Response of the Blood Glucose to Glucocorticoids in Man

Determination of the Hyperglycemic Potencies of Glucocorticoids

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To estimate the potencies of new glucocorticoids, experiments are usually conducted to measure the intensity of several of the physiologic effects produced by the drug. The effect of a glucocorticoid on carbohydrate metabolism is usually measured by determining the degree to which it is capable of promoting the deposition of glycogen in the livers of experimental animals. Although there have been disparities in some instances, the "liver glycogen" potencies of glucocorticoids in animals have correlated in a general way with their potencies in other respects such as inhibition of inflammation, inhibition of secretion of adrenocorticotrophic hormone and depression of the number of circulating eosinophiles.

On the other hand, disparities between the results of experiments in animals and man[1,2] have necessitated the development of better methods of measuring the hyperglycemic potencies of glucocorticoids in man. In testing the potencies of these drugs in man, their effects on carbohydrate metabolism have not usually been used as an index of potency. This is probably because there are certain obstacles which have been encountered in trying to determine quantitatively the hyperglycemic effects of glucocorticoids in human subjects. The measurement of liver glycogen is, of course, not generally feasible, and the hyperglycemic effects of these drugs vary greatly from individual to individual.[3,4] Furthermore, under some experimental conditions, no appreciable effect was produced on glucose tolerance by the administration of even large doses of glucocorticoids.[5,7] Lastly, under certain circumstances no effect on the fasting blood glucose had been noted after the administration of these drugs.[6,7]

On the other hand, it has been shown previously that under the proper circumstances impairment of glucose tolerance could be produced regularly by the administration of two doses of several different glucocorticoids,[8] and furthermore, that the degree of impairment produced was well correlated with the potency of the drug being tested.[8] While there were substantial variations in the hyperglycemic responses from subject to subject, the responses of each individual, from day to day, to equivalent doses of glucocorticoids were fairly consistent in magnitude.

The relatively predictable hyperglycemic effect on oral glucose tolerance tests produced by several glucocorticoids under the circumstances of our previous experiments were encouraging, so it was decided to explore further some of the factors which influence response of the blood glucose to glucocorticoids by testing the effects of these drugs on intravenous glucose tolerance and on the fasting blood glucose. Another purpose of the experiments was to evaluate certain methods of establishing the hyperglycemic potency of a glucocorticoid.

METHODS

The glucocorticoids were administered by mouth. The blood glucose determinations were done by the method of Nelson[9] on venous blood. The subjects were healthy adults varying in age from twenty to fifty-six years, the vast majority of whom were between twenty and thirty-five years of age. There were approximately equal numbers of males and females. The subjects were not placed on formal diets during testing but were questioned concerning their diets and no individuals were tested who had in any way restricted their diets previous to or during the experiments. At least forty-eight hours elapsed between each test with a drug. The effect of the glucocorticoid on the fasting blood glucose was estimated by comparing the level of the blood glucose after the drug with the fasting blood glucose at the same hour on a previous control day or days. (The average intra-individual variability of the control fasting blood glucose values from day to day, based on triplicate tests in ten randomly chosen individuals, was 4.3 mg. per cent

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with a standard deviation of 3.2 mg. per cent.)

The effect on glucose tolerance was measured by comparing the blood glucose one hour after an intravenous glucose load of 25 gm. on a control day with the one-hour blood glucose after the drug. The glucose was administered in two to four minutes as 50 ml. of 50 per cent glucose and the test timed from the beginning of the injection. (The one-hour blood glucose is, of course, not the best possible index of glucose tolerance. However, since it is possible to identify with a few tests a small difference in glucocorticoid potency using this simple method of estimating glucose tolerance, it does seem adequate for this purpose.)

FACTORS WHICH INFLUENCE THE RESPONSE OF THE BLOOD GLUCOSE TO GLUCOCORTICOIDS

Effect of glucose loading. It is apparent from examining the data in table 1 that glucose loading increases the sensitivity of the blood glucose to the administration of prednisolone. The administration of 10 mg. of prednisolone four hours and eleven hours before an intravenous glucose load of 25 gm. produced an elevation of the one-hour blood glucose which averaged 41 mg. per cent over control values. On the other hand, the elevations of the fasting blood glucose averaged only 18 mg. per cent after the same treatment. The substantial variations in the responses among individuals are apparent.

Sensitivity of fasting blood glucose to glucocorticoids. Although the fasting blood glucose is not very responsive to the administration of glucocorticoids it is sufficiently responsive under certain circumstances to enable one to estimate the hyperglycemic potency of a glucocorticoid without including glucose loading as part of the test. It was found, for example, that a small but consistent effect was produced on the fasting blood glucose when 15 mg. of prednisolone was administered four hours prior to the glucose determination (table 2). Table 2 also shows that 5 mg. produced a less consistent effect which was not statistically significant. As will be indicated in the text immediately below, the fasting blood glucose is more sensitive to the glucocorticoid if the drug is administered eight hours before the determination.

TABLE 1

Effect of prednisolone on fasting blood glucose and on glucose tolerance

	Elevation* of blood glucose in mg. per cent produced by two 10 mg. doses of prednisolone†	
Subject No.	Fasting glucose	One-hour glucose
1	17	20
2	19	67
3	15	29
4	29	69
5	11	51
6	6	—2
7	35	44
8	29	56
9	11	20
10	8	51
Mean	18	41

*The elevation of the fasting blood glucose was determined by comparing the fasting blood glucose at 10 a.m. on a control day with the fasting blood glucose at that time after administration of the drug. The elevation of the blood glucose one hour after an intravenous glucose load produced by the drug was determined by comparing the one-hour blood glucose on a control day with the one-hour glucose on the day the drug was administered.

†Administered orally four hours and eleven hours before the fasting blood glucose and the intravenous glucose.

TABLE 2

Effect of two different doses of prednisolone on fasting blood glucose

	Elevation* of fasting blood glucose in mg. per cent four hours after prednisolone	
Subject No.	5 mg.	15 mg.
1	8	11
2	9	8
3	18	11
4	12	11
5	13	21
6	0	10
7	—3	9
8	—10	4
9	—4	2
10	3	6
11	10	6
12	—2	11
Mean	4.5	9

*Over the mean of two fasting blood glucose values on control days at the same hour (10 a.m.). The hyperglycemic effect of 15 mg. was statistically significant ($p<.01$) and that of 5 mg. was not. When 5 mg. prednisolone was administered eight hours before a fasting blood glucose it produced a significant effect (see text).

The delayed hyperglycemic effect of glucocorticoids. It will be apparent from examining table 3 that when 40 mg. hydrocortisone was administered eight hours before a blood glucose determination a greater effect was produced than that produced when this hormone was administered four hours before the fasting blood glucose determination. This phenomenon is of particular interest because it has been shown that an insignificant amount of the hormone is present in the blood eight hours after it is administered orally in doses even larger than these.[10]

It is also of interest in this connection that when this same dose of hydrocortisone was administered by mouth to ten subjects, in this laboratory, the eosinopenic effect was significantly greater at four hours than at eight

TABLE 3

The "delayed" hyperglycemic effect of hydrocortisone

Subject No.	Fasting blood glucose in mg. per cent at 8:00 a.m. Four hours after 40 mg. hydrocortisone	Eight hours after 40 mg. hydrocortisone
1	92	94
2	98	115
3	75	77
4	70	73
5	73	82
6	85	100
7	92	87
8	80	87
9	80	80
10	96	109
Mean	84	90
	$p<.03$	

The order of testing was randomized.

hours ($p<.01$).

Further evidence that the hyperglycemic action of a dose of a glucocorticoid is prolonged has been accumulated in this laboratory. Subjects were given 10 mg. of prednisolone four hours before a fasting blood glucose. On another occasion the test was repeated adding a second dose eleven hours before the blood glucose determination. The results of this experiment are recorded in table 4. It may be noted that the blood glucose values were significantly higher ($p<.01$) when this dose was included even though it was administered eleven hours before the test. These results may be compared with those of Duncan,[7] who found no elevation of the fasting blood glucose and no impairment of intravenous glucose tolerance two hours after 200 mg. of cortisone.

TABLE 4

Hyperglycemic effect of prednisolone administered eleven hours before a fasting blood glucose determination

Subject No.	Elevation* of fasting blood glucose in mg. per cent after prednisolone: Four hours after one dose of 10 mg.	After two 10 mg. doses (four and eleven hours before determination)
1	0	17
2	24	30
3	12	19
4	15	15
5	3	15
6	9	29
7	15	15
8	0	6
9	13	35
10	12	29
Mean	10	21
	$p<.01$	

*Over a control value on a previous day at the same hour (10 a.m.).

It seems likely that the latter negative results were due to the fact that the glucose tolerance tests were done before the onset of the hyperglycemic action of cortisone. In this laboratory only three intravenous glucose tolerance tests have been made as early as two hours after a single 10 mg. dose of prednisolone. In each instance the drug produced no significant effect.

It may be noted that when 5 mg. of prednisolone was administered four hours before fasting blood glucose determination, the small effect was not statistically significant (see table 2). On the other hand, when 5 mg. of prednisolone was administered to ten additional subjects eight hours before a fasting blood glucose a highly significant effect was produced ($p<.01$). On still another occasion, ten subjects responded significantly under these circumstances (see figure 1).

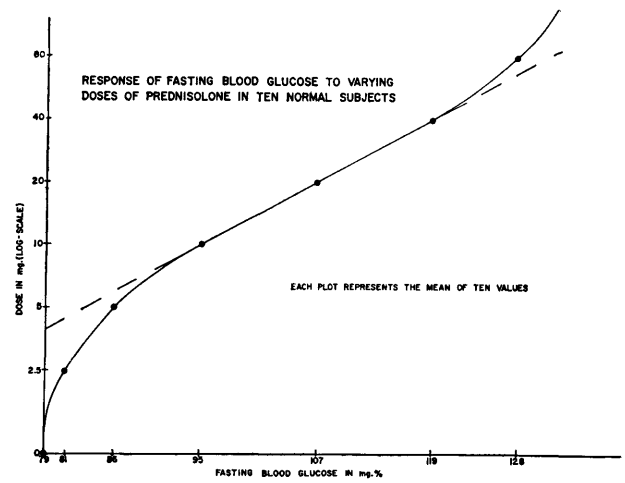

FIG. 1. The relationship of dosage of prednisolone plotted logarithmically to the response of the fasting blood glucose in normal subjects. The drug was administered by mouth eight hours before the fasting blood glucose determination. The order in which the various doses were administered was randomized. The broken line shows that as the dose was raised from 10 mg. through 40 mg. the magnitude of the responses obtained was directly related to the dosage logarithmically expressed.

That the peak of hyperglycemic action of a 40 mg. dose of hydrocortisone occurred earlier than twelve hours after administration by mouth was shown when ten subjects exhibited significantly greater blood glucose values at 8:00 a.m. eight hours after the drug on one occasion than at 8:00 a.m. twelve hours after the drug on another occasion ($p<.02$). The order of the tests was randomized.

Our experience concerning the delay in the onset of hyperglycemic action of glucocorticoids is similar to the experience of Glenn, Stafford and Bowman,[11] who found recently that the maximum effect on the production of

liver glycogen in rats occurred about eight hours after the administration of hydrocortisone subcutaneously, at a time when there was an insignificant amount of the hormone in the blood. They accumulated additional data which suggested that the deposition of liver glycogen might be secondary to a peripheral "nonhepatic" effect of the hormone.

It is apparent that the data presented in this paper do not permit conclusions concerning the precise time at which the peak hyperglycemic action occurs after a glucocorticoid is administered orally. This point is being explored in this laboratory. Our preliminary studies suggest that the peak action occurs six to eight hours following administration of prednisolone and of hydrocortisone by mouth, although the data are not adequate as yet to permit a final conclusion. Furthermore, it is not known whether the peak of action occurs at the same hour irrespective of the dosage used.

The effect of heredity on the hyperglycemic response to glucocorticoids. Fajans and Conn[4] found that nondiabetic persons with a family history of diabetes exhibited greater hyperglycemic responses to cortisone than did persons with no family history of diabetes. In this laboratory it was found that nondiabetic subjects with a family history of diabetes exhibited significantly greater hyperglycemic responses to prednisolone and prednisone than a control group.[3] Furthermore, the hyperglycemic responses of identical twins were found to be strikingly familiar. For example, of twenty subjects the two who showed the greatest responses to glucocorticoids were twins and the two who showed the smallest responses were also twins.

The correlation between potency and hyperglycemic response. Table 5 shows the fasting blood glucose values eight hours after the administration of 10 mg. of prednisolone and after 15 mg. The order of testing was randomized. It is of interest that this relatively small difference in potency was established after testing only ten subjects since p was less than .02. These results suggested that this particular method was a simple but sensitive way of establishing the hyperglycemic potency of a dose of glucocorticoid.

The relationship between dosage and the intensity of hyperglycemic response was explored further by using another method. Ten subjects were given doses of prednisolone eleven hours before and four hours before an intravenous glucose tolerance test. Their blood glucose values one hour after a load of glucose 25 gm. were compared with their one-hour blood glucose values at the same hour on a control day. The elevations of one-hour blood glucose produced by the 10 mg. doses, and by the 15 mg. doses of prednisolone administered in alternating order, are recorded in table 6. Since their responses were significantly greater after the 15 mg. doses ($p<.01$) it would appear that this particular method is also capable of identifying relatively small differences in potency.

TABLE 5

The hyperglycemic response to 10 mg. and to 15 mg. of prednisolone

	Fasting blood glucose in mg. per cent eight hours after prednisolone		
Subject No.	Control	10 mg.	15 mg.
1	79	87	92
2	83	83	87
3	80	87	92
4	69	79	96
5	77	87	90
6	69	83	96
7	73	79	79
8	83	96	92
9	79	87	98
10	80	83	95
Mean	77	85	92

10 mg. produced a significant effect ($p<.01$).
15 mg. produced an effect significantly greater than 10 mg. ($p<.02$).

The relationship between the size of the dose administered and the response of the fasting blood glucose was more completely explored by testing the responses of ten normal subjects, eight hours after seven different

TABLE 6

The response of the one-hour intravenous tolerance test to prednisolone

	Elevation* of one-hour blood glucose produced by prednisolone in mg. per cent	
Subject No.	Two 10 mg. doses†	Two 15 mg. doses
1	20	27
2	67	81
3	29	63
4	69	129
5	51	64
6	—2	25
7	44	62
8	56	76
9	20	32
10	51	71
Mean	41	63
	$p<.01$	

*The elevation of the blood glucose produced by the drug one hour after an intravenous glucose load of 25 gm. was determined by comparing the one-hour blood glucose on a control day with the one-hour blood glucose on the day the drug was administered.
†Administered orally four hours and eleven hours before the glucose load.

doses of prednisolone. The results of these experiments are recorded in figure 1. The responses to doses of 2.5, 5, 10, 20, 40 and 80 mg. were plotted graphically (dosage logarithmically plotted). It may be noted that when these plots were joined an S-shaped curve was formed, suggesting that very low doses of the order of 2.5 mg. produce little if any response, and that when doses of 80 mg. were administered, the point of maximum response was being approached. It is of interest that the plots of the responses to doses of from 5 mg. to 40 mg. fall in a line which is relatively straight and that the line joining the plots of doses of 10 mg. to 40 mg. is quite straight. Apparently, in this range of dosage, there is an excellent correlation between the log of the dose and the response. It is of further interest that even though only ten subjects were used, doubling the dose invariably resulted in responses which were greater to a statistically significant degree since p was less than .02 in each instance.

EXPERIMENTAL DESIGN IN TESTING THE HYPERGLYCEMIC POTENCIES OF GLUCOCORTICOIDS

Since there is a good correlation between the size of the administered dose and the hyperglycemic responses under certain conditions described above, it has been possible to design methods of establishing the hyperglycemic potency of a glucocorticoid of unknown potency.

