Admittedly, it is too early to predict what a role RIHSA will play in the diagnosis and localization of intracranial lesions. However, advantages are many: (a) It is much less expensive than diiodofluorescein (DIF*), (b) 400-500 μc will give about the same counting rate as 1 mc of DIF, (c) RIHSA stays in the tissue longer and therefore permits repeated counting, and (d) an increase in differential uptake by the focus on the 2nd and 3rd days survey will serve to confirm the presence of a lesion demonstrated in the initial counting.

The only disadvantage of this method is the uptake by the thyroid gland of I^{131} split off RIHSA. Although stable iodine serves to block this uptake, experience is too limited to say anything definite as to the amount of radiation the thyroid gland might receive as a result of RIHSA administration. However, with the adoption of scintillation type counters, it is possible that the counting rate will be increased to such an extent that the dosage of RIHSA can be greatly reduced to a much safer level.

It is our feeling that RIHSA and DIF may act in a more or less identical manner in the body. When DIF is administered, it may combine physically with the serum albumin of the patient. In other words, DIF is merely used as a reagent to tag the serum albumin of the patient. This hypothesis is being investigated.

Received April 3, 1951. P.S.E.B.M., 1951, v77.

Diminished Adrenal Cortical Function in Diabetes as Shown in Eosinophil Response to Stress of Surgery. (18721)

JAMES B. FIELD AND ALEXANDER MARBLE.

From the George F. Baker Clinic, New England Deaconess Hospital, Boston.

The relationship between the adrenal glands and the pancreas in diabetes mellitus has been the subject of investigation for many years. Recently several observations have been made which suggest, if anything, a reduction of adrenal cortical function in diabetes. Miller and Mason(1) measured the 17-ketosteroids in the urine of 64 adult diabetic patients and found that 88% of the values were below the average normal, while 27% fell below the minimal normal value. They were unable to correlate the excretion of 17-ketosteroids with either the age of the patient or the severity of the diabetes. No mention was made of a possible relationship to the duration of the disease. These investigators concluded that diabetes often has an effect on the adrenal glands which results in a lowered excretion of 17-ketosteroids which is not related to the degree of impairment of carbohydrate metabolism. This finding of reduced 17-ketosteroid excretion in diabetes has been reported by several other workers(2-4). Forbes *et al.*(3) postulated that the decrease was due to the accompanying secondary malnutrition rather than the diabetes *per se*.

The 11-17 oxysteroid excretion in diabetes has also been measured(5,6). Although none of the series is large enough to be statistically significant, the results seem to confirm the trend toward lowered adrenal cortical function in diabetes. The mean value for five diabetics as measured by Talbot was 0.058 mg/sq.m of body surface per day as compared to a mean value of 0.132 mg/sq.m of body surface per day for normals. Three of his 5 patients

1. Miller, S. and Mason, H. L., *J. Clin. Endocrinol.*, 1945, v5, 220.

2. Fraser, R. W., Forbes, A. P., Albright, F., Sulkowitch, H., and Reifenstein, E. C., Jr., *J. Clin. Endocrinol.*, 1941, v1, 234.

3. Forbes, A. P., Donaldson, E. C., Reifenstein, E. C., Jr., and Albright, F., *J. Clin. Endocrinol.*, 1947, v7, 264.

4. Wilson, D. L., Forsham, P. H., Thorn, G. W., and Frawley, T. F., *Proc. Am. Diabetes Assn.*, 1950, v10, 25.

5. McArthur, J. W., Personal communication.

6. Talbot, N. B., Personal communication.

with diabetes had values below the lower limits of normal, while 3 of McArthur's 7 cases also had definitely diminished excretion of 11-17 oxysteroids. Wilson *et al.*(4) have also concluded from their experiments with pituitary adrenocorticotrophic hormone (ACTH) that the adrenal function in diabetes appears to be somewhat less than normal.

The present study was undertaken in an effort to learn more about the level of adrenal cortical function in diabetes mellitus by observing the eosinophil response of diabetics undergoing major surgery. In general the level of circulating eosinophils is closely related to adrenal cortical activity. The changes in circulating eosinophils following major surgical procedures have been reported by various investigators(7-9). Within 4 hours after operation there is a marked and sustained reduction in the eosinophil count, which is followed by an "eosinophilia" often greater than the pre-operative level. The initial eosinopenia may be construed as further evidence of the role of the adrenal cortex in the "alarm" reaction in man. Roche, Thorn, and Hills(9) have shown that in normal people undergoing major surgery the eosinophils are depressed at least 50% of the pre-operative level on the second post-operative day, approximately 48 hours after operation.

