Measurement of the Response to Insulin

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In the present study a comparison has been made of the responses to insulin in diabetic and nondiabetic patients. The approach to the measurement of the action of insulin was based on its capacity to increase the rate of utilization of administered glucose.

METHOD

In order to achieve a relative degree of constancy with respect to the various dynamic factors involved in carbohydrate metabolism, a continuous intravenous infusion of 5 per cent glucose in water was administered to fasting patients, at a steady rate of approximately 240 mg. of glucose per min., during a 2-hr. period. Venous blood samples were drawn before, and at intervals of 30, 60, 75, 105, and 120 min. after the start of the infusion. The blood glucose concentrations were determined by a modification of the Somogyi-Nelson technic.[1]

To measure the effect of insulin, 5 units of regular insulin per sq. m. of body surface were injected intravenously, 60 min. after the start of the 2-hr. glucose infusion. In the diabetic patients who had been receiving insulin previously, all insulin was withheld during the 24 hrs. preceding the test.

RESULTS

Observations have been made in a total of 97 individuals. These included 54 diabetics (11 with glucose alone, and 43 with glucose and insulin), and 43 nondiabetics (7 with glucose alone, and 36 with glucose and insulin).

The curves of the mean values of the blood glucose concentrations obtained in the nondiabetic individuals are shown in Figure 1, and those of the diabetic patients in Figure 2. In comparing the groups of nondiabetics and diabetics who were given glucose without insulin, it is apparent that the mean blood glucose concentrations rose (1) more rapidly, and (2) for a longer period of time before achieving relative stability, in the diabetic than in the nondiabetic group. After the administration of insulin, the mean blood glucose values decreased more rapidly in the diabetic group than in the nondiabetic.

The rate of fall of the blood glucose concentrations,* in terms of mg. per 100 cc. per min., during the 45-min. period following the injection of insulin, was used as the index of response to the administered insulin. The mean value of this index in the diabetic group was 1.67 ± 1.52, and in the nondiabetic one was 1.11 ± 0.49. The greater standard deviation in the diabetic group is a reflection of the wider range of variability observed among the individual indices of these patients (Figure 3). There did not appear to be any positive relationship between the indices of response to insulin in the individual patients and either (1) the levels of the blood glucose concentrations immediately preceding the injection of insulin (Figure 4), or (2) the daily requirements of insulin for clinical control of the diabetes (Figure 5).

DISCUSSION

These observations demonstrate the difficulties inherent in an attempt to measure precisely the action of insulin, in terms of changes in concentration of glucose in the peripheral blood. Even though, with the procedure described, two factors were controlled, namely the administration of glucose and of insulin, the wide variation in the observed responses to insulin would indicate that the alterations in blood glucose levels were undoubtedly influenced by a multiplicity of undetermined endogenous factors. The only conclusion which would appear justifiable from these results is that, under the conditions of the experiments, the apparent responses to

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* This was calculated from the formula for linear regression: Rate of fall $= SXY/Sx^2$, where x = time in minutes and Y = blood glucose concentration.[2]

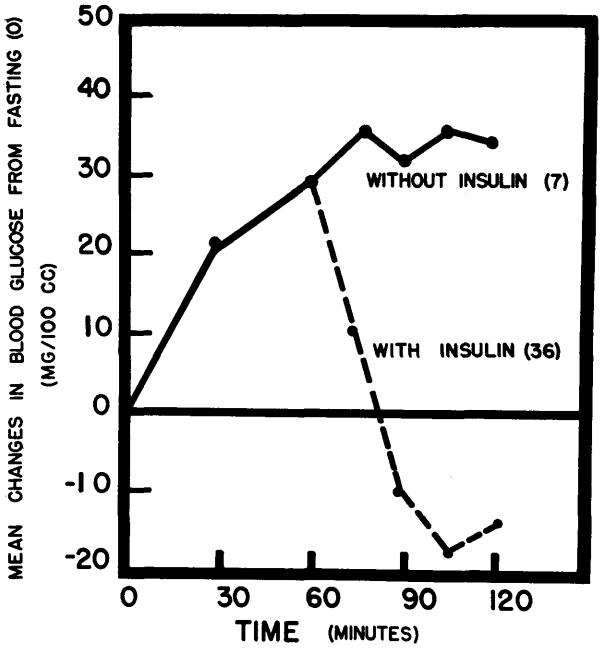

FIGURE 1. Nondiabetic patients. Changes in the mean values of blood glucose concentrations during continuous intravenous infusion of glucose without insulin (solid line), and after insulin (broken line). See text for details.

