think that mitral valvotomy should be undertaken in suitable centres even where cardiac catheterization is not available.

Mitral valvotomy should be considered in all patients with mitral stenosis who are progressively disabled. Orthopnoea and recurrent pulmonary oedema are special indications. The risk of recurrent rheumatic carditis in patients under 20 years of age should make one more hesitant, and the presence of active carditis is one of the few contraindications to operation.

It must also be considered as an alternative to termination of pregnancy and sterilization; it has been carried out successfully in three women during their pregnancies, which have then terminated normally.

Time alone will tell how long the improvement after mitral valvotomy can last and whether fibrosis or recurrent carditis will again lead to severe stenosis of the mitral valve. In the two or three years that have elapsed since the earliest operations there has been no evidence of relapse.

We wish to thank our many colleagues who have been actively interested in the wide problems of mitral stenosis and who have helped in the investigation and treatment of these patients. The Guy's group are particularly indebted to Dr. H. E. Holling, of the Medical Research Council Unit.

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ADRENAL CORTICAL FUNCTION AT DEATH AS MEASURED BY LEVEL OF CIRCULATING EOSINOPHILS

BY

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In recent years it has been shown that the chief function of the adrenal cortex is to aid the organism in adapting to stress, either internal or external (Selye, 1949, p. 111). When an organism is subjected to stress an "alarm reaction" is set up, according to the observations of Selye. It is during the countershock phase of this reaction that the adrenal gland is called into play. There is evidence of hyperfunction of the cortex of this organ as demonstrated anatomically and physiologically. There then ensues a stage of resistance during which this hyperactivity subsides and the organism shows signs of recovery. If, however, the stressor persists, the stage of exhaustion ensues and hyperactivity of the cortex again comes into play (Selye, 1946).

The evidence as presented by Selye (1946, 1949) to support these concepts is clear-cut and generally accepted. The picture becomes obscure about exactly what takes place in the adrenal cortex if the stress continues until the organism dies. There seems to be a question whether the stage of hypersecretion of cortical products continues until death ensues or if the opposite occurs and the cortex fails and the organism succumbs in a state of hypoadrenalism.

Grossly, the adrenal is heavier than normal and the cortex appears hypertrophied in animals and humans

dying after prolonged stress (Selye, 1937; Armstrong and Heim, 1938; Sarason, 1943; Tepperman *et al.*, 1943). This is not a positive indication, however, of hyperfunction of the gland at the time of death, since changes occurring previously might have persisted in spite of subsequent failure.

Sarason (1943) and Rich (1944) both describe histological changes in the adrenal glands of patients dying from acute illnesses which they interpret as resulting from an increased demand for adrenocortical hormones. Selye (1949, p. 852) describes similar degenerative changes, but also points to the cellular hypertrophy during the exhaustion stage which "may or may not be accompanied by an overproduction of corticoid substances" (Selye, 1946). The haemorrhagic changes in the adrenal following severe burns and in meningococcal infection (Waterhouse-Friderichsen syndrome) are well known (Hartman and Brownell, 1949).

It is obvious from these conflicting reports that morphological studies are inconclusive. Selye (1950, p. 299) summarizes by stating: "During the stage of exhaustion cytolytic phenomena, infarction and necrosis prevail; otherwise the changes resemble those seen in the alarm reaction (corticoid overproduction). A more detailed characterization is not yet possible, since comparatively few data are available concerning adrenal changes in this stage."

Adrenal functional studies during exhaustion are scarce. Selye (1950, p. 223) states: "Unfortunately, up to now no systematic investigations have been published concerning the urinary elimination of corticoids throughout the three stages of the general adaptation syndrome. Presumably, in the stage of exhaustion the adrenal function becomes deficient when the structure of the gland breaks down."

Selye (1950) noted, however, that in chronically ill and debilitated patients the corticoid secretion (p. 223) as well as the 17-ketosteroid excretion (p. 227) is low. He felt that this corresponded to the stage of resistance when corticoid secretion is less intense than during the alarm reaction. Almy *et al.* (1950), in a similar group, noted a poor eosinopenic response to adrenalin which led him to suspect that inadequate adrenal function may play a part in determining the course of illness. Furthermore, the clinical picture of the terminally ill debilitated patient resembles that of Addison's disease.

