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The plasma concentrations of hydrocortisone and corticosterone following acute myocardial infarctions

Hugh L. Moffet
Yale University

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FOLLOWING ACUTE MYOCARDIAL INFARCTIONS

HUGH LAMSON MOFFET
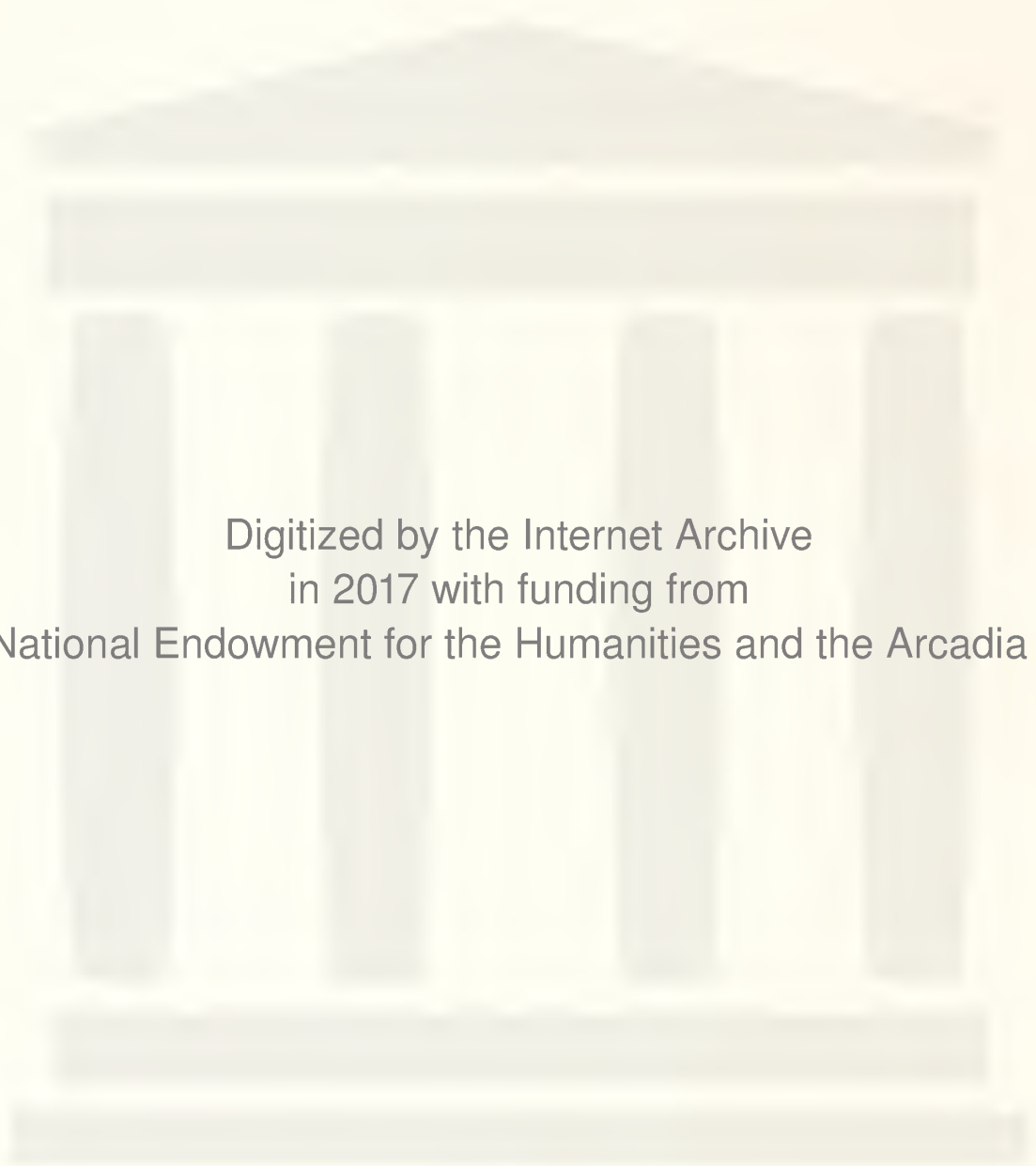
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FOLLOWING ACUTE MYOCARDIAL INFARCTIONS

A thesis presented to the

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by

Hugh Lamson Moffet, A.B.
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Department of Internal Medicine

Yale University School of Medicine
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Introduction

The purpose of this thesis is to add to the data on the
concentration of adrenal cortical hormones in human blood
under various circumstances--with the ultimate goal of attempt-
ing to understand the function of the adrenal gland so that
man may apply this knowledge for the prevention and treatment
of disease. Acute myocardial infarction was chosen as a
stimulus in which to determine adrenal cortical response,
because this condition represents an acute physiological
emergency which usually can be accurately diagnosed and the
time of onset fairly well determined.

This study raises three types of problems. The first
is to determine which compounds are the adrenal cortical
hormones. For a compound to be considered an adrenal secre-
tion it must be present in the adrenal venous blood in higher
concentrations than in the peripheral venous blood, which is
assumed to be equivalent in content to adrenal arterial blood.
For an adrenal secretion to be considered a hormone, it must
be active; that is, it must produce specific, repeatable
physiological effects when administered in small amounts to
humans. Hydrocortisone (cortisol) and corticosterone have
been isolated and identified by strict chemical criteria in
human adrenal venous blood in relatively high concentrations--
concentrations sufficient to produce the same physiological

effects which occur when they are injected in pure form into humans. Hence they can be considered true adrenal cortical hormones.

The second problem is that of devising accurate and specific methods to measure these hormones. The earliest methods of measuring the activity of the adrenal cortex utilized bioassay techniques based on the effects of the hormones on experimental animals. Later, after the hormones had been chemically identified and synthesized, chemical tests specific for a portion of the steroid molecule were used. These tests were first applied to urine because the concentration of the hormones or their metabolic products was higher in urine than in the peripheral blood. Later methods were developed for the extraction of the cortico-steroids from plasma and the efficient separation and isola-tion of individual steroids. When knowledge about the gross activity of the adrenal cortex is desired, the simplest techniques may suffice. However, when accurate measurement of the amounts of hydrocortisone per se and corticosterone per se are needed, more specific and hence more complicated methods involving separation and isolation of these cortico-steroids must be used.

The third problem is to discover to what extent and under what circumstances an isolated plasma level of the hormone reflects the function of the adrenal cortex. The concentration of a substance in the blood depends upon the rate it enters and the rate it leaves the blood, assuming

the blood volume is constant. A single measurement of the plasma concentration of an adrenal hormone at a given moment does not necessarily reflect either the rate of its secretion or its rate of utilization. However, by determination of such isolated plasma values, we can calculate the rates of utilization of exogenously administered hormone under various conditions. Using this information about utilization, an estimate can be made of the rate of secretion of the hormone under similar conditions by measuring isolated endogenous peripheral venous blood levels rather than the continuous measurement of adrenal venous blood levels.

The experimental evidence for these concepts and the rationale, methods, and results of studies of adrenal function after myocardial infarction are presented in subsequent sections of this thesis.

Historical Background

The earliest published description of the adrenals was written in 1563, by Bartholomaeus Eustachius (11), who recognized their glandular structure and distinguished them from the perirenal fat. He called them the "glandulae renibus incumbentes" and henceforth their name has been some sort of description of their anatomic location. Thomas Bartholinis distinguished the adrenal medulla in 1651.(7)

For about three hundred years nothing was known of the function of the adrenals. They were variously regarded as padding or support for other organs, fetal kidneys, receptacles for chyle, glands to absorb a Humour, ancillary parts of the gonads, or glands which functioned to prevent the formulation of renal calculi.(3) In 1716 the Academy of Science of Bordeaux offered a prize for the best thesis on the subject: "What is the function of the suprarenal gland?". Montesquieu was appointed judge and, in his characteristic manner, exposed the sophistry of the essays and awarded no prize.(3)

The first significant advance in the investigation of the function of the adrenals was the work of Thomas Addison, who described three cases of "idiopathic anaemia" associated with pathological changes of both adrenal glands.(5) He continued to study and delineate this syndrome, which has become known by his name.(6)

Greatly influenced by Addison's work, Brown-Séquard performed experiments indicating that bilateral adrenalectomy was fatal to experimental animals.(9) Attempts to reproduce his results, however, were complicated by the presence of accessory adrenal tissue and inexpert surgery; and it was not until the end of the ninet eenth century that the essentiality of the adrenals became accepted.(12) Epinephrine was isolated and synthesized in the early 1900's, but it was soon evident that this hormone could not support life in adrenalectomized animals.

Gaunt and Eversole have summarized the many early experimental studies based on adrenalectomy, which recorded what is now known to be accurate information about adrenal cortical functions.(12) However, it was not until about 1927-1930, when definitive evidence that the cortex secreted life-essential hormones was obtained, that the modern era of logical, systematic investigation of the adrenal cortex began. In 1927, Hartman, et al. (14), showed that ox adrenal cortical extracts significantly prolonged the life of adrenalectomized cats. He called this essential hormone (s) "cortin". Also in 1927, Rogoff and Stewart showed that "interrenalin", an extract prepared from dog adrenal cortices, prolonged the life of adrenalectomized dogs.(23) In 1929, methods were developed for preparing the first really potent cortical extracts (14,22, 23), and Rogoff and Stewart published favorable results with the use of adrenal cortical extract in nine cases of clinically diagnosed Addison's disease.(24)

Since 1930, there has been intensive research in this field, and many new adrenal functions have been discovered. Human urine was found to have adrenal cortical-like properties.(21) The electrolyte changes in Addison's disease were rediscovered and studied.(10,13,18) The effects of the adrenal cortical hormones on carbohydrate metabolism were studied. (8, 19) Selye emphasized the relation of the adrenal cortex to "stress", and defined and elaborated a concept of adrenal-mediated diseases (25), which has stimulated much research.

All of these early studies were based on methods utilizing adrenalectomy or crude cortical extracts. A major advance came with the isolation of crystalline "cortin" in 1934.(17) In 1935, Steiger and Reichstein synthesized desoxycortico-sterone (27), which was successfully used by Simpson in the treatment of Addison's disease.(26) When synthetic cortisone became available, it was discovered to be useful in the treatment in diseases seemingly unrelated to the adrenal, such as rheumatoid arthritis.(16) Most recently, aldosterone, the active principle of the amorphous fraction of cortical extracts, was isolated and identified.(20)

There have been numerous methods developed for measuring the physiological functions of the human adrenal cortex. Some methods attempted to quantitate the hormone level of the plasma by bioassay methods.(42,47) Other methods measured the hormones by their effects on electrolytes or eosinophils (91,93) or by the chemical determination of the corticosteroid breakdown products in the urine.(92)

The bioassay methods are useful as ways to define the effects of a hormone and to test the activity of pure compounds. However, "the chemical study of endocrine secretion plays an...essential role in endocrinology...by setting limits to speculation."(67b) The remainder of this paper will be concerned with the direct chemical methods of measuring the adrenal hormones themselves in the plasma, the evidence for the usefulness and accuracy of these methods, and the data obtained.

Review of Recent Literature

<u>Methods</u>:

Gold has recently published an excellent, detailed review of the methods for measuring plasma corticosteroids and the results of a number of clinical studies.(38) Gemzell(37) and Morris and Williams(40) also give brief historical reviews of early methods.

In 1948 Corcoran and Page made the first attempt to measure the adrenocortical hormones in human peripheral blood by quantitative chemical methods, applying crude methods previously used on urine.(35) Since then, there have been many methods, which usually have the following general steps:

1. <u>Extraction</u>: of steroids from plasma or other fluids, removing lipids etc.

2. <u>Separation</u>: of corticosteroids from each other and from other steroids. Not all methods make such a separation.

3. <u>Identification</u>: of a specific steroid by bioassay, rate of migration or other physical or chemical properties.

4. <u>Quantification</u>: of the specific corticosteroid, usually by using a color reaction and comparison with a known amount.

5. <u>Controls</u>: of the above methods by parallel extractions, colormetric blanks, use of duplicates, etc.

Porter and Silber developed a color reaction useful for quantitating cortisone and related corticosteroids in 1950.(43)

Nelson and Samuels described the first practical method for extracting plasma and measuring the 17-hydroxysteroids using this color reaction.(41) In subsequent studies, hydrocortisone (cortisol) is tacitly assumed to be the only 17,21-dihydroxy-20-ketosteroid measured. Bush, following methods of Zaffaroni and others(33,48), developed the use of paper chromatography to separate the steroids.(34) Abelson and Bondy used alkaline fluorescence with potassium-tert-butoxide as a method to quantitate delta-4-3-ketosteroids.(29) Sweat developed the use of sulfuric acid-induced fluorescence to measure steroids. (45) Bondy et al., developed the use of C^{14} labeled radioactive hormones to quantitate the hormone lost during the experimental procedures, and his paper(30) describes in detail the method used in this study.

For details of the other methods of extraction, color reactions, controls, and quantification of corticosteroids, see Gold's recent review(38) and the references at the end of this thesis.(References 29-48)

Evidence for secretion of hydrocortisone (cortisol) and corticosterone by the human adrenal:

In 1953 Romanoff, et al.,(82,83,76), published evidence for the isolation of hydrocortisone (Kendall's Compound F) and corticosterone (Kendall's Compound B) from human adrenal vein blood. In a patient undergoing adrenalectomy for carcinoma of the prostate and stimulated by ACTH, they obtained 500 ml. of adrenal venous blood. From this they isolated enough of Compounds F and B to prove their identity by melting-point

determination, infra-red analysis, ultra-violet absorbtion, and several color reactions. Several other biologically inactive steroids with the A ring reduced--the tetrahydro-corticosteroids --were tentatively identified, but no cortisone was isolated. In a similar study on adrenal venous blood from a patient under- going adrenalectomy for carcinoma of the breast, identical results were obtained. This group of workers concluded that hydrocortisone is the predominant 11-oxy steroid in human adrenal venous blood.

Bush(68) and Hudson and Lombardo(78) have also submitted evidence that the _major_ plasma corticosteroid in humans is hydrocortisone. Sweat(86) has also summarized the evidence for the presence of Compounds F and B in human adrenal and peripheral venous blood and the evidence for those steroids which might possibly be present. Bush(67b) has summarized the experimental studies on the secretion of the adrenal cortex in animals and collected data on the ratio of F to B concentra- tions. Although he states that the F to B ratio may have no physiologic significance, he has stimulated efforts to deter- mine F/B ratio in humans.

Data on adrenal function:

Several authors have pointed out that an important problem in the study of plasma hydrocortisone and corticosterone concentrations is that of getting a method which is both simple and specific.(31,32) Many of the methods which are simple also have the difficulty of not separating and identifying compounds

F and B with certainty. Borth discusses the relative speci-
ficity of six of the color reaction used and points out the
virtue of paper chromatography in the separation step.(32)

Using various methods of extraction and measurement,
much data has been obtained in the past five years on the
concentration of nonconjugated corticosteroids in humans
under various physiological and pathological circumstances.
In most studies, 17-hydroxycorticosteroids are tacitly as-
sumed to be equivalent to hydrocortisone. Some of these
results are summarized in the following paragraphs.

Compound F (hydrocortisone):

The values for hydrocortisone concentrations in normal
subjects vary with the method used. See Table 1. for normal
values using the method of Bondy, et al.,(30). In normal
humans there is a diurnal variation in the 17-hydroxycorti-
costeroid concentration, with a peak in the morning(51,54c,
55,59) and also a normal day to day variation.(52) The level
of 17-hydroxycorticosteroid rises gradually with pregnancy,
probably due to placental secretion, and rises sharply in
labor; but there is no change in the concentration in toxemic
pregnancies.(40,49,54b)

ACTH stimulates a definite rise in 17-hydroxycorticosteroids
in normals.(54,64,78) Pregnant patients and those with Cushing's
disease respond with an excessive rise of 17-hydroxycortico-
steroid when given ACTH, while those with Addison's disease,
hypopituitarism and adrenogenital syndromes respond poorly or
not at all.(54,78)

Emotional stress may elevate hydrocortisone levels slightly; "pre-operative tension," twice normal; and operation itself, four times the normal.(56,64)

The metabolism of hydrocortisone has been studied by administering the C^{14}-labelled hormone and following the radioactivity of the hormone and its metabolites in the plasma and as they are excreted in bile, urine and feces.(60,61,62) Hydrocortisone is reduced to the dihydro and tetrahydro forms and may become conjugated with one of several compounds-- primarily glucuronic acid.(60) The hydrocortisone glucuronides can be measured as the additional 17-hydroxycorticosteroid found after deconjugation with beta-glucuronidase.(46,83,88) Bongiovanni has asserted that under some clinical circumstances the level of conjugated corticosteroids (in spite of their lack of hormonal activity) may be more useful than that of free hydrocortisone.(31)

In normal humans half of exogenously administered hydro- cortisone disappears in about one to two hours.(60-62) In patients with cirrhosis of the liver, conjugation of hydro- cortisone is impaired.(61,58) Hydrocortisone levels are ele- vated in dying patients, because of slowed removal rather than increased secretion, as there is still an increase after stim- ulation by ACTH.(36) Hydrocortisone utilization is faster in patients with thyrotoxicosis, slower in cases of myxedema and normal in patients with Addison's disease.(61)

Gold has recently reviewed much of the published work on plasma 17-hydroxycorticoids in newborns, children, pregnant women, liver disease, surgical studies, various endocrinological conditions, and the use of ACTH as a test of adrenal function. (38)

Compound B (corticosterone):

Compound B is present in human plasma in smaller amounts than Compound F(67a,67b,78,82,86), and the detection and measurement of B requires procedures much more complicated than the measurement of 17-hydroxycorticosteroids. Hence much less is known about the stimulus, function, and metabolic fate of corticosterone.

Infusion of C^{14}-labelled corticosterone into humans has indicated that it is more rapidly conjugated to its glucuronides than hydrocortisone and is excreted to a relatively greater extent in bile.(81) Because Compounds F and B differ in their rate of disappearance from the blood stream and the plasma B levels are changing more rapidly than the F levels, the plasma F/B ratio is relatively useless as a guide to the relative rates of secretion of these two hormones. The variability of the human F/B ratio reported by various authors (67a-88) seems to refute Bush's suggestion that this ratio is a constant.(67b)

Studies using experimental animals must be interpreted with the knowledge that there is a marked species variation in the secretion and metabolism of corticosterone.(67b)

Corticosterone is the predominant corticosteroid secreted by rabbits, and rats apparently secrete no hydrocortisone at all. (67b) It is not surprising that ACTH stimulates corticosterone secretion in species which secrete no hydrocortisone.(84,85) The utilization of corticosterone in rats does not seem to be increased by stress.(87)

Bondy has shown that exogenous ACTH does raise plasma corticosterone levels in humans in most cases,(67a) but the primary endogenous stimulus for secretion of this hormone by humans has not yet been clearly established; because this hormone has not been adequately studied in clinical situations.

Other data obtained from experimental animals have not yet been confirmed in the human. Compound B, like Compounds A and F, leads to increased fat deposition in chicks and mice. (71,77) While Compound F decreases resistance and lessens the immune response to certain infectious diseases in rabbits, Compound B does not have these effects.(79) Compound B secretion is less well sustained than the F secretion during hemorrhagic shock in dogs; and low B levels may be associated with high F levels in an inverse dissociation, according to adrenal venous cannulation studies in dogs.(73,74)

A final criticism is that not all the methods used to measure corticosterone are accurate and specific(73,88) and data obtained by such methods must be confirmed by more precise methods.

The Adrenal Cortex and Acute Myocardial Infarction

The most comprehensive study of the function of the
adrenal cortex in the early phases of acute myocardial infarc-
tion was published by Forssman in 1954.(92) He summarizes the
earlier investigation of this problem, all of which utilized
eosinophil counts or measurement of urinary steroids. The
studies of urinary steroids are few, but in general, show an
increased urinary excretion of corticosteroids in the early
stages of cardiac infarcts. Other studies utilizing eosino-
phil counts agree that there is often an initial eosinopenia
in infarcts, but there have been conflicting opinions concern-
ing the diagnostic and prognostic value of this method.(91,93)

Forssman studied 100 men and 38 non-diabetic women with
EKG-proved acute myocardial infarctions.(92) He found a
marked eosinopenia within 12 hours, followed by a gradual
increase to normal values from the second to the eighth post-
infarct day. He realized that adrenalin could cause an eosino-
penia in the absence of adrenal cortical hormones, as shown by
Thorn in studies on patients with Addison's disease.(28)
However, he argues that in his series the eosinopenia did
represent an increase in circulating adrenal corticosteroids
because parallel measurement of the adrenalin and nor-adrenalin
in the urine showed that the secretion of these adrenal medul-
lary hormones in his series of infarcts was not enough to produce
eosinopenia.

Forssman also found the urine glucocorticoids and 17-ketosteroids were double the normal amount on the first day after the infarction, falling gradually to normal values by the sixth day. He found no correlation between the degree of eosinopenia and the white blood cell count or temperature curves. He found a greater and more persistent eosinopenia in the 42 fatal cases than in the non-fatal cases.

There have been few published studies before 1957 which record the plasma level of hydrocortisone following acute myocardial infarction and apparently none which measured the plasma level of corticosterone.

Oka(94,95) measured serial plasma 17-hydroxycorticosteroids between 8 and 9 a.m., using the Porter-Silber technique in 12 cases of myocardial infarction, 9 cases of stenocardia (angina pectoris), and 21 cases of cerebral vascular accidents. He found the mean 17-hydroxycorticoidsteroid level was twice normal on the second day of infarction and fell to normal levels between the 15th and 22nd day. He found the mean hydrocortisone level in angina pectoris was $1\frac{1}{2}$ times normal on the 3rd day after the attack and was normal by the 15th day. The mean values in cerebral vascular accidents were higher, being 3 times normal.

However, like the eosinophil studies, he found an occasional very low response by the adrenal cortex. Oka concluded that plasma F levels were not significantly useful in differentiating myocardial infarction and simple angina pectoris and

postulated that pain and fear were as important as myocardial damage as factors in producing elevated hydrocortisone levels.

Engel(89,90) measured serial eosinophil counts and serial 17-hydroxycorticosteroids by the Nelson and Samuels(41) method in 5 EKG-confirmed cases of acute myocardial infarctions, 3 cases of angina pectoris and 9 other acute clinical situations. He found very high values in the early hours after infarction-- up to 5 times(!) the normal or convalescent values.

The studies previously cited and this thesis are stimulated by essentially the same questions: To what extent does the "stress" of an acute myocardial infarction stimulate adrenal cortical activity? Are the adrenal cortical functions correlated with any other observations noted in this condition? This paper utilizes the timing of measurements suggested by the earlier studies, but in addition, an attempt is made to distinguish the functions of corticosterone and hydrocortisone by separate measurement.

Methods and Experimental Procedures

Selection of patients:

Over a three month period, all patients admitted to the
New Haven Unit ward service of the Grace-New Haven Community
Hospital with an admitting diagnosis suggestive of possible or
probable acute myocardial infarction were screened as possible
cases. Because the blood specimens were not obtained until
the first morning after admission, patients who died within
24 hours after admission were not included in this study.
In three months of new admissions, only one patient who sur-
vived myocardial infarction for 24 hours after admission was
known to have been omitted--because he was accidently over-
looked until 5 days after admission.

Eleven cases of acute myocardial infarction were studied.
Seven of the ten control cases were thought to have possible
infarctions on the morning after admission, and two cases were
selected as examples of acute chest pain which were probably
not due to myocardial infarction. The other control case was
selected because of the presence of anoxia, cyanosis, and shock.