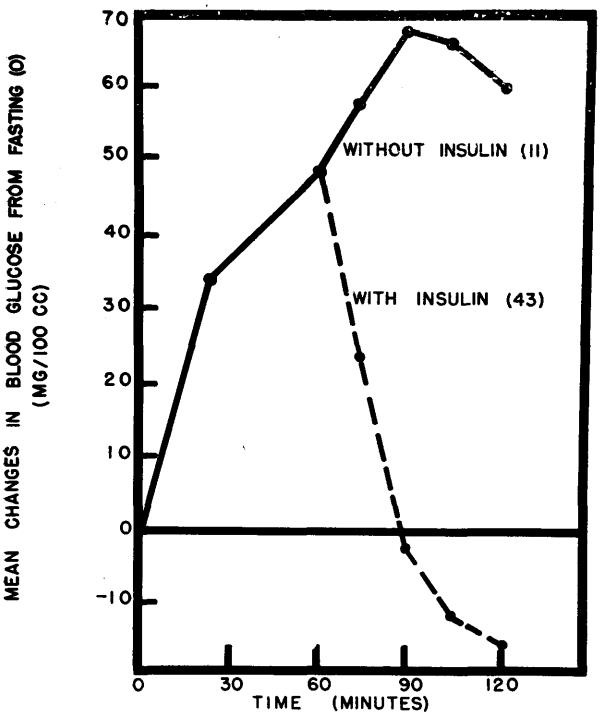

FIGURE 2. Diabetic patients. Changes in the mean values of blood glucose concentrations during continuous intravenous infusion of glucose, without insulin (solid line), and after insulin (broken line). See text for details.

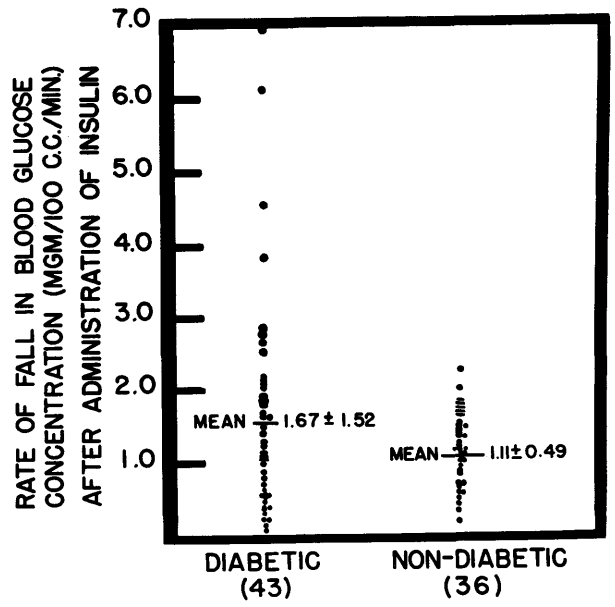

FIGURE 3. Distribution of individual responses to insulin.

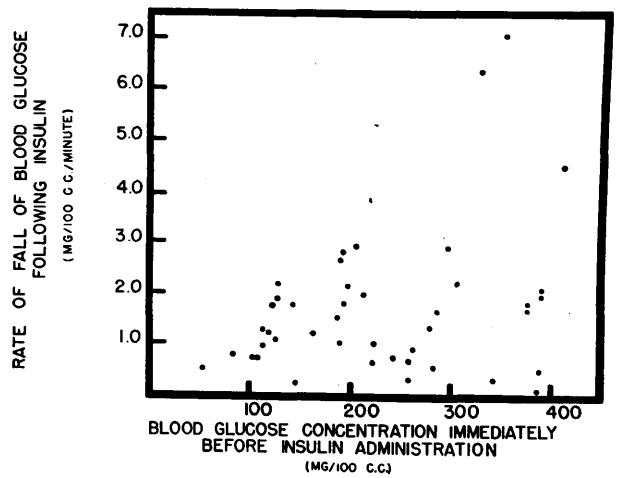

FIGURE 4. Relationship between the responses to insulin in the diabetic patients and their blood glucose levels prior to injection.

insulin in the group of diabetic patients were equal to, or slightly greater than, those observed in the nondiabetic individuals. Therefore, these observations would lend support to the thesis that diabetes mellitus is probably not associated with an inhibition of the peripheral action of insulin.