Thus the meagre evidence available at the present time suggests that the adrenal cortex breaks down during the exhaustion stage of the general adaptation syndrome, and this failure may be involved in, or even lead to, the death of the organism. On the other hand, the evidence is not unequivocally in favour of this hypothesis, and some of the studies seem to indicate that there is actually adrenal hyperfunction during this stage. A clarification of this enigma would have obvious clinical significance. If the adrenals were proved to be in a state of failure in the terminal stages of illness, treatment with the available cortical hormones would be expected to prolong life, and in some cases might actually prevent death by maintaining the resistance of the organism until the stress could be eliminated.

An accurate method for measuring adrenal cortical activity has been added to the medical literature—the measurement of the circulating eosinophil level (Thorn *et al.*, 1949). This index was used when functional studies were carried out during some phases of the adaptation syndrome. A pronounced eosinopenia

(which indicates adrenal hyperactivity) has been shown to occur during the alarm reaction, with a return to normal levels during the stage of resistance (Dalton and Selye, 1939). Selye (1950, p. 405) states, however, that "no systematic investigations [of haematological changes] have yet been carried through to the later periods of the stages of resistance and exhaustion."

In order to help clarify the functional status of the adrenal cortex during the final phase of exhaustion and at death, a study of the level of circulating eosinophils in a selected group of terminal cases was undertaken.

Methods and Materials

A total of 325 eosinophil counts were done on 116 individuals. These were divided into a control group and an experimental group (Table I). The latter consisted of

TABLE I.—Summary of Results

	No. of Patients	No. of Counts	Counts < 30/c.mm.	
			No.	%
Controls	54	108	11*	10
Experimental group:				
Survivors	12	75	39	52
Dead	50	142	105	74
Total	116	325	155	47.7

* Acutely ill patients.

62 moribund patients with a variety of diseases, and was further subdivided into 12 who survived and 50 who died. All patients were selected from the wards of the Atlantic City Hospital, the criterion for selection being the clinical impression that the patient was critically ill and probably would not survive.

Serial eosinophil counts (daily when feasible) were done up to the time of death or until the patient had recovered sufficiently to be sitting up in a chair. All patients who died had counts within 24 hours of death and as close to the time of death as possible. In five instances blood drawn from the jugular vein within one hour of death was used, since there was an exact correlation between the level of eosinophils immediately before death and the level within the four hours after death. This correlation was confirmed in a small series of patients.

TABLE II.—Comparison of Eosinophil Counts on Control Groups with Final Counts on Dying Patients

Group	No. of Patients	No. of Counts	Range		Average Eos./c.mm.	Stand. Dev.	% Below 30 Eos./c.mm.	Critical Ratio
			Low	High				
Control A	8	8	211	1,931	830	650	0	3.5
" B	15	15	44	272	149	63	0	8.3
" C	6	60	5.5*	471	116	84	8*	9.9
" D	25	25	0*	416	84	79	24*	4.8
Experimental	50	50	0	78	7.2	15	94	—

* Patients acutely ill or receiving A.C.T.H.

$$\text{Critical ratio} = \text{diff. between averages} \div \sqrt{\frac{(\text{stand. dev.})^2_{\text{control}}}{\text{Number (con.)}} + \frac{(\text{stand. dev.})^2_{\text{exp.}}}{\text{Number (exp.)}}}$$

Critical ratio of 3 or above establishes significance. (1,000 to 1 chance of results being reversed on a repetition of the experiment.)

The control group consisted of 54 patients, on whom 108 eosinophil counts were done (Table I). These patients were subdivided into four groups (Table II) as follows:

Group A consisted of eight individuals with a known allergic background and an eosinophilia as shown by peripheral blood smear. These were included merely to assure the reliability of our counting method.

Group B was made up of 15 healthy hospital employees selected at random.

The patients in Group C were selected as follows: six beds were picked at random from the medical ward and daily eosinophil counts were done on the next patient admitted to that bed.