The criteria for acute myocardial infarction were 1) a
probable clinical diagnosis of myocardial infarction and 2)
two or more serial EKG's showing typical evolution of an infarct--
as read by the cardiology staff. Those patients classified as
"acute coronary insufficiency" had a clinical diagnosis of

possible or probable myocardial infarction, EKG evidence consistent with myocardial ischemia, but no typical evolution of an infarct on three or more serial EKG's.

Technique of measurement:

The details--including reagents, sources of error, accuracy and rationale--of the techniques which were used to measure plasma hydrocortisone and corticosterone in these cases have been described in detail by Bondy, et al.,(67a); and so only the broad outline will be given here.

It was decided to draw the samples for determination at a fixed time of day, because of the diurnal variations which had been previously noted.(51,55,59) The hours between 9 and 11 a.m. were chosen because the normal values in this laboratory had been obtained at about this time, and this also allowed us to get fasting specimens. Convalescent specimens were obtained at the same hour as the first specimen.

Eighty to one hundred ml. of blood were obtained from the antecubital vein in a heparinized syringe, centrifuged immediately, and the plasma frozen. The plasma was thawed within two months and the hormones then measured immediately.

Duplicates were measured whenever there was more than a total of 25 ml. of plasma available; i.e., in all but 2 cases. In a few other cases only one of the duplicates was technically satisfactory. The following is a description of the experimental processing of a single plasma specimen.

A known amount of C^{14}-labelled hydrocortisone and C^{14}-labelled corticosterone is added to the plasma, followed by 0.5 ml. of 1N. NaOH. The mixture is stirred and promptly extracted three times with redistilled chloroform. The corticosteroids in the chloroform extract are separated by their distinctive rates of migration on filter paper in a 70% methanol-toluene paper chromatography system. The point to which the unknown amounts of Compounds F and B have migrated is measured as the same distance a known control spot of F and B has migrated--this control spot being recognized by its ultra-violet fluorescence. The spots of Compounds F and B from the plasma extract are then each cut out and eluted from the paper into ethanol. The ethanolic eluate is evaporated to dryness. An organic base (potassium tert-butoxide) is added and the fluorescence of each hormone compared to a standard curve--utilizing a Farrand fluorometer. Thus the hydrocortisone or corticosterone extracted from the plasma can be quantitated.

The proportion of each hormone which was lost in the process of extraction and separation can be determined by comparing the radioactive labelled hormone recovered in the ethanolic eluate to the original labelled hydrocortisone or corticosterone added, by the use of a scintillation counter. It is assumed that the added labelled hormone and the hormone present originally are lost in the same proportion during the extraction and elution.

Before using the technique on samples of patients' blood, practice determinations were done on samples of plasma with

known amounts of added labelled hydrocortisone and cortico-
sterone until about 75% of the radioactive steroid was re-
covered and there was close agreement of duplicate values.

Clinical Summaries

The hospital record unit-numbers are given in parentheses, following the patient's initials. All significant clinical and laboratory data at the time the blood was drawn are listed. The adrenal cortices were within normal limits in all autopsied cases. All temperatures were taken rectally.

Acute myocardial infarctions:

1. I.B.(87942), was a 73 year old blind white man with a history of angina for 5 years and auricular fibrillation for 2 years. Two weeks before admission he developed an increasing need for nitroglycerin. He then had severe oppressive chest pain unrelieved by nitroglycerin, profuse sweating, and a relative fall in blood pressure. Admission EKG showed a wandering pacemaker and serial EKG's showed the evolution of a posterior-lateral infarct. He had no fever or leucocytosis at anytime during his hospital course, and was discharged after 25 days.

   $F=19.7$; $B=2.8$: 26 hours after onset of pain, while patient was in O_2 tent.
   $F=18.1$; $B=3.8$: 13 days after onset of pain. Good clinical condition.

2. T.B.(27670) was a 43 year old Negro man with no history of heart disease. Three days before admission he had severe, crushing substernal pain and stopped work, went home, and rested. One hour before admission he had a similar pain, radiating to the neck and left arm, weakness, profuse sweating, and relative hypotension. His blood pressure fell to 50 by palpation, but his pulse never rose above 80. He had no other signs of shock. By the 10th hospital day his blood pressure was 110/70 and remained at that level until his discharge on his 21st hospital day. He never had a leucocytosis, but his fever reached a peak of 102° on the 2nd day. Serial EKG's showed evolution of a posterior-septal infarct. Serial measurement of transaminase and lactic dehydrogenase showed a peak on the 3rd hospital day.

2.   T.B.(27670) con't.
     F=12.5; B=3.6: 14 hours after 2nd pain, appearing very
                    acutely ill. Pulse was 80. B.P. was
                    50 by palpation.
     F=6.9; B=10.3: 10 days after admission, in good clini-
                    cal condition.

3.   F.J.(452180) was a 63 year old white man with angina
     for 6 years and was admitted because of 4 episodes of
     severe angina in one day. He had intermittent fever
     up to 101° for the first 10 days. On the 10th day he
     developed severe chest pain and EKG's (previously normal)
     showed acute posteriolateral infarction. A typical evolu-
     tionary pattern and right bundle branch block developed.
     No fever or leucocytosis developed and he was discharged
     after 27 days in the hospital.

     F=14.6; B=0.5: 3 hours after pain and EKG changes.
                    Patient appeared well.
     F=5.4; B=0:   11 days after this attack; good clini-
                    cal condition.

4.   W.K.(450991), a 37 year old white conductor, had angina
     for 4 years and a proved myocardial infarction 4 months
     previously. He had typical chest pain, shock, leucocy-
     tosis, fever up to 103° on the 3rd day, and evolution of
     a posterior infarct by serial EKG's. His course was
     marked by a pleural effusion, occasional vomiting and a
     varying heart block. He was discharged against advice
     on the 12th day.

     F=37.9; B=5.6: 24 hours after onset of pain; acutely ill;
                    B.P. was 120/100 on IV nor-epinephrine,
                    in O_2, temp=101°.
     F=17.2; B=5.4: 12 days after onset, in good clinical
                    condition and afebrile.

5.   R.E.(A97323), a 66 year old white man, had a similar
     attack 1 year ago, but the EKG was ambiguous. While
     walking, he had severe substernal pain, severe dyspnea,
     profuse sweating, and was given O_2 by firemen. On
     admission he had hypotension, basilar rales, and WBC
     of 12,000. EKG showed an old posterior infarction and
     acute anterioseptal infarction, but evolving pattern
     was obscured by old infarction. He had no fever through-
     out his 21 day course.

     F=8.2; B=1.7: 26 hours after onset of pain. Good clini-
                   cal condition.
     F=7.5; B=0:   13 days after onset, in good clincal
                   condition.

6. F.M.(C34889), a 54 year old obese white man, had hypertension for 9 years, and an anterior myocardial infarction 6 years previously, followed by dyspnea on exertion, orthopnea, periodic ankle edema and angina ever since. He had a sudden onset of severe substernal and left shoulder pain, nausea, sweating, increased dyspnea, and relative hypotension. His 27 day course was marked by leucocytosis up to 14,00 on the 3rd day, rectal temperature peak of 100° on the 2nd day, and EKG's showing LVH and evolution of an acute posterior infarction. Butanol extractable iodine was 3.1 micrograms %; total cholesterol was 308 mg.% of which 28% was free cholesterol. Fatty acids were 18 mg.%.

   F=17.0; B=3.3: 5 hours after onset of pain. He was
                  slightly dyspneic and had basilar rales.
   F=9.9; B=2.3: 13 days after onset of pain, in good
                  clinical condition.

7. A.Mc.(B78290-Autopsy 12102), a 68 year old white woman had a 5 week history of angina, which was worse on the day of admission. She had a knife-like pain in the chest both arms, sweating, and a feeling of impending death. EKG showed an acute anterior infarction. WBC was 15,000 on the 2nd day; the fever peak was 101.5° on the 2nd day. Her 29 day course was complicated by episodes of ventricular tachycardia and premature beats, treated with quinidine and pronestyl, and a hypotensive episode on the 2rd day which responded to IV fluids. She died suddenly on the 29th day, probably because of ventricular fibrillation. Autopsy was unremarkable except for organizing infarct and recent thrombus in the coronary arterial branch supplying the area.