The generally accepted "inhibitory" effects[3,4] of anterior pituitary and adrenal cortical hormones upon the action of insulin should, perhaps, be reconsidered from the point of view of possible independence of action of the pituitary and adrenal hormones, with respect to gluconeogenesis,[5,6] and of insulin, with regard to glycolysis.

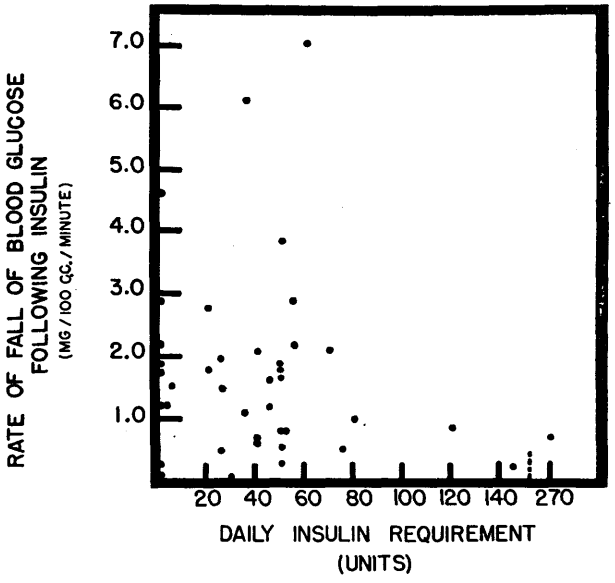

FIGURE 5. Relationship between the responses to insulin in the diabetic patients and their daily clinical requirements.

The measurement of the action of insulin, when limited to the determination of changes in glucose concentration, without the use of isotopically labelled glucose, glucose precursors or glycogen, may be determined as much by the total amount of glucose available from both endogenous and exogenous sources, as by the capacity of each unit of insulin to accelerate the utilization of a specific quantity of glucose.

SUMMARY

1. A comparison has been made, by the methods described, of the changes in blood glucose concentrations in response to the administration of glucose, and of glucose and insulin, in diabetic and nondiabetic patients.

2. The response to insulin which was observed in the group of diabetic patients appeared to be equal to, or slightly greater than, that in the nondiabetics.

3. The relative degrees of response in the individual diabetic patients were apparently unrelated to their daily clinical requirements for insulin, or to the blood glucose levels prior to the administration of insulin.

4. The difficulties inherent in attempting to measure precisely the action of insulin in terms of changes in peripheral blood glucose concentrations are stressed.

5. It is suggested that the apparent "inhibitory" effects of the anterior pituitary and adrenal cortical hormones upon the peripheral action of insulin may be reconsidered from the standpoint of possible independence of the glycolytic activity of insulin and the glyconeogenetic actions of the pituitary and adrenal hormones.

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DISCUSSION

FRANK N. ALLAN, M.D., (*Boston*): This paper recalls to mind my experience when I became a member of the team engaged in insulin research at the University of Toronto in 1922. Professor Macleod assigned to me the task of studying the glucose equivalent of insulin. My approach was to determine the number of grams of glucose utilized per day in relation to the dosage of insulin, the glucose of the diet and other factors.

I found that as the dose of insulin was increased, the effect per unit became less and that as the amount of glucose fed was increased, the effect per unit became greater. I was able to work out logarithmic formulae to show the correlation. But, unfortunately, it proved impossible to use these data as the basis for the assay of insulin as had been hoped, because of the influence of other variable factors. Of course, all of us apply these principles in practice with patients. We know that doubling the dose of insulin does not double its effect; thus patients tend to have protection from the effects of overdosage. We also know that the carbohydrate in the diet can be increased without a proportionate increase in the insulin requirement.

The whole problem of the quantitative measurement of the response to insulin deserves study from every aspect; this may eventually lead to better understanding of the mechanism of insulin action.

HENRY T. RICKETTS, M.D., (*Chicago*): The figures showing the decline in the blood sugar of diabetic patients given insulin indicate a wide range, as Dr. Alpert himself pointed out, the rate of fall varying from 0.01

to 7.0 mg. per 100 cc. per min. It is evident also from these data, that not all diabetics are as sensitive to insulin as the average normal person, although on the whole, most of them seem to be equally sensitive, or somewhat more so.