Group D consisted of 25 patients selected at random by the haematology laboratory technician while doing routine blood counts throughout the hospital.

The stain and direct counting technique used was as outlined by Pilot (1950).

Investigations by Rud (1947) in Norway, who did 27,000 eosinophil counts, and Best and Samter (1951) in the United States have shown that there is a wide variation in the normal range of eosinophils (30–250 per c.mm.), with a mean of 126. Even though a count of 30 cells is considered eosinopenic by some authorities (Recant *et al.*, 1950), this was accepted as the lower limit of normal for this study.

The American authors also point out that there are rapid and appreciable short-term fluctuations as well as diurnal variations. In allergy, counts up to 1,500 were common and occasionally rose as high as 4,000 eosinophils per c.mm. However, normal individuals were found to maintain within broad limits the same general level of eosinophils over prolonged periods. The authors therefore conclude that the average change in a sufficiently large, homogeneous, well-controlled group should be a significant measure of pituitary-adrenal function (Best and Samter, 1951).

An attempt was made to determine the eosinophil level as close to the time of death as possible; consequently conditions such as fasting, time of day, etc., could not be controlled. However, counts were done at all times during the night and day and under a variety of conditions, and therefore should represent an unbiased sample.

Results. I: Control Group

A total of 108 eosinophil counts were done on 54 individuals, with the following results (Table I). Of the entire group only 10% had fewer than 30 eosinophils per c.mm.

FIG. 1.—Comparison of Results in Control Groups B, C, and D with the results in the experimental group. This graph shows that most of the counts in the control groups are normal, in contrast to the low counts in the patients who died.

Breakdown into subdivisions showed the following (Table II and Fig. 1):

Group A: Eosinophilia.—All subjects had a circulating eosinophil level above 200, the maximum being 1,931 per c.mm.

Group B: Healthy Hospital Personnel.—This group averaged 149 eosinophils per c.mm., with a range of 44 to 272.

Group C: Serial Counts on Six Patients Selected at Random.—The average count was 116 for this group, in spite of the fact that they were ill patients undergoing stress. Only five of the 60 counts were below 30, and four of these were on patients with a recent myocardial infarction, which is known to cause an eosinopenia (Recant *et al.*, 1950; Gabrilove, 1950).

Group D: Single Counts on 25 Patients Selected at Random.—This group averaged 84 eosinophils per c.mm., with over three-fourths of the patients having normal counts

in spite of the fact that many were acutely ill. This is actually a very poor group of controls, although (as with Group C) biased in the opposite direction, since it contained patients with the following conditions: ruptured appendix, one-day post-gastrectomy, spontaneous abortion, acute infections, and one patient who was receiving A.C.T.H. The entire 24% of eosinopenic results occurred in these patients, all of whom had conditions known to cause a reduction in eosinophils (Laragh and Almy, 1948; Davis and Hulit, 1949; Coppinger and Goldner, 1950; Gabrilove, 1950; Roche *et al.*, 1950).

The control group taken as a whole tends to correlate with previous studies (Rud, 1947; Best and Samter, 1951), and hence assures the validity of the technique used in this study. Furthermore, this group demonstrates that even in hospital patients, except when very acutely ill, a marked eosinopenia seldom occurs.

II: Moribund Patients

A total of 142 eosinophil counts were done on 50 moribund patients who succumbed to their illness: 94% (47 of 50) had fewer than 30 eosinophils per c.mm. on the day of death. In fact, 56% (28) had none and 82% (41) had a count of less than six. Tests of reliability were applied, the counts being compared at death with each of the control groups, and the differences were found to be statistically significant (Table II).

The three patients with counts above 30 were unique in that they all died suddenly though previously well. All three had been carrying on normal activity until less than five hours before death. It is felt that the eosinophil level had not had enough time to respond fully to the stress. It is probable that if they had lived a few more hours they too would have had an eosinopenia.

It is known that the normal eosinopenic response to adrenal cortical activity is a delayed one (Last *et al.*, 1950) with a gradual decline to subnormal levels over a period of hours (Forsham *et al.*, 1948). In fact, this decline is usually preceded by a transient eosinophilia (Forsham *et al.*, 1948).