Methods and materials. Measurement of the eosinophil levels was done using venous blood by a modification of the method of Dunger as described by Hills *et al.*(10). The blood was collected in tubes containing balanced oxalate. If the counts were not done immediately, the blood was refrigerated. However, all counts were done within 24 hours after the blood was drawn. The ACTH (Armour) and 17-hydroxy-11-dehydrocorticosterone (Cortone, Merck & Co.) tests were performed using 25 mg of ACTH intramuscularly and 100 mg of Cortone orally. After doing an initial count, ACTH or Cortone was administered, and 4 hours later another eosinophil level was obtained. A fall in the eosinophils of 50% or more of the initial level indicates a normal adrenal cortical response and in all probability eliminates the possibility of adrenal cortical insufficiency(11). The Cortone was given mixed with 60 cc of orange juice. In normal people this amount is sufficient to reduce the number of circulating eosinophils by at least 50% in 4 hours(12). All of the tests were done in the morning, and meals were arranged so that the second level was obtained at least 3 hours after the last meal.

Results. The eosinophil level was determined on the second post-operative day in 25 diabetic and 13 non-diabetic patients undergoing major surgery. In each case a pre-operative count was done on the morning of operation. The average fasting circulating eosinophil level in the 25 diabetics was 247/cu mm, while in the 13 non-diabetics it was 287/cu mm. Ten of the 25 diabetics showed an eosinophil count on the second post-operative day which was depressed less than 50% of the pre-operative level. On the other hand, all of the 13 non-diabetic patients had eosinophil levels which were decreased more than 50% of the pre-operative count (Fig. 1). The difference between these two

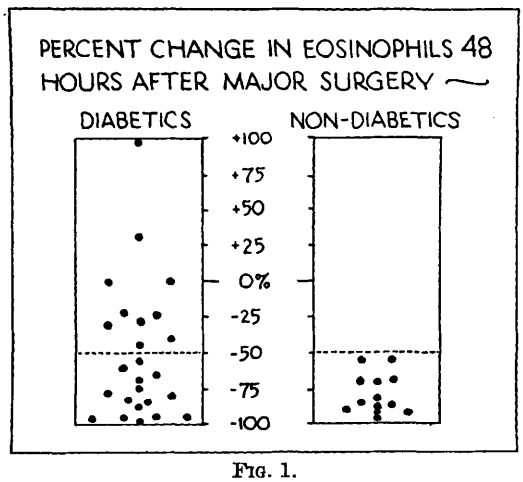

FIG. 1.

7. Laragh, J. H., and Almy, T. P., PROC. SOC. EXP. BIOL. AND MED., 1948, v69, 499.

8. Gabrilove, J. L., *J. Clin. Endocrinol.*, 1950, v10, 637.

9. Roche, M., Thorn, G. W., and Hills, A. G., *New Eng. J. Med.*, 1950, v242, 307.

10. Hills, A. G., Forsham, P. H., and Finch, C. A., *Blood*, 1948, v3, 755.

11. Thorn, G. W., Forsham, P. H., Prunty, F. T. G., and Hills, A. G., *J.A.M.A.*, 1948, v137, 1005.

12. Forsham, P. H., Personal communication.

TABLE I. Comparison of the Effects of Similar Operations in Diabetics and Non-diabetics.

Operation	% change in eosinophils		
	Diabetic with abnormal response	Diabetic with normal response	Non-diabetic
Hysterectomy	+28	-58	-70
Sympathectomy	+97		-57
Lobectomy	-25	-67	-89
Cholecystectomy	+ 1	-70	-73

groups is statistically significant. A deliberate attempt was made to include the same type of operation in both the diabetic and non-diabetic series. In the group of 10 diabetics who demonstrated diminished adrenal cortical function the following operations were represented: sympathectomy, hysterectomy, exploratory thoracotomy, exploratory laparotomy, lobectomy, thigh amputation, and cholecystectomy. Table I shows a comparison of the effects of similar operations on the eosinophil response in diabetic and non-diabetic patients.

Five diabetics who exhibited diminished eosinophil and thereby probably decreased adrenal cortical response to the stress of surgery were given 4-hour ACTH tests. In each case the fall in eosinophils was less than 50%, with a range of —2% to —39%. These tests were done during the third to seventh post-operative days when the number of eosinophils had again risen toward normal. This seemed to indicate some degree of adrenal cortical insufficiency inasmuch as non-diabetics exhibited a normal response to 25 mg of ACTH during the second to fifth post-operative days(9). However, the possibility still remained that the abnormal response in the diabetic was not due to adrenal inadequacy, but to unresponsiveness of the eosinophil itself. To demonstrate that the eosinophils were sensitive to adrenal cortical hormones, Cortone tests were performed in the 5 patients previously tested with ACTH. In every one the number of eosinophils dropped more than 50% in 4 hours. The range was from —51% to —85%. The results of the ACTH and Cortone tests in these five diabetics are shown in Fig. 2.