The situation is a little like that of the insulin content of the pancreas, of which Dr. Wrenshall spoke yesterday. He said that, on the whole, the pancreas of the adult diabetic has about half the insulin content of the normal pancreas, but certainly in some diabetics the pancreas contains even more insulin than the average normal pancreas. So, there is a very wide range in the diabetic individual, as compared with the normal, with respect both to his response to insulin and the insulin content of his pancreas.

I am not entirely sure that we can use Dr. Alpert's results to show that diabetes is primarily a matter of insulin deficiency. He does not claim so in any strong terms, and I think we should keep our minds open on this question.

I hope very much that he will be able to apply this technic, which seems to be a very useful one and which is being employed, I think, by increasing numbers of workers to cases of outspoken insulin resistance.

Nitrogen Equilibrium

One of the most frequent misconceptions is that of the significance of nitrogen equilibrium. The attainment of this equilibrium has been interpreted by some authors as signifying normoproteinia, i.e., a normal protein status; and the minimum of protein requirements for nitrogen balance has been equated with the protein requirements of the body. This identification may be justified in the normal individual, where only maintenance is required, but becomes pernicious when applied to the ill. As the body is deprived of adequate protein intake, its protein and caloric needs are correspondingly reduced-as reflected in decreasing azoturia. This has been shown in the professional starvers Levanzin and Succi, and recently confirmed in the dog by Allison. With each day's loss of proteins from the body and further reduction of tissue mass, a lower and lower protein and caloric intake is required to attain equilibrium, so that nitrogen balance reached at such a low plane is more an indication of hypoproteinia than of normoproteinia. In fact, the ease of attaining equilibrium has been suggested as a means of detecting hypoproteinia.

How this misconception may affect clinical practice is illustrated in the shift of attitude in the dietetic regimen in pulmonary tuberculosis. Some three decades ago, a rich diet of eggs, milk, and meats, i.e., a high protein diet, was advised as an important therapeutic measure in this disease. However, in 1926, there appeared a report showing that it took no higher protein intake to achieve nitrogen equilibrium in cases of tuberculosis than in normal persons. This has been interpreted to mean that the protein needs of the tuberculous were no higher than those of the normal person, and an intake of 90 gm. of proteins a day was recommended, with the warning that a higher intake might prove deleterious by provoking increased respiratory activity (because of the specific dynamic action of proteins).

Accordingly, in the most recent authoritative texts on tuberculosis, rich protein feeding is scarcely mentioned, while the possible deleterious effect of increased specific dynamic action has been stressed. While it is true that the maintenance of good protein nutriture is not the only therapeutic measure in tuberculosis, the seriousness of the neglect of this factor, to which such an unbalanced attitude could lead, is well attested by the findings of Chortis concerning the much more rapidly fatal outcome of hypoproteinic tuberculous patients.

Nitrogen equilibrium is only a method of biological bookkeeping and its value is at best circumstantial. Small balances either way are not significant, since the margin of error is high. Accordingly, slow small losses of protein may not be detectable by this method.
Potassium balance has been used as a check on nitrogen balance and so also has weight, but both are subject to several sources of error. Perhaps a better check might be the total body solids as determined by subtracting the total body fluids from the body weight. The gain in total body solids would, however, represent not only protein gains, but corresponding gains in minerals.

From "Review: The Fundamentals of Clinical Proteinology" by Co Tui, M.D., in the *Journal of Clinical Nutrition,* March-April, 1953.

Evaluation of Blood Sugar Tests in Medical Practice

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The following observations are based on a review of glucose tolerance tests and single blood sugar determinations which have been performed on patients in the Carruthers Clinic in the four-year period ending December 31, 1952. Nearly all the patients were ambulatory. All blood sugar estimations were done on venous blood using the Folin-Wu method and a Leitz photoelectric colorimeter.

A total of 685 tests on 617 patients was performed during this period. This survey does not include results of routine blood sugar examinations on diabetic patients under treatment. It is not the policy of our clinic to order blood sugar estimations routinely on each new admission. However, we make every effort to discover early diabetes, and single blood sugar estimations or glucose tolerance tests are performed whenever the history, signs, or symptoms present any suspicion of diabetes.

The various indications for taking the blood sugar tests are listed in Table 1, which also shows the number and percentage of tests taken for each category, and the number and percentage of positive tests under all headings. A rather large group comprising 120 tests had to be defined under the heading "Miscellaneous," representing such conditions as dysuria, polyuria, various endocrine disturbances, brain injuries, poisoning, tiredness, convulsive disorders, dizziness, blindness and various psychoneurotic complaints.

