Hypoglycemic Actions of Phenethyl-, Amyl-, and Isoamyl-Diguanide

Robert H. Williams, M.D., Donald C. Tanner, M.D., William D. Odell, M.D

Seattle

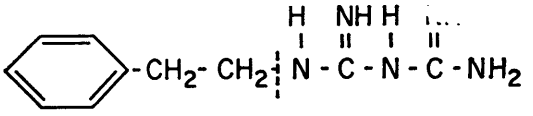
Phenethyldiguanide* (PEDG), a drug capable of producing hypoglycemia,[1,2] has recently been used in the treatment of diabetes.[3,4,5] This paper will discuss mechanisms by which the compound produces hypoglycemia. It will also evaluate the clinical usefulness of PEDG as well as that of related compounds, amyl- and isoamyl-diguanide (figure 1).

EXPERIMENTAL OBSERVATIONS

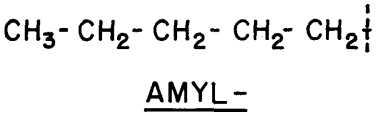
Mechanism of Action of Phenethyldiguanide: PEDG could produce hypoglycemia by causing: (a) wastage of food in urine or feces, (b) decreased gluconeogenesis, (c) increased insulin effect, or (d) increased glucose utilization, other than via insulin. These are considered respectively.

Wastage of Food in Urine or Feces: Hypoglycemia could result from an action comparable to that of phloridzin, but studies have shown that PEDG decreases glycosuria rather than increases it. Whether or not it decreases food absorption has not been reported, but it can cause a profound hypoglycemia in animals fasted for more than forty-eight hours and can also cause it in eviscerated animals. Therefore, mechanisms other than decreased food absorption must be very important.

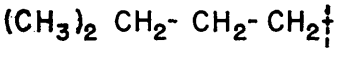
Decreased Gluconeogenesis: PEDG produces a marked decrease in liver glucose output,[2] the hepatic vein glucose becoming equal to that of the portal vein and vena cava. This is due neither to inhibition of glucose-6-phosphatase nor to increased storage of liver glycogen.[6] Indeed, in fasting guinea pigs, PEDG causes a marked depletion of liver glycogen, and this is not replenished even after administration of a large quantity of alanine.[6]



PHENETHYLDIGUANIDE (PEDG)



AMYL-



ISOAMYL-

FIGURE 1

The very low content of glycogen in the liver of guinea pigs so treated may account for the failure to obtain an increase in blood glucose concentration following glucagon and epinephrine.[2]

Since the foregoing studies suggested that PEDG decreases gluconeogenesis, nitrogen balance studies were conducted. A decrease was observed in both nitrogen excretion and urea formation.[6,7] However, as shown in the following experiment, PEDG administration caused the liver glycogen to remain at a subnormal level in spite of the administration of a large dose of glucose (figure 2).

Fifteen guinea pigs were allowed to feed for two hours twice daily for two days, and were then fasted for forty-eight hours. After this, they were divided evenly into three groups. Each animal in one group was injected subcutaneously with 20 mg./kg. of PEDG. Thirty minutes later this and another group were injected subcutaneously with 5 per cent glucose in saline (2 gm./kg.). The third group was given saline alone. The animals treated with PEDG were sacrificed 2½ hrs. later and the glycogen content of each liver was measured.

Presented in large part at the Seventeenth Annual Meeting of the American Diabetes Association on June 2, 1957, in New York City.

From the Department of Medicine, University of Washington School of Medicine, Seattle, Washington.

*This compound has also been designated as DBI, phenethylformamidinyliminourea and phenformin.

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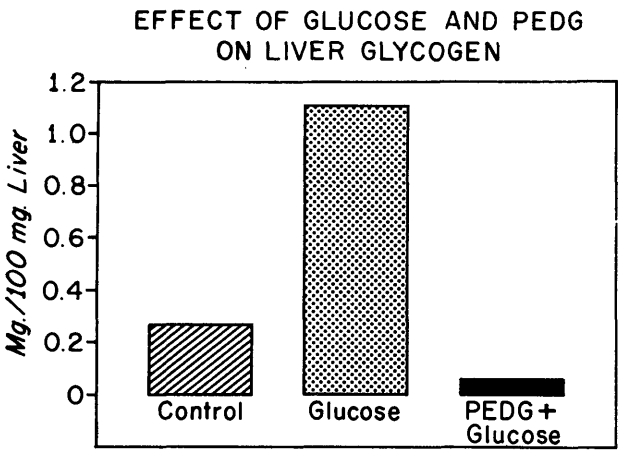

FIG. 2. The liver glycogen is expressed in terms of the amount of glucose liberated from glycogen.

A comparable experiment was done in which a smaller dosage (15 mg./kg.) of PEDG was given. This amount proved to be less effective in depressing the glycogen content and produced much less hypoglycemia.[2]

Whereas the foregoing studies suggest that PEDG decreases gluconeogenesis and thereby produces hypoglycemia, this is not its only mechanism, since in PEDG-treated, hepatectomized guinea pigs it produces a much greater hypoglycemia than that found in untreated hepatectomized animals.[2] This led to a consideration of the drug's effect on the supply of insulin.

Increased Insulin Effect: As reviewed recently,[8] there is much to suggest that tolbutamide increases insulin secretion and, therefore, the role of the pancreas in PEDG hypoglycemia was studied. It was found that although PEDG did produce a definite hypoglycemia in depancreatized[2] and in alloxanized animals,[1] it had a much greater effect on intact animals.

The question then arose as to whether the drug decreased the degradation of insulin caused by "insulinase." Whereas large quantities of PEDG (12 mM/L.) caused significant inhibition of degradation of insulin in vitro, doses sufficient to produce marked hypoglycemia caused only slight inhibition in vivo.[2,6] Moreover, as will be shown in the next section, though certain of the actions of PEDG and insulin are similar, the two differ in many respects.

Increased Glucose Utilization: Whereas PEDG, like insulin, increases the glucose uptake in the rat diaphragm,[6] it is unlike the hormone in that it may lead to a decrease in the glycogen concentration rather than an increase. The question now arises as to whether the drug causes an increased rate of glucose oxidation. In guinea pigs treated with PEDG followed by glucose-C^{14}, there was no increase in the CO_2 or $C^{14}O_2$ expired.[6] However, through the aid of Dr. Robert H. Silver, it was found that there was an increase in respiratory quotient (R.Q.). After subcutaneous injection of 20 mg./kg. of PEDG in three guinea pigs, the R.Q. values were as follows, with the respective control volumes in parentheses: Initial, 0.77±.03 (0.76±.02); forty minutes, 0.78±.02 (0.74±.03); eighty minutes, