theory the output of cortisone or of cortisol can be estimated by extraction of the urine at pH 1 and application of the specific Porter-Silber reaction to the slightly purified extract. In practice, however, this is an unreliable technique for two reasons (Cope and Hurlock, 1952). First, other substances in the extracts act as non-specific chromogens and seriously interfere with the colour measurement. Secondly, small but very variable and unpredictable quantities of chromogenic metabolites, especially of tetrahydrocortisone, will be found in these extracts. These will react with the reagent and may often contribute more than half the total colour. Indices of adrenal function based on application of the Porter-Silber reaction to urine extracts which have not been purified by chromatography are therefore not recommended for this purpose.

In contrast to these methods, the 17-ketogenic steroid content as measured by the method of Norymberski *et al.* (1953) is relatively simple to estimate and the method is suitable for most routine laboratories. Excretion of 17-ketogenic steroids seems to follow reasonably closely the changes in adrenal function as judged by cortisone or cortisol excretion. The extent to which this is so may be judged by the results in Cases 1, 3, and 5. But if this criterion of adrenal cortical activity is used—and it is probably a valid one—it should be borne in mind that there is often a delay of about 24 hours in the fall in excretion rate of these metabolites. If the inhibition of adrenal activity is only of short duration this fall in 17-ketogenic steroid excretion may not have time to develop fully and a brief adrenal inhibition may be missed. This occurred in the case reported by Cope and Harrison (1955). A period of

five days' administration of the drug should provide ample time for maximal changes to take place.

It has been our impression that the 17-ketosteroids respond much less certainly to changing adrenal cortical activity and that measurement of the ketogenic steroids is greatly preferable.

The halogen-substituted steroid 9α-fluorohydrocortisone is not unique in its ability to inhibit production of cortisol by the adrenal gland. Cortisone given by mouth will do the same. But it cannot be used for the investigation of Cushing's syndrome because part of the dose will be converted to cortisol and some of this will appear in the urine, obscuring the inhibition of endogenous production of cortisol. Some of the administered cortisone will be degraded into 17-ketosteroids, similarly obscuring any fall in the endogenous production of these substances. It may be noted that, for this reason, no reduction in 17-ketosteroid excretion had been observed as a result of oral cortisone therapy in Case 1, although 9α-fluorohydrocortisone produced almost complete inhibition of the cortisol output.

The recently introduced drugs prednisone and prednisolone also produced adrenal inhibition, though probably rather less intensely than 9α-fluorohydrocortisone. These drugs have the disadvantage that they need to be used in much larger dosage and that their own metabolism leads to the excretion in the urine of significant amounts of ketogenic substances. While these do not interfere appreciably with the measurement of cortisone and cortisol excretion, they do seriously interfere with the observation of changes in the endogenous 17-ketogenic steroid output. These drugs therefore are not recommended for the proposed diagnostic test if 17-ketogenic steroid excretion is to be used as the criterion of changing adrenal activity.

A further substance, "amphenone," has been found to cause adrenal cortical inhibition. It seems almost certain that this will prove unsuitable for the test, because Thorn *et al.* (1956) have reported the effective inhibition of adrenal function with this drug in a patient with adrenal cortical carcinoma. It must be presumed that amphenone acts on a different part of the steroid metabolic chain.

9α-fluorohydrocortisone thus emerges as the drug of choice for use in this test. Owing to its potency relatively small doses are needed.

It will be observed that the dose of 9α-fluorohydrocortisone given daily to the boy with the tumour was less than that given to the adults. The dose was approximately in proportion to the body weight. It may be objected that the dose given per gramme of functioning adrenal tissue was much less than in the case of the patients with adrenal hyperplasia. While this is true, the output of cortisol was only moderately raised in this tumour patient, and in proportion to the intensity of the cortisol production the dose given was comparable to that received by the other subjects. In practice it will rarely be possible to adapt the dose to the weight of adrenal tissue, since this will usually be quite unknown before operation. Only partial inhibition was obtained in the most severe of the cases of hyperplasia we have investigated (Cope and Harrison, 1955), and this suggests that it may prove desirable to adjust the dose of 9α-fluorohydrocortisone used in the test to the intensity of cortisol production in each individual case.

Summary

The halogen-substituted steroid 9α-fluorohydrocortisone produces almost complete inhibition of cortisol production by the human adrenal.

Inhibition of cortisol production has been produced by the drug in three cases of Cushing's syndrome due to adrenal hyperplasia.

Cortisol production by a large adrenal cortical carcinoma was completely uninfluenced by 9α-fluorohydrocortisone.

The results support the belief that the adrenal inhibition test will prove of value in distinguishing Cushing's syndrome due to adrenal hyperplasia from cases of the syndrome due to carcinoma.

Our thanks are due to Miss Elizabeth Black and to Miss Olwen Jenkins for performing most of the analyses; to the Medical Research Council for a grant for the former; and to Dr. Russell Fraser and Dr. Dynski-Klein for permission to study Cases 1 and 5 respectively.