Many tests were performed for several reasons: for example, family history, obesity, and skin lesions. These tests have been allotted to the indication with the highest priority according to the following list: glycosuria, family history of diabetes, skin lesions, paresthesia, miscellaneous, and obesity. Obesity was listed as a cause only when the excess weight was 10 per cent or more over the optimal body weight.

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GLUCOSE TOLERANCE TESTS

The glucose tolerance tests comprised a fasting sample and a sample taken one-half, one, one-and-a-half, and two hours after ingestion of 100 gm. of glucose in solution. The return of the blood sugar to 120 or 130 mg. per 100 cc. two hours after glucose ingestion is now commonly accepted as the significant diagnostic factor. With Duncan[1,2] we have adopted the less strict criterion of 130 mg. The inadequacy of fasting blood sugar determination as a sensitive screening test is brought out by the fact that of 120 abnormal glucose tolerance tests, 83 (69 per cent) showed a fasting blood sugar below 130 mg. While it is well known that mild diabetics may have normal fasting blood sugar, I could find no similar statistical data on this subject in the literature. The objection that these normal readings might be due to self-imposed dietary restrictions just previous to taking the glucose tolerance test can be met by the fact that particular care was taken to instruct patients to follow a diet providing a minimum of 300 gm. of carbohydrate for three days previous to the glucose tolerance tests. No subject had had insulin for at least one week preceding the test, and it was made sure that the patients were free from febrile complications and hyperthyroidism. As initially mentioned, only a few of our patients were hospitalized while their glucose tolerance tests were being made, and none of them could be considered as bedridden. This is important, since Blotner[3] has shown that bed rest results in abnormal blood sugar curves.

Lawrence[5] has coined the term "oxyhyperglycemia" for a condition which is common in cases in which there is rapid emptying of the stomach, especially after gastroenterostomy or partial gastrectomy. After administration of glucose the blood sugar rises rapidly from a normal fasting level to over 200 or even 300 mg. per 100 cc., but returns rapidly to the fasting level in normal time. This curve is not indicative of diabetes mellitus. Eight of our cases fall into this group. Marble[4] believes that one

TABLE 1
Summary of tests for diabetes

Reason for test	Kind of test: Glucose tolerance		Fasting blood sugar		Postprandial blood sugar		Exton-Rose		Modified tolerance		Total tests		Positive tests	
	Total	Abnormal	Total	Abnormal	Total	Abnormal	Total	Abnormal	Total	Abnormal	No.	%	No.	%
Glycosuria	84	44 (52.4%)	103	45 (43.7%)	50	18 (36.0%)	25	14 (56.0%)	6	3 (50.0%)	268	39.1	124	46.3
Family history	81	42 (51.8%)	20	2 (10.0%)	20	7 (35.0%)	14	8 (57.1%)	3	0	138	20.1	59	42.8
Skin lesions	14	7 (50.0%)	13	5 (38.5%)	1	0	2	0	1	0	31	4.5	12	38.7
Paresthesia, neuritis, pruritus	16	7 (43.7%)	15	1 (6.7%)	14	5 (35.7%)	4	3 (75.0%)	0	0	49	7.2	16	32.7
Miscellaneous	31	8 (25.8%)	58	11 (18.9%)	22	6 (27.3%)	6	6 (100.0%)	3	2 (66.7%)	120	17.6	33	27.5
Obesity	18	12 (66.7%)	25	4 (16.0%)	22	8 (36.4%)	8	7 (87.5%)	6	1 (16.7%)	79	11.5	32	40.5
Totals	244	120 (49.2%)	234	68 (29.1%)	129	44 (34.1%)	59	38 (64.4%)	19	6 (31.6%)	685	100.0	276	40.3

cannot disregard the height to which a glucose tolerance curve goes, whereas authorities like Duncan,[1,2] Lawrence,[5] and Mosenthal[6] give little heed to the peak of the curve, provided that the blood sugar returns to 130 mg. or below by the end of two hours. In the 124 glucose tolerance tests which satisfied this requirement and were therefore interpreted as nondiabetic, 51, or 41 per cent, showed a rise in blood sugar over the accepted critical peak level of 170 mg. at some time during the examination. On this basis alone, these tests could have been wrongly interpreted as indicative of diabetes. Adding to these 51 cases the 83 abnormal tests with normal fasting blood sugar, one perceives that 134 of 244 glucose tolerance tests, or 55 per cent, yielded information which could not have been obtained if only a single test had been employed.