   F=35.3; B=5.2: 14 hours after onset of pain, in O2,
                  occasionally vomiting.
   F=27.9; B=0.6: 24 days after onset, in good clinical
                  condition, 1 day before she had a return
                  of vomiting and daily fever spikes, which
                  continued until her death.

8. P.Mc.(B78290), was a 57 year old white man who had had hypertension for at least 6 years, a posterior infarction 2 years previously, intermittent claudication for several months, and chest and shoulder pain similar to that with previous infarction for 5 days. He had an increase in chest pain, severe dyspnea, faintness, and sweating the day before admission. His course was complicated by calf tenderness, increasing dyspnea and pulmonary edema and congestion, enlarged tender liver and venous distension not controllable by digitoxin, and disorientation. He gradually became comatose and extremely dyspneic and expired on the 33rd day. Cause of death

8.   P.Mc.(B78290) con't.
     was felt to be recurrent pulmonary emboli but an autopsy
     was not done. EKG's showed an evolving acute antero-
     septal infarction. WBC was highest (15,000) on day of
     admission and the peak of his fever was 101° on the 1st
     day.

     F=14.3; B=0.4: 36 hours after the increase in pain,
                    patient was alert and appeared in good
                    condition. Temp=100°
     F=15.0; B=0:   10 days after onset. He was wheezing
                    slightly but otherwise in good condition.

9.   M.P.(455786), was a 76 year old white woman who had had
     diabetes for 15 years, and a posterior infarction 5 years
     previously, followed by angina and occasional ankle edema.
     She had increasing anginal pain for 3 days before admis-
     sion, then a dull ache substernally and in left arm and
     neck, not relieved by nitroglycerin and similar to the
     pain of her previous infarct. She had hypotension and
     slight pulmonary edema on admission. She had no leucocy-
     tosis, but had a fever peak of 102° on the 1st day.
     Serial EKG's showed signs of her old infarct and a new
     evolving anterior septal infarct.

     F=9.9; B=1.0: 16 hours after onset of pain, in good
                    clinical condition except for temp=101°.
     F=13.0; B=1.2: 14 days after onset, appeared more weak
                    and chronically ill than previously, but
                    no objective evidence of a change in her
                    clinical condition.

10. M.V.(C45468), was a 59 year old obese Portugese man with
     a history of hypertension for 10 years angina and several
     episodes of paroxysmal nocturnal dyspnea in the last year.
     He had a burning retrosternal pain, dyspnea, dizziness
     and a feeling of suffocation on the day of admission and
     was found to have a few moist basilar rales and a gallop
     rhythm. He had daily fever peaks of 100° for the first
     week but no leucocytosis. Serial EKG's showed an evolv-
     ing anteriolateral infarct. He was discharged after
     17 days.

     F=14.8; B=1.2: 18 hours after onset; good clinical
                    condition.
     F=9.5; B=.0: 11 days after onset; good clinical
                    condition.

11. C.P.(C49305--Autopsy 11873), was a 63 year old Negro man
     with a questionable infarct 4 months previously. He had
     dull anterior chest pain radiating to the right shoulder,
     but denied other symptoms. On admission he had a gallop

11.   C.P.(C49305--Autopsy 11873) con't.
rhythm, hypotension and sweating. He had no fever or
leucocytosis on admission. On the 4th day he had a
psychotic episode, shouting for the police, and on the
6th day fell out of bed, cutting his scalp. He had
pneumonia, with bloody sputum and fever spikes of 102-
104° from the 10th day until his death on the 33rd day.
Autopsy showed an old and a recent myocardial infarct,
pulmonary infarcts, a cerebellar infarct, and a lung
abscess. Early EKG's were suggestive of an acute infarct
but the typical evolutionary pattern did not occur until
between the 10th and 20th day.

   F=16.5; B=2.1: 38 hours after onset of pain; during
                  episode of lethargy and hypotension,
                  relieved by demerol. Afebrile.
   F=18.9; B=8.7: 12 days after onset; pneumonia, temp=101°
                  but appearing more alert than before.

Other cases of acute anterior chest pain:

Acute Coronary Insufficiency:

1.   A.N.(63558--Autopsy 11883), was a 64 year old white
woman with hypertension for 4 years and an infarct
4 years previously, followed by angina and progressive
orthopnea. One year previously she had been admitted
for acute coronary insufficiency without a proved in-
farction. She had 2 weeks of increasing angina, worse
on the day of admission, when she also had increased
sweating, dyspnea, orthopnea, relative hypotension,
and moist basilar rales. She had a fever of 100° for
the first 8 days and an eleveated WBC of 12,000 on the
1st day. She had several bouts of angina during her
19 days in the hospital. Admission EKG showed acute
ischemia and a prolonged P-R internal, but serial trac-
ings showed no signs of evolving infarct. Four weeks
after discharge she had an acute infarction and died
immediately after admission, probably with ventricular
fibrillation. Autopsy showed myocardial scarring and
old and recent coronary occlusion.

   F=5.6; B=3.7: 36 hours after onset of pain, in good
                  clinical condition except for a few
                  moist basilar rales.
   F=17.6; B=0.2: 11 days after onset; appeared in good
                  condition.

2.   P.L.(450899), was an 81 year old white man with an
infarct 4 years before, right-sided heart failure for

2.   P.L.(450899) con't.
     2 years, and a leg amputated for gangrene 1 year before.
     He had severe, crushing chest pain, radiating to neck
     and shoulders, nausea, sweating, and suffocation. On
     admission he had occasional gallop rhythm, premature
     ventricular beats and moist basilar rales. His tempera-
     ture was 100° for the first six days and spiked to 103°
     on the 7th day. WBC was 15,000 on the 1st and 4th day.
     Serial EKG's showed an old posterior infarct and chang-
     ing diphasic and inverted T waves, and was suspicious of
     an infarct, but not diagnostic. He was discharged after
     12 days.

     F=27.0; B=2.0: 38 hours after onset. Temp=100°, "alert,
                    agile, talkative".
     F=10.1; B=6.2: 12 days after onset; afebrile but appear-
                    ed lethargic.

3.   F.Z.(A82615), a 55 year old white man, had angina for 2
     years, with attacks progressing in frequency for the 2
     weeks before admission. He was admitted with severe sub-
     sternal pain, sweating, nausea, and a brief relative
     hypotension. He had slight edema, moist basilar rales.
     He had on admission temperature of 100.5° but was afe-
     brile and asymptomatic throughout his uneventful 13 day
     course. Serial EKG's showed depressed S-T segments and
     inverted T waves, but no changes diagnostic or suggestive
     of acute infarction.

     F=10.8; B=0: 19 hours after onset, in good clinical
                  condition.
     F=8.2; B=0: 9 days after onset, in good clinical
                  condition.

4.   A.S.(B13250), was a 53 year old white man with a history
     of an infarct 9 years before with occasional angina after-
     wards. He was admitted with a history of increasing
     dyspnea for 3 weeks and persisent angina, orthopnea, and
     moderately severe dyspnea on the day of admission.
     Digitalization and bed rest led to a diuresis and 10 lb.
     weight loss. He was discharged after 7 days, with a
     diagnosis of angina, cardiac insufficiency, and pulmon-
     ary edema. Two EKG's were unremarkable. No fever or
     leucocytosis.

     F=20.2; B=1.6: 24 hours after onset of pain; markedly
                    orthopneic but otherwise in good condition.

Pulmonary Infarctions:

5. C.C.(30246), was a 66 year old white man with a 6 year
    history of hypertension and angina for 4 months. Before
    admission he had acute anterior chest pain, dyspnea, and
    sweating. This subsided after 8 hours. and he was free
    of pain for 6 hours, after which he had another similar
    episode with radiation of pain down both arms. He was
    given O_2, and his 21 day course was uneventful. Serial
    EKG's were suggestive of an acute infarction, but were
    obscured by idioventricular complexes. Review of trac-
    ings led to EKG diagnosis of pulmonary emboli. He had
    no fever or leucocytosis.