FIG. 2.—Falling eosinophil level in a dying patient. This patient died in a few hours from a cerebral haemorrhage. This is an accelerated example of the typical eosinopenic response found in the patients who died. The two-hour level may represent the end of the initial eosinophilia usually demonstrated immediately after onset of stress.

Fig. 2 represents an accelerated example of the typical eosinopenic response found in the dying patients. The eosinophil count in this woman was at a normal level two hours after the onset of a cerebral haemorrhage, but fell rapidly to a low level before her death. Recant *et al.* (1950) describe a similar response in a patient with an acute coronary occlusion.

The general trend in the experimental group was a slowly falling level of eosinophils up to the very moment of death. If the patient remained moribund over a protracted period of time the eosinopenia persisted without fluctuation. It often remained at the zero level for days. Of the 142 counts done on this group, only 37 were above 30 eosinophils per c.mm.

The diseases responsible for death in these patients constitute a representative sample of those usually seen in an active general hospital. Cerebrovascular accidents, malignancy, and heart disease head the list. The majority of the patients were in the older age groups.

The average length of stay in hospital was 7.4 days, and the range was from "dead on arrival" to 96 days. However, 34% died within 24 hours of admission and 74% within the first week.

III: Survivor Group

These 12 patients were moribund, and were considered to be terminal cases when serial eosinophil counts were begun. The patients recovered, and, since the results proved interesting, they are reported. This group serves as a check on both the experimental and the control groups, since the initial counts were low, as in the former group, and the subsequent counts normal, as in the latter group.

All these patients had an initial eosinopenia—in fact seven (58.3%) had no eosinophils. All counts had risen to normal levels by the time the patients had recovered enough to be up in a wheel-chair.

These results parallel those of Elliott (1950), working with patients in congestive failure, and also with Gabrilove's (1950) group of patients with coronary occlusion and those who had had an operation. Hain (1951) described similar changes in children with acute febrile illnesses.

Discussion

This is the first attempt to study the function of the adrenal gland in terminal states by observations on its physiological activity, although Recant *et al.* (1950) noted eosinopenia in several patients in their group who were in terminal stages of disease.

It is apparent from the results that, if the circulating eosinophil level is a reliable index of corticoid activity, there is no failure of the adrenal cortex during the terminal stages of illness. In fact, the evidence presented here indicates that the cortex is in a constant state of hyperfunction and hypersecretion until the very moment of death. If this be true, supplementary therapy with cortical hormones would be of no value in the moribund patient unless specifically indicated by the nature of the disease.

The findings also suggest that the return to adrenal hyperfunction demonstrable as an organism passes from the stage of resistance of the general adaptation syndrome to the stage of exhaustion persists throughout its entirety.

Dr. S. Sevit (1951), studying the eosinophil level in burned patients, reached a similar conclusion to my preliminary report on eosinophil levels at death (Jennings, 1951). He states: "Therefore the eosinophil changes in five out of eight fatal cases suggested that hyperactivity of the adrenal cortex was present before death: in another patient there was evidence suggesting that adrenocortical failure had occurred, and in two others the evidence was inconclusive."

Since the life of the eosinophil is believed to be of short duration it might be postulated that failure of the bone marrow to continue production of these cells may occur terminally and account for the eosinopenia. This seems unlikely in the light of all the investigations on stress and the speed with which the eosinopenia can take place (Fig. 2). This would also be inconsistent with the rising leucocyte count which often occurs as a terminal event. Such a theory could readily be disproved by demonstrating an eosinophilia in a terminal untreated case of Addison's disease.

There is a lack of correlation between the findings reported here and the well-known acute adrenal insufficiency demonstrated by the Waterhouse-Friderichsen syndrome and following severe burns (Hartman and Brownell, 1949). In both of these conditions there is apparently primary haemorrhage into the adrenals. Nevertheless, Dr. Sevit's observations on fatally burned patients indicated adrenal hyperfunction, so histological findings may not be a reliable index of cortical function.