FASTING BLOOD SUGAR TESTS

Taking the foregoing observations into consideration, it is not surprising that the percentage of abnormal findings in the fasting blood sugar tests was much lower than in the glucose tolerance tests—29 per cent against 49 per cent.

POSTPRANDIAL BLOOD SUGAR TESTS

Most of the postprandial tests were made after an ordinary meal, and in only a few instances was a special test meal prescribed. These tests were made at various intervals after eating, generally one hour. Any reading over 170 mg. per 100 cc. was considered abnormal, and any reading below 130 mg. was considered normal, regardless of the time interval between the meal and the taking of the sample. The tests between 130 and 170 mg. were reviewed to ascertain the time interval between the meal and the taking of the sample and were assessed accordingly. It is, of course, important that this time relation be known. A reading which may be normal one hour after a meal could be highly abnormal after two hours.

EXTON-ROSE TESTS

The number of Exton-Rose tests performed at this clinic has decreased every year. This test is perhaps more convenient to perform than the standard glucose tolerance test, but its accuracy has been questioned.

MODIFIED TOLERANCE TESTS

Nineteen tests are recorded as modified glucose tolerance tests. They all comprised one fasting and one postprandial blood sugar reading. In six tests this sample was taken forty-five minutes after ingestion of 50 gm. of glucose; in the remaining thirteen the specimen was taken one hour after the ingestion of a meal rich in carbohydrates. The number of these tests performed is, however, too small to be statistically significant.

SUMMARY AND CONCLUSIONS

1. Over 40 per cent of 685 blood sugar tests per-

formed on 617 patients suspected of having diabetes yielded abnormal readings.

2. Abnormal findings numbered 29 per cent of the fasting blood sugar tests, compared with 49 per cent of the glucose tolerance tests.

3. Normal fasting blood sugar levels were found in 69 per cent of cases in which the glucose tolerance test indicated diabetes.

4. Forty-one per cent of otherwise normal glucose tolerance tests reached a peak level of over 170 mg. per 100 cc.

5. Nearly 55 per cent of 244 glucose tolerance tests yielded information which could not have been obtained had a single test been employed.

6. A normal fasting blood sugar is of little value for excluding mild diabetes.

7. If postprandial blood sugar values are employed for diabetic case findings, the time interval between food ingestion and taking of the sample must be noted and the test interpreted accordingly.

8. If only a single test can be employed, it appears that one taken two hours after the ingestion of 100 gm. of glucose has the highest selectivity. Failing this, a postprandial test is of greater diagnostic value than a fasting blood sugar reading.

9. These studies demonstrate the necessity of integrating the laboratory findings with the clinical picture.

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Antivivisection Activities

Antivivisectionists, and American Humane Association strategists lined up with them, appeared rudely shocked by the recent move of the Washington, D. C., Commissioners to provide a means for selling the District's condemned pound animals for use in research and teaching. The enemies of medical progress had been boasting all year about having stopped three pound-bills in state legislatures and admitted that they were totally unprepared for the D. C. action. The inside story of the development in Washington is this: With the opening of Congress last year, an attempt was made by Rep. Auchincloss in New Jersey to turn the D. C. municipal pound over to a private animal welfare group with a law disguised to look like an economy measure. In the ensuing uproar from medical scientists all over the country, it was divulged that the D. C. pound annually showed a profit of over $50,000 and that 6,000 animals were killed there every year that could be used for research if Poundmaster Marks, an old antivivisectionist, would release them. Local scientific and political leaders of the District then took a hand in working out the present arrangement which was incorporated in the D. C. reorganization plan. Latest development at this writing was the hearing on January 25 at which antivivisectionists presented 53 witnesses, ranging from testimony that there was no such disease as rabies to solemn assurance by Dr. Hoxey that he had found cure for cancer without animal experimentation. Antivivisectionists, as in all campaigns, wrote letters furiously from all parts of the country. The total, however, was only 12,000, indicating a serious drop in antivivisectionist strength throughout the nation.

If the Washington arrangement goes through, and it appears likely, it will mark the second substantial victory for medical research proponents in the still-young year. A series of amendments to the Illinois pound law went into effect on the first of this year, giving force to that measure. They had been passed through both houses of the Illinois legislature at its last session without a single dissenting vote. Principal amendment is the one which places humane societies with pound contracts in the same status with regard to the law as municipal pounds.

From an editorial in the *Bulletin for Medical Research,* Jan.-Feb. 1954.