    $F=15.3$; $B=0$: 18 hours after onset of pain; in good
    clinical condition.
    $F=5.6$; $B=0$: 15 days after onset; in good clinical
    condition.

6. J.W.(418425), was a 64 year old white man with a prob-
    able infarct 2 years before followed by left bundle
    branch block and pulmonary edema, but not confirmed by
    EKG. He had angina since then and two admissions for
    chest pain and dyspnea without EKG evidence of myocar-
    dial infarction. He had lues in 1935, ?x-ray evidence
    of aortitis and a murmur of aortic insufficiency. On
    admission he had acute substernal pain, dyspnea, sweat-
    ing slight ankle edema, and a tender enlarged liver.
    He had a history of thrombo-phlebitis 6 months before
    and on admission had palpable calf veins and diffuse
    moist inspiratory rales and expiratory rhonchi. On the
    1st day he had x-ray evidence of a right lower lobe
    pulmonary infarct. He died on the second day with acute
    pulmonary edema. EKG showed ectopic ventricular focus,
    ST-depression and T wave inoersion. WBC was 11,500.
    No fever. No autopsy was done.

    $F=14.3$; $B=5.6$: 12 hours after onset of the pain, patient
                  was orthopneic, slightly dyspneic at rest,
                  18 hours before death.

Pulmonary Edema and Trauma:

7. S.H.(453986), was a 63 year old white man with a history
    of occasional dependent edema, and episodes of dyspnea
    for 5 years, and a fractured arm 5 weeks before admission.
    He was admitted in moderate pulmonary edema with slight
    cyanosis, after being struck by an auto. He had a fever
    of 101° for 7 days and then was afebrile for the rest of
    his 38 day hospital course. He had no leucocytosis. He
    had a moderate anemia and lethargy for his entire course,

7. S.H.(453986) con't.
    but no conclusive diagnosis was reached. EKG's on the
    first 2 days were unremarkable.

    F=28.0; B=0: 5 hours after the accident; temp=101°;
                 apathetic and orthopneic.
    F=2.0; B=0: 22 days after onset; apathetic, but no
                 clinical findings.

Anxiety Reaction; ? Gastritis:

8. D.C.(451376), was a 34 year old white ambulance driver
    with no history suggestive of cardiovascular disease.
    Two days before admission, following heavy drinking, he
    had oppressive retrosternal pain, nausea, and vomiting.
    The physical exam, laboratory studies, EKG, and 2 day
    hospital course were unremarkable. Three days after
    discharge he returned to the outpatient clinic with abdo-
    minal discomfort and a history suggestive of a mild
    gastritis.

    F=20.6; B=1.3: 3 days after onset of pain and 1 hour
                   after he had been assured he did not
                   have a "heart attack", which he had
                   thought had happened.

Acute Benign Pericarditis:

9. P.A.(44893), was a 37 year old white man with no history
    of cardiovascular disease. He was awakened by a sharp
    retrosternal pain, aggravated by breathing or leaning
    forward, and a shaking chill. He had had a similar pain
    5 months previously and a respiratory infection 2 weeks
    before. Physical exam, laboratory studies and 13 day
    hospital course were unremarkable. The clinical diagno-
    sis was acute benign pericarditis; other causes of peri-
    carditis were ruled out.

    F=3.5; B=0.2: 12 hours after onset of pain.

Cyanosis; Anoxia:

10. M.W.(449973--Autopsy 11890), was a 48 year old white
     female with a long history of chronic pulmonary disease
     and a previous episode of CO_2 of 37 mEq/L, weakness and
     black outs. She was put in a respirator on 3 occasions
     and required a tracheotomy and thyroid therapy because
     of a butanol-extractible iodine of 1.2 micrograms%.
     She was in critial condition throughout her 35 day course

10. M.W.(449973--Autopsy 11890) con't.
     with respiratory rates from 20 to 50 per minute, CO_2
     values from 37 to 40 mEq/L, and bouts of cyanosis.
     Autopsy showed pulmonary fibrosis and emphysema, cor
     pulmonale, and a fibrotic thyroid gland.

     $F=27.2$; $B=0.4$: on 24th hospital day; slight cyanosis, in
                        respirator, blood pressure maintained by
                        I.V. nor-epinephrine; CO_2 was 39; she had
                        received 25 mg. of tri-iodotyrosine once.
     $F=26.1$; $B=2.0$: on 31st day, slight cyanosis. Not in
                        respirator; comatose, anuric; blood pres-
                        sure was 60/20, maintained on nor-epine-
                        phrine. Had had 7 days of tri-iodosine
                        therapy. CO_2 was 34. Respirations were
                        50 per minute.

Summary of Laboratory Data

Patient	Plasma extracted	Radioactive F recovered	F values	Average of F duplicates	Radioactive B recovered	B values	Average of B duplicates
	ml.	%	µg%	µg%	%	µg%	µg%
P.A.(1)*	18.5	56.2	2.18	3.5	51	0.4	0.4
	18.5	68.0	4.92		0		
T.B.(1)	25.0	50.0	12.5	12.5	50	3.6	3.6
(2)	20.0	111.	6.9	6.9	88	10.3	10.3
I.B.(1)	17.5	69.8	19.1	19.7	37	5.7	2.9
	17.5	63.8	20.2		41	0	
(2)	20.0	55.2	19.2	18.1	29	4.15	3.3
	18.0	67.8	17.0		51	3.4	
C.C.(1)	20.0	103.	13.4		68	0	0
	7.0	65.6	17.2	15.3			
(2)	15.0	85.5	4.5	5.6	67	0	0
	15.0	79.5	6.6		68	0	
D.C.(1)	17.1	68.8	20.9	20.6	69	0	1.4
	17.1	62.2	20.3		76	2.7	
R.E.(1)	20.0	64.5	9.9	8.2	81	2.7	1.7
	20.0	86.5	6.5		72	0.75	
(2)	20.0	90.5	8.5	7.5	69	0	0
	18.5	86.5	6.5		56	0	
S.H.(1)	20.0	96.4	28.0	28.0	99	0	0
(2)	20.0	55.8	6.9	2.8	50	0	0

* Numbers in parentheses refer to the acute (1) and convalescent(2) plasma.

µ.g.% = micrograms / 100 ml. plasma

Patient	Plasma extracted	Radioactive F recovered	F values	Average of F duplicates	Radioactive B recovered	B values	Average of B duplicates
	ml.	%	μg%	μg%	%	μg%	μg%
F.J.(1)	19.0	56.7	15.8	14.6	68	1.0	0.5
	19.0	79.4	13.4		70	0	
(2)	20.0	85.0	4.7	5.4	57	0	0
	20.0	63.0	6.0		61	0	
W.K.(1)	17.8	50.7	37.4	37.9	61	3.2	5.6
	10.0	52.4	38.4		65	8.0	
(2)	20.0	63.6	16.2	17.2	50	6.4	5.4
	18.0	72.3	18.1		64	4.45	
P.L.(1)	19.1	68.7	27.0	27.0	98	0.3	2.0
					25	3.8	
(2)	25.0	40.0	5.9	10.1	65	4.4	6.2
	25.0	44.3	14.4		46	8.0	
A.Mᶜ(1)	15.0	79.5	40.6	35.3	75	3.7*	5.2*
	15.0	75.6	30.0		68	6.7*	
(2)	15.0	61.6	25.3	27.9	58	0.4*	0.6*
	15.0	69.6	30.6		64	0.9*	
P.Mᶜ(1)	15.5	117	12.3	14.3	74	0	0.4
	16.0	114	16.2		83	0.7	
(2)	21.0	69.3	13.8	15.0	57	0	0
	21.0	70.6	16.3		53	0	
F.M.(1)	21.5	59.5	17.2	17.0	71	4.2	3.3
	21.5	51.6	16.9		43	2.4	
(2)	18.9	49.3	9.9	9.9	44	2.9	2.2
					68	1.5	
A.N.(1)	20.0	27.8	7.5	5.6	43	3.9	3.7
	19.4	69.5	3.7		53	3.5	
(2)	20.0	85.0	17.4	17.6	79	0.4	0.2
	20.0	83.2	17.8		98	0	

*=Sweat's method of sulfuric acid fluorescence was used.