Our studies shed no light on the fate and function of the eosinophil during stress, but our results in acutely ill patients seemed to parallel the work of previous authors who demonstrated a fall in the eosinophil count during the acute stress (Elliott, 1950; Gabrilove, 1950; Hain, 1951) and a return to normal during recovery.

Nevertheless, the eosinophil level seemed to be of only slight prognostic significance, since it was low in all acutely ill patients even when it was apparent from the nature of their illness that they were not critically ill. The rise in eosinophils usually lagged behind the appearance of clinical improvement, similar to the delayed fall seen in stress.

However, a rising level of eosinophils in a patient who continues to appear moribund is a good prognostic sign. This was recognized by clinicians years ago (Sodeman, 1950).

In rare instances a very low level may be an indication of impending death in a patient in whom this is not apparent clinically. This occurred in two of our patients in whom an eosinopenia was discovered before the approach of death was apparent.

This study is limited, but is presented in order to stimulate further exploration into the changes which take place in the organism before death. A larger group of terminal patients should be investigated in an attempt to correlate the histological appearance of the adrenals with the level of corticoid secretion and the eosinophil level as well as any other adrenal functional studies which may be available. This should yield valuable information about the hormonal changes occurring at the end of the exhaustion stage of the general adaptation syndrome.

Summary

A carefully controlled series of 50 moribund patients suffering from a variety of diseases was followed by serial eosinophil counts until death. In 47 (94%) the eosinophil count fell to zero or close to zero and remained so until death. Suddenness of death seemed to be an important factor in the three patients who failed to develop an eosinopenia. The eosinophil count rose from low levels to normal in 12 other patients who recovered from the moribund state.

This study indicates that the adrenal cortex apparently does not fail during prolonged stress, but continues to show hyperactivity up to the very moment of death; consequently supportive therapy with cortical substances is not indicated in terminal states.

The eosinophil count seems to be of only limited prognostic significance in such cases, since changes usually accompany or lag behind the clinical findings rather than precede them.

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THE CONDUCT OF PREGNANCY COMPLICATED BY DIABETES MELLITUS

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Most authorities advise and the majority of maternity centres practise early termination of pregnancy at about the 36th week in diabetic women. It is well recognized that intrauterine death may occur in the later weeks of pregnancy, and the aim of early termination is to remove the foetus from the harmful influence of the diabetic expectant mother. Recent work (Fouracre Barnes *et al.*, 1950) suggests that this harmful influence may be due to overactivity of the maternal anterior pituitary gland. If this is so, the foetus will have been subjected to it throughout pregnancy, and intrauterine death may represent a late effect. However, early termination of pregnancy, whilst removing the foetus from the influence of the lethal factor, produces an immature infant who has already been subjected to its harmful effects and who is less able to withstand extrauterine life than an immature infant of a normal mother.

Early Termination

Peel and Oakley (1950) recommended early termination of pregnancy. In their series of 123 diabetic pregnancies there were 12 in which intrauterine death occurred (presumably before induction of labour or caesarean section was due to be carried out). In the remaining 111 treated by premature termination of pregnancy four babies were fresh stillborn and 20 died in the neonatal period. Similar results with early termination of pregnancy were reported by White (1949) in a series of 361 diabetic pregnancies. Neonatal death is thus a large factor in the production of the total foetal death rate in diabetic pregnancies treated by early termination. Since in most clinics early termination is advised, it is not surprising that there are few recorded individual series of diabetic pregnancies which have been allowed to proceed to spontaneous termination.

In a previous article (Fouracre Barnes, 1950) an attempt was made to evaluate the results of termination against those when the pregnancy was allowed to proceed to spontaneous termination. The foetal salvage rate in 22 diabetic pregnancies terminated at 36 weeks was 41%, whereas in 23 diabetic pregnancies treated over the same period and allowed to terminate spontaneously the salvage rate was 43.5%. Thus the foetal salvage rate for the two methods of delivery was approximately the same. Although intrauterine death occurred more often when the pregnancy was allowed to proceed (43.5% as compared with 27.3%), neo-