It would appear that the following points are of importance in determining the hyperglycemic potency of a glucocorticoid: (1) The response of the blood glucose to the glucocorticoid must be compared with the response in a control situation *in the same individual.* The interindividual variation in response is so great (see table 1) that a much larger number of tests would have to be made in order to demonstrate statistically significant differences in potency between two drugs if a paired control system was not being used. Such data are analyzed using a paired control t test. (2) If a very small amount of a drug is available, glucose loading could be included as part of the control test, and the test with the drug in order to "sensitize" the blood glucose to smaller doses of the drug or drugs. (3) Allowance must be made for the delayed onset of the hyperglycemic effect (see table 3). (4) Randomization of the order of testing is desirable when the potencies of several doses of drugs are being compared in series, and at least forty-eight hours should elapse between tests. Although we have noticed no cumulative effect in testing a small series of single doses of drugs in the same subject under the conditions described under Methods, there is a possibility that under certain conditions previous tests might affect the results of a subsequent test. Furthermore, there is a possibility that technical factors in the determinations of glucose might produce slightly different results from day to day on samples containing identical amounts of glucose. (5) Selection of appropriate dosages. A dose must be used as a standard which will produce responses consistently, but this dose should not produce a maximum response. The dosage required to elevate the blood glucose regularly depends upon the type of test carried out. It is apparent from the data in figure 1 that a single dose of a glucocorticoid equivalent in potency to 5 mg. of prednisolone when administered by mouth eight hours before the fasting blood glucose determination will produce a hyperglycemic effect regularly, and that the administration of a dose which is substantially more potent will result in substantially greater responses. In the dosage range of 5 mg. to 80 mg. the response expressed arithmetically was very closely correlated with the dose logarithmically expressed.

During preliminary studies several methods of estimating hyperglycemic potency of glucocorticoids were used. It appears that the most satisfactory is the simple method described above in which hyperglycemic potency is measured by comparing the fasting blood glucose eight hours after the drug is administered orally with the fasting blood glucose at the same hour on a control day. The subjects are instructed not to eat after 7:00 p.m. on either day. Under these conditions a standard dose of glucocorticoid of known potency has been used (usually 5-20 mg. of prednisolone or 40-80 mg. of hydrocortisone) with which the potency of the new drug is compared. An example of such an experiment will be cited below.

TESTING THE HYPERGLYCEMIC POTENCY OF A GLUCOCORTICOID OF UNKNOWN POTENCY

The principles discussed above have been applied in testing the hyperglycemic potencies of a series of glucocorticoids. These results have been the subject of a separate report.[1] The results of an experiment designed to establish the hyperglycemic potency of 6-methyl prednisolone (Medrol) are reported here in order that they may serve as example of the applicability of the method.

On three separate occasions single doses of 15 mg. 6-methyl prednisolone, 15 mg. prednisolone, and 22.5 mg. of prednisolone were administered by mouth in random order to each of ten healthy subjects, at intervals of not less than two days. Eight hours after the drug was administered a fasting blood glucose was determined at 8:00 a.m. The results, which are recorded in table 7, indicate that it was possible to identify clearly the small difference between the potency of the 15 mg. doses of prednisolone and the 22.5 mg. doses of prednisolone

TABLE 7

The relative hyperglycemic potencies of prednisolone and 6-methyl prednisolone

Subject No.	Fasting blood glucose values in mg. per cent eight hours after drug: Prednisolone 15 mg.	6-methyl Prednisolone 15 mg.	Prednisolone 22.5 mg.
1	105	87	107
2	95	85	95
3	87	83	95
4	94	83	102
5	96	94	94
6	85	83	85
7	98	87	105
8	100	82	92
9	96	95	110
10	100	110	114
Mean	96	89	100
		$p<.04$	$p<.01$

The order of testing the drugs was randomized.

This table contains data previously reported (West, K. M.: "The Eosinopenic and Hyperglycemic Potencies of Glucocorticoids in Man." *Metabolism,* July (Part II), 1958). The data are reproduced by permission of *Metabolism.*

($p<.01$). This again confirmed the sensitivity of the method. Medrol was found to be more potent than prednisolone milligram for milligram ($p<.04$). The mean response to 22.5 mg. prednisolone was greater than to 15 mg. Medrol. However, this difference is not statistically significant. These data suggest that the hyperglycemic potency of Medrol is about 30 per cent greater than prednisolone.

In testing the potencies of the new corticoids, we have found that, in general, six to twelve subjects must be tested in this manner in order to distinguish clearly a difference in potency between a control dose and a dose which is twice as potent or half as potent. When doses which differ only as much as 50 per cent are tested, ten to thirty pairs of tests are usually required before statistically significant differences are apparent.