Patient	Plasma extracted	Radioactive F recovered	F values	Average of F duplicates	Radioactive B recovered	B values	Average of B duplicates
	ml.	%	μg%	μg%	%	μg%	μg%
C.P.(1)	15.0	82.6	16.5	16.5	64	2.1	2.1
(2)	14.5	35.1	18.9	18.9	64	8.7	8.7
M.P.(1)	14.0	71.6	9.7	9.9	65	1.4*	1.0
	14.0	69.6	10.1		72	0.6	
(2)	20.0	77.3	11.5	13.0	73	0.9	1.2
	20.0	25.3	14.5		29	2.3	
A.S.(1)	17.5	63.8	20.2	20.2	81	3.1	1.6
	17.5	lost			65	0	
M.V.(1)	22.0	69.1	11.5	14.8	74	1.2	1.2
	22.0	68.5	18.2		69	1.2	
(2)	17.5	90.2	10.5	9.5	65	0	0
	17.5	78.7	8.4		55	0	
J.W.(1)	19.4	48.8	14.4	14.3	56	8.1	5.5
	19.4	63.0	14.2		67	3.0	
M.W.(1)	24.0	55.9	25.2	27.2	82	0.67	0.4
	24.0	62.3	29.2		92	0.21	
(2)	17.0	97.0	23.0	26.1	73	1.8	2.0
	17.0	82.5	29.2		80	2.2	
F.Z.(1)	14.5	64.9	8.9	10.8	87	0	0
	14.5	54.2	12.6		82	0	
(2)	15.0	83.1	6.5	8.2	98	0	0
	15.0	81.8	9.9		90	0	

*=Sweat's method of sulfuric acid fluorescence was used.

Table 1:   Normal Values of Plasma hydrocortisone and corticosterone using Bondy's method.(30,67a)

	Number of Subjects	micrograms/100 ml. plasma	
		Range	Mean $\pm$ S.D.
Hydrocortisone (cortisol)	33		8.1 $\pm$ 3.6
	29	4-17.7	10.2 $\pm$ 3.6
Corticosterone	29	0-5.0	1.3 $\pm$ 2.5

$$S.D. = \sqrt{\frac{\text{sum of (mean-each value)}^2}{\text{number of values} - 1}}$$

Table 2: Plasma hydrocortisone

Acute myocardial infarctions:

Case No.	Age & Sex	Plasma F in micrograms/100 ml.		
		Days after onset		
		1 -- 2	10-14	24-31
1.	73M	20	18	
2.	43M	13	7	
3.	63M	15	5	
4.	37M	38	17	
5.	66M	8	8	
6.	54M	17	10	
7.	68F*	35		28
8.	57M*	14	15	
9.	76F	10	13	
10.	59M	15	10	
11.	63M*	17	19	
Mean ± S.D.		18±10	12±5	

Control Cases:

Case No.	Age & Sex	Plasma F in micrograms/100 ml.		
		Days after onset		
		1 -- 2	10-14	24-31
1.	64F	6	18	
2.	81M	27	10	
3.	55M	11	8	
4.	53M	20	---	
5.	66M	15	6	
6.	64M*	14	---	
7.	63M	28		2
8.	34M	21	---	
9.	37M	4	---	
10.	48F*			27 26
Mean ± S.D.		16±9	10±5	

*=fatal cases

Table 3: Plasma corticosterone

Acute myocardial infarctions:

Case No.	Age & Sex	Plasma B in micrograms/100 ml.		
		Days after onset		
		1 -- 2	10-14	24-31
1.	73M	2.8	3.8	
2.	43M	3.6	10.3	
3.	63M	0.5	0	
4.	37M	5.6	5.4	
5.	66M	1.7	0	
6.	54M	3.3	2.3	
7.	68F*	5.2		0.6
8.	57M*	0.4	0	
9.	76F	1.0	1.2	
10.	59M	1.2	0	
11.	63M*	2.1	8.7	
Mean ± S.D.		2.5±1.8	2.9±3.8	

Control Cases:

Case No.	Age & Sex	Plasma B in micrograms/100 ml.		
		Days after onset		
		1 -- 2	10-14	24-31
1.	64F	3.7	0.2	
2.	81M	2.0	6.2	
3.	55M	0	0	
4.	53M	1.6	---	
5.	66M	0	0	
6.	64M*	5.6	---	
7.	63M	0	0	
8.	34M	1.3	---	
9.	37M	0.2	---	
10.	48F*			0.4;2.0
Mean ± S.D.		1.6±2.0	1.3±2.8	

0= less than 0.1 μ.g.%

*=fatal cases

Table 4: F/B ratio

Case	Diagnosis	F/B ratio	
		Acute 1st or 2nd day	Convalescent 10th-31st day
W.K.	Acute M.I.	6.8	3.2
A.Mc	" "	6.8	46.5
M.P.	" "	9.9	10.8
M.V.	" "	12.3	(95)
I.B.	" "	6.8	4.8
R.E.	" "	4.8	(75)
P.Mc	" "	35.8	(150)
F.J.	" "	29.2	(54)
T.B.	" "	3.5	6.7
F.M.	" "	5.2	4.5
C.P.	" "	7.8	2.3
A.N.	Coron. insuff.	1.5	70
F.Z.	" "	(108)	(82)
P.L.	" "	13.5	1.6
C.C	" "	(153)	(56)
A.S.	" "	12.6	———
J.W.	Pulm. emboli.	2.6	———
D.C.	Anxiety reation	1.5	———
S.H.	Trauma & Pulm. edema	(280)	(28)
P.A.	Benign pericarditis	87.5	———
M.W.	Chronic pulm. dis. with anoxia, shock	———	68.0;13.0

If B = 0, it was calculated in all cases as 0.1 μ.g.%.

( ) = calculated from a B value of 0.1 μ.g.%.

Table 5: Hydrocortisone and corticosterone levels in patients that appeared very critically ill at the time of venipuncture.

Patient	Condition at time of measurement	plasma F in u.g.%	plasma B in u.g.%
T.B.	b.p. = 50 by palpation; (eventually rose to 110/70) no other signs of shock, except drowsiness. Adm. EKG showed extensive myocardial infarct.	12.5	3.6
W.K.	b.p. = 120/100 on I.V. nor-epinephrine; in O_2 tent; T=101°. Adm. EKG showed extensive infarct.	37.9	5.6
A.M^C.	in O_2 tent; occasionally vomiting; T=100°; Adm EKG showed severe infarct with repeated bouts of premature beats and ventricular tachy-cardias.	35.3	5.2
M.W.	slightly cyanotic; in res-pirator; b.p. maintained by I.V. nor-epinephrine.	27.2	0.4
" "	b.p. 60/20 on I.V. nor-epinephrine: anuric and coma-tose; slightly cyanotic, not in respirator.	26.1	2.0
C.P.	during episode of unrespon-siveness and hypotension (rapid soft pulse, b.p. 80/20) pitting edema of arms and legs.	16.5	2.1
	Mean ± S.D.	25.9 ± 10.0	3.3 ± 2.1
	Mean of all other values in this study	14 ± 7	2.0 ± 2.6

Table 6: Nine hydrocortisone and corticosterone determinations in the five fatal cases