REFERENCES

- Cope, C. L., and Harrison, R. J. (1955). *British Medical Journal*, 2, 457.
— and Hurlock, B. (1952). *Ibid.*, 2, 1020.
— (1954). *Clin. Sci.*, 13, 69.
Gibson, G., and Norymberski, J. K. (1954). *Ann. rheum. Dis.*, 13, 59.
Jailer, J. W., Gold, J. J., and Wallace, E. Z. (1954). *Amer. J. Med.*, 16, 340.
Medical Research Council (1951). *Lancet*, 2, 585.
Norymberski, J. K., Stubbs, R. D., and West, H. F. (1953). *Ibid.*, 1, 1276.
Thorn, G. W., Renold, A. E., Goldfien, A., Nelson, D. H., Reddy, W. J., and Hertz, R. (1956). *New Engl. J. Med.*, 254, 547.
Wilkins, L., Gardner, L. I., Crigler, J. F., Silverman, S. H., and Migeon, C. J. (1952). *J. clin. Endocr.*, 12, 257.

ACUTE HYPERPARATHYROIDISM WITH ELECTROCARDIOGRAPHIC CHANGES

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Acute hyperparathyroidism is an extremely rare condition, and every case may therefore be regarded as worthy of record. Only isolated reports on definite or suspected cases are to be found in the literature. Seven proved cases have been reported, all of which were fatal (Hanes, 1939; Oliver, 1939; Arnold, 1940; Smith and Cooke, 1940; Mellgren, 1943). Doubtful cases were described by Dawson and Struthers (1923), Herxheimer (1926), and Herzenberg (1933). These four cases also ended fatally.

Acute parathyroid intoxication caused by a chief-cell adenoma of the parathyroid glands has a different clinical picture from that usually associated with chronic hyperparathyroidism. The main features are a rapid onset of anorexia, vomiting, constipation, loss of weight, and lassitude developing into increasing drowsiness and asthenia. Abdominal pains may be severe, almost resembling an acute abdominal disease. There may be slight fever, and the pulse rate is disproportionately rapid. This syndrome may be devoid of skeletal findings, while impaired renal function is regarded as characteristic (Mellgren, 1943; Spence, 1953). The acute crisis may supervene on long-standing chronic hyperparathyroidism as in our case. Death may ensue after several days; early diagnosis is therefore imperative, as treatment may be life-saving, as borne out in our patient.

The electrocardiographic findings have rarely been recorded (Ballin, 1932; Kellogg and Kerr, 1936). In our

patient the electrocardiographic changes, together with the clinical presentation, led to the correct diagnosis.

Case Report

A 57-year-old farmer was seen on July 4, 1955. Two weeks previously, while driving his car, he developed a sudden, momentary substernal chest pain which was so severe that he had to stop his car and rest. He consulted his doctor, who took an electrocardiogram which was sent to a consultant physician for an opinion. The physician advised bed rest and a further E.C.G. in one week.

The patient also complained of severe epigastric pain and a blown-up feeling in the abdomen over the past fortnight. He was very nauseated and had continuous headache. The chest pain recurred several times in these two weeks. He also noticed increasing weakness and lassitude and had a feeling of lameness in the arms.

For a number of years he had been slightly breathless on effort. He was always constipated, and said that his bowels had not acted for the previous week. Micturition was normal.

On further questioning he stated that 15 years ago he consulted a physician because of backache. Ten years ago he was diagnosed as having a peptic ulcer, confirmed by x-ray examination, and was treated in a country hospital for four weeks on a milk diet and alkalis. He volunteered the information that the treatment made him feel weak and gave him pins-and-needles in his hands. Although a subsequent x-ray examination showed healing of the ulcer, he felt worse after treatment. For two years thereafter he had paraesthesiae and weakness of his legs. Since then he has never had a milk diet for his ulcer.

Six years ago he was x-rayed again because of dyspepsia, and one year later he was admitted to a hospital for investigation of abdominal pain, backache, and heaviness in the chest. The x-ray picture showed no abnormality, but a gastric test meal revealed achlorhydria, and ever since then he has taken "acidulin" capsules with an occasional alkali powder.

One year ago he was treated by an orthopaedic surgeon for "chronic back strain." He had leg traction, but his backache did not improve.

Six months ago he had a complete dental clearance because the "infection was poisoning his system." Gum healing was greatly delayed. For many years he has had recurrent mild episodes of bronchospasm and sinusitis.

His usual diet included porridge with milk daily, cream and cheese three or four times a week, and two eggs for breakfast daily. He took fresh orange juice several times a week. He drank tea or coffee with milk about six times a day and occasionally took raw eggs for his weakness. He would often take a full glass of milk when the fresh milk came from the farm, but the milk tended to cause substernal heaviness, and he therefore did not drink the latter more than twice a fortnight. He had always been inclined to vomit after "sweet foods." There was no history of polyuria or polydipsia. He had lost 10 lb. (4.5 kg.) in weight in the past two weeks.

On physical examination the most striking features were the marked pallor and extreme asthenia. He could barely walk or talk and was very depressed. His temperature was 99.8° F. (37.7° C.) and pulse rate 100 a minute. His eyes were normal. An arcus senilis was present. He was edentulous. A doubtful fullness was present in the region of the right lower pole of the thyroid gland. The cardiovascular system was essentially normal. The blood pressure was 160/100, but the subsequent readings were in the neighbourhood of 130/80.

Surprisingly, the tendon reflexes were present and brisk, and apart from marked muscular hypotonia the central nervous system was normal. The rest of the examination was negative. Fluoroscopy showed some unfolding of the aorta.