DISCUSSION

It may be deduced from the data above concerning the hyperglycemic time-action characteristics of hydrocortisone and prednisolone that their physiologic time-actions in this respect do not coincide with the curves described by their blood levels. It may be that the time-action curves in other physiologic respects of glucocorticoids do not reflect directly their rates of disappearance from the blood. For example, Ely and associates[10] found that the half time of a dose of intravenously administered hydrocortisone averaged ninety minutes as compared to an average half time for prednisolone of 192 minutes. On the other hand, the author found that the eosinopenic time-action curves of these two drugs were indistinguishable when doses of similar potency were administered (20 mg. hydrocortisone and 5 mg. prednisolone).[1] It has been found in this laboratory that the following glucocorticoids have very similar eosinopenic time-action curves when administered orally in doses of similar potency: hydrocortisone, prednisolone, 6-methyl, prednisolone, 9-alpha-fluorohydrocortisone, and triamcinolone.[1]

It appears that the biologic time-action curve of a dose of a glucocorticoid depends on the potency of the dose which is in turn dependent on the size of the dose and the molecular configuration of the glucocorticoid. Thus, milligram for milligram, highly potent glucocorticoids such as prednisolone and 9-alpha-fluorohydrocortisone are "longer acting" than less potent glucocorticoids such as hydrocortisone, but when the more potent drug is administered in doses equivalent in potency to a dose of the less potent glucocorticoid it is not longer acting.

On the other hand, it is possible that the hyperglycemic time-action curves of different glucocorticoids are not similar, even when they are administered in doses of comparable potency. Although there is very little direct evidence available concerning this point, our experience to date suggests that the hyperglycemic time-action curves are similar when doses of comparable potency of different glucocorticoids are administered. For example, it was found that 10 mg. of prednisolone was equivalent in hyperglycemic potency to 40 mg. of hydrocortisone, irrespective of whether the doses of the drugs were administered 4, 8, 11, or 11½ hours before the blood glucose determinations,[1-3] and the relative hyperglycemic potencies of prednisolone and 6-methyl, prednisolone were in the same ratio at four hours and eight hours after they were administered.[1]

Since, under the conditions described above, there was a very good correlation between the potency of a dose of a glucocorticoid and the magnitude of the hyperglycemic response, and since it was possible to identify relatively small differences in potency by testing only a few subjects, it has become possible to estimate in human beings quickly and easily the hyperglycemic potency of a new glucocorticoid.

The hyperglycemic potencies of several of the newer glucocorticoids have been established recently in this laboratory using the methods described in this paper. The details of those experiments are reported elsewhere.[1] It is of interest, however, that the hyperglycemic potencies in man of all the glucocorticoids tested in this laboratory have been closely correlated with their anti-inflammatory potencies in man. This suggests that one

may deduce the anti-inflammatory potency of a glucocorticoid by testing its hyperglycemic potency in a few subjects using the simple technics described in this paper.

SUMMARY

Although the fasting blood glucose in man is not as responsive to the administration of glucocorticoids as is the blood glucose in the course of the intravenous glucose tolerance test, small elevations in fasting blood glucose were consistently produced under certain conditions by a single dose of a glucocorticoid. The magnitude of the hyperglycemia was variable from subject to subject but in each subject the magnitude of response produced by a single dose correlated well with the potency of the dose administered at certain levels of dosage.

Evidence is presented suggesting that the peak of hyperglycemic action of hydrocortisone occurs about six to eight hours after a dose is administered orally at a time when the peak of eosinopenic action has passed.

A simple method of determining the hyperglycemic potency of a glucocorticoid is described.

SUMMARIO IN INTERLINGUA

Factores Que Affice Le Responsa Del Glucosa De Sanguine Al Administration De Glucocorticoides In Humanos: Le Determination Del Potentias Hyperglycemic De Glucocorticoides

Ben que le glucosa del sanguine in humanos in stato jejun es minus responsive al administration de glucocorticoides que in le test de toleration pro glucosa intravenose, micre elevationes del glucosa sanguinee in stato jejun esseva effectuate regularmente sub certe conditiones per un dose unic de glucocorticoide. Le magnitude del hyperglycemia esseva variabile ab un subjecto al altere, sed in omne individuo, le magnitude del responsa producite per un dose unic se monstrava ben correlationate con le potentia del dose administrate a certe nivellos de dosage.

Es presentate datos a provar que le maximo del action hyperglycemic de hydrocortisona occurre circa sex a octo horas post le administration de un dose oral, quando le maximo del action eosinopenic ha passate.

Es describite un simple methodo pro determinar le potentia hyperglycemic de un glucocorticoide.

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