Case	Remarks	plasma F in u.g.%	plasma B in u.g.%
A.M^c 68F	myocard. infart.; 14 hours after onset.	35.3	5.2
" "	24 days after onset; 5 days before death from ventric. fibrillation.	27.9	0.6
P.M^c 57M	myocard. infarct.; 36 hours after onset.	14.3	0.4
" "	10 days after onset; 23 days before death from recurrent pulm. emboli.	15.0	< 0.1
C.P. 63M	myocard. infarct; 38 hours after onset.	16.5	2.1
" "	12 days after onset during bout of pneumonia; 21 days before death from lung abscess and pulm. infarcts.	18.9	8.7
J.W. 64M	Pulm. infarcts.; 12 hours after onset; 18 hours before death; in acute pulm. edema.	14.3	5.6
M.W. 48F	chronic pulm. insufficiency; hypothyroidism; 24th hosp. day; in shock, cyanotic.	27.2	0.4
" "	4 days before death from respiratory and right heart failure; in shock, comatose.	26.1	2.0
	Mean ± S.D.	21.8 ± 7.8	2.8 ± 3.0

Discussion

Hydrocortisone values (Table 2.):

The mean plasma hydrocortisone level for myocardial infarctions and for control cases did not differ significantly from each other in the first two days of hospitalization. There were two cases of myocardial infarction with high hydrocortisone levels of 35 and 38 μ.g.%, but these were severe infarctions which presented no diagnostic problem in the original clinical examination and electrocardiogram. In nine cases in which the diagnosis was doubtful in the first three days of the illness, the plasma hydrocortisone levels in this early period ranged from 6-28 μ.g.%, with two non-infarcts having the two highest values:

Non-infarcts		Infarcts	
case	F level	case	F level
C.C	15	I.B.	20
F.Z.	11	M.P.	10
A.N.	6	P.MᶜC	14
P.L.	27		
S.H.	28		
J.W.	14		

Thus, in this series, the plasma hydrocortisone levels were not useful in establishing the early diagnosis of myocardial infarction in doubtful or borderline cases.

The mean value for plasma hydrocortisone in 62 normal healthy individuals was 9.1 ± 3.6 μ.g.% (Table 1.). The mean values for both infarcts and controls were significantly

elevated during the acute phase of the illness, and were almost double the normal mean value. After ten days of hospitalization, presumably during a period of convalescence, both the mean control and infarct hydrocortisone levels were only slightly elevated above the normal mean. This suggests that, in general, hydrocortisone levels are high in the acute phases of a disease and fall to normal during convalescence.

In nine determinations done on five patients who died of their disease, four of the hydrocortisone levels were above 26 μ.g.%, but four were within the normal range of 4-18 μ.g.%. (Table 6) The level found in the determination made nearest to the time of death was 14.3 μ.g.%, done eighteen hours before death of acute pulmonary edema. Most of the fatal cases terminated suddenly. Only one case (M.W.) corresponded to the group of chronically ill, slowly dying patients who had high plasma 17-hydroxycorticosteroids values immediately before death.(63) Several non-fatal cases also had high values, so the hydrocortisone level was not useful in predicting which cases would be fatal.

During the early acute phase of the two cases of myocardial infarction previously mentioned, the hydrocortisone levels above 35 μ.g.% corresponded to a very severe clinical condition. However, the values were within the normal range of 4-18 μ.g.% in two other cases of acute infarction that were also in a critical clinical condition at the time the blood was drawn. (T.B.; C.P.--See Table 5) One subnormal value of 3.5 μ.g.% was obtained 12 hours after the onset of the acute pain of

acute benign pericarditis. A high value of 20.6 µ.g.% was found in a case of "cardiac anxiety". Hence we can conclude that the hydrocortisone level during the acute phase of an illness is elevated as a rule, although not always to a degree consistent with the clinical severity.

F/B ratio (Table 4.):

The hydrocortisone/corticosterone ratios in these patients showed a wide range--from 1.5 to 280. If those values of corticosterone which were 0.1 µ.g.% or less are excluded, the range of all the F/B ratios was 1.5 to 87.5, and the median and the mode were both 6.8. The F/B ratio for a given individual was not constant, and there was no inverse dissociation of the hydrocortisone and corticosterone levels as suggested by Elman.(73) The actual level of corticosterone in the plasma seems to be a more useful figure than the F/B ratio.

Corticosterone values (Table 3.):

The mean values of plasma corticosterone were lower than the mean values for hydrocortisone. The range of plasma corticosterone was from zero to 10.3 µ.g.%. In all determinations in which levels of zero (less than 0.1 µ.g.%) were found, the added labelled corticosterone was recovered in good proportion.

The mean corticosterone value in the acute phase of eleven infarcts was 2.5 ± 1.8 µ.g.%, compared with a normal mean of 1.3 ± 2.5 in 29 normal persons. No myocardial infarction in the acute phase had a corticosterone level of zero, although this hormone was often not detected in other situations.

The mean value in 6 determination of Compound B in situations in which the patient appeared very critically ill at the time the blood was drawn was 3.8 ± 2.1 u.g.%--which is significantly higher than the normal mean (P>.02), but not significantly higher than the mean of all the other corticosterone values measured in this series. The mean Compound B value in the acute phase of infarction was also not significantly higher than the mean of all other B values in this series. The three highest plasma corticosterone values (6.2, 8.7, and 10.3 u.g.%) were all found at least ten days after admission to the hospital.

On the basis of these experiments it can be concluded that in the early stages of a myocardial infarction and during a time when a patient clinically appears critically ill, corticosterone is not significantly elevated above the level which might be found at any other time in the course of the same hospitalized patient. One explanation for this finding is that an acute illness does not increase the secretion of corticosterone by the adrenal cortex. An alternative explanation is that because of the rapid disappearance of corticosterone from the blood stream, no elevation or only a transient elevation of plasma level occurs. This disappearance might be due to increased reduction or conjugation or more rapid utilization of corticosterone during "stress". It is also possible that blood samples were not obtained soon enough after the onset of the acute illness to detect any elevated corticosterone levels which may have been present. Nevertheless, if the stimulus for adrenal secretion of corticosterone occurs repeatedly during the

first 24 hours of an acute illness, we might have expected to find at least one very high corticosterone value among the determinations made during this acute period.

Many more plasma corticosterone determinations in various clinical situations and more experiments on the conjugation and utilization of corticosterone by humans will be necessary to determine conclusively the stimulus for secretion and the function of this hormone in man.

Summary

1. The general problems of the rationale, methods, and significance of the measurement of plasma adrenocortical hormones are discussed.

2. The history of the methods of measuring the function of the adrenal cortex is outlined, with particular emphasis on the evolution of the technique used in this thesis.

3. The results of other clinical studies on plasma levels of hydrocortisone (Compound F) and corticosterone (Compound B) and on adrenal cortical function in myocardial infarction are summarized.

4. The plasma hydrocortisone and corticosterone levels were measured in 21 patients--11 with EKG-proved acute myocardial infarctions and 10 control cases with acute chest pain from other causes.

5. The mean hydrocortisone levels were elevated to about the same degree in the acute phases of the myocardial infarction and the controls: 18 ± 10 and 16 ± 9 μ.g.% respectively, with a normal value in this laboratory of 9.1 ± 3.6 μ.g.%. After 10 days in the hospital, the values fell to near normal levels in both infarcts and controls.

6. It was concluded that the plasma hydrocortisone level is of little value in distinguishing which patients will die or in distinguishing which patients have myocardial infarcts if there is a difficult problem of differential diagnosis. In general, the hydrocortisone levels are normal in convalescence and elevated in the acute phase of an illness to a degree proportional to the clinical severity of the disease, although there were a few exceptions.

7. The F/B ratios showed a wide range with no regular patterns, and it was concluded that this ratio is a less useful measurement than actual Compound B levels.

8. The mean corticosterone level in the acute phases of myocardial infarctions was 2.5 ± 1.8 μ.g.%; in six selected determinations where the patient appeared critically ill, 3.8 ± 2.1; in all other cases except these last six, 2.0 ± 2.6; and in normal persons, 1.3 ± 2.5 μ.g.%.

9. It was concluded that the plasma corticosterone level in
    acutely ill patients is not elevated above those values
    which might be found at any other time in the patient's
    hospital course. This absence of elevated corticosterone
    levels may be due to absence of increased secretion
    during acute illness or to rapid disappearance from the
    blood stream due to increased conjugation or utilization.

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