In order to determine whether the abnormal response exhibited by some diabetics represented an earlier occurrence of the normal third-day "eosinophilia" or a complete inability to react to the stress of surgery with any marked eosinopenia, the eosinophil levels of 8 patients were followed for several days post-operatively. In addition a count was obtained from 4 to 10 hours after operation. The results are illustrated in Fig. 3. In each case there was a marked reduction in eosinophils immediately following surgery. This eosinopenia continued until the second post-operative day when the eosinophil levels had risen to more than 50% of the pre-operative level in the patients with an abnormal re-

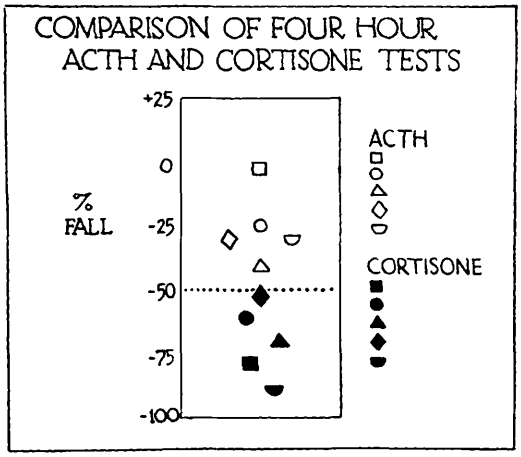

FIG. 2.

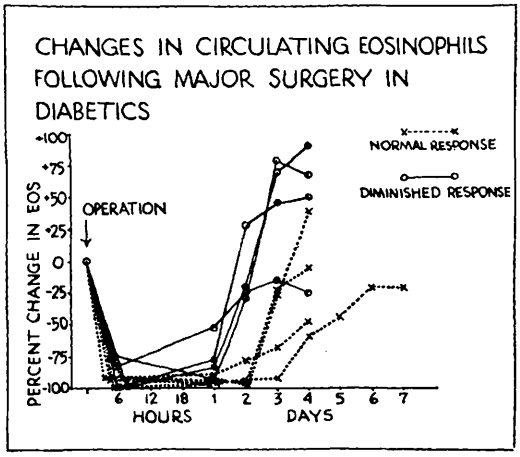

FIG. 3.

sponse. It was evident that the adrenal cortex was capable of responding normally to the initial stress of the operation, but that its reserve capacity was insufficient to maintain the eosinopenia for 48 hours.

The average age of all the diabetics who displayed an abnormal response was 50.6 years, and they had had diabetes for an average of 12.7 years, while the normally-responding diabetics averaged 57.1 years in age and had had their disease 8.4 years. Although the series is not large enough to be statistically significant in respect to this point, it suggests a correlation between the duration of the diabetes and the presence of diminished adrenal cortical response. There was no relationship between the severity of the diabetes as measured by the insulin requirement and the type of adrenal response to surgery.

Discussion. These observations tend to confirm the suggestion that adrenal function in diabetics is somewhat less than normal. Despite the presence of diminished adrenal cortical response, these diabetics did as well postoperatively as did the other diabetics and the non-diabetics. If one is willing to assume that adjustments are continually being made to maintain the body's normal internal environment, then the decreased adrenal cortical function in diabetes can be postulated as a compensatory change in the direction of restoring the balance between insulin and its antagonistic factors. As a result of their experiments on patients with Addison's disease and Cushing's syndrome, Wilson *et al.*(4) have proposed that the effect on carbohydrate metabolism of primary dysfunction of either the pancreatic islet cells or the adrenal cortex is often counterbalanced by compensatory functional changes in the other.

Forbes *et al.*(3) have explained the occurrence of lowered 17-ketosteroid excretion in diabetes on the basis of the secondary malnutrition of diabetes rather than the disease *per se*. This raises the possibility that the reduction of adrenal cortical function observed in this study is also a manifestation of secondary malnutrition. However, this seems unlikely when consideration is given to the patients in this experiment. All of the diabetics were patients of the George F. Baker Clinic and were hospitalized for several days prior to operation. During this period their diabetes, usually already under satisfactory control, was managed more strictly and their general nutrition improved. In this connection it is known that a high-protein diet increases adrenal cortical activity. Prior to hospitalization almost all of these diabetics were leading normal lives and were in average nutritional condition. Also against the contention that malnutrition played an important part in the reduced adrenal cortical function is the observation that three of the non-diabetic controls had tuberculosis and still exhibited a normal response to the stress of surgery. Three cases are scarcely enough to be significant, but they do suggest that poor nutrition is not necessarily the cause of the diminished adrenal cortical response seen in diabetes.

Summary. 1. The levels of circulating eosinophils as a measure of adrenal cortical response to the stress of surgery were followed in 25 diabetics and 13 non-diabetics. Ten of the 25 diabetics showed diminished adrenal cortical function as indicated by an eosinophil count on the second post-operative day which was depressed less than 50% of the preoperative level. Four-hour ACTH and Cortone tests were done on 5 of these 10 diabetics and confirmed the presence of reduced adrenal cortical reserve. The adrenal cortex was capable of responding normally to the initial stress of surgery, but its reserve capacity was insufficient to maintain the eosinopenia for 48 hours. There is a suggestion that the abnormal adrenal response can be correlated with the duration of the diabetes. 2. The possibility is discussed that this decrease in the duration of the activity of the adrenal may be a compensatory change which results from the relative insulin deficiency of diabetes mellitus.

We wish to thank Dr. Peter H. Forsham for his helpful suggestions and criticisms and Drs. Herbert D. Adams, Bentley P. Colcock, and Richard H. Overholt for permission to use their patients as controls.

Received April 11, 1951. P.S.E.B.M., 1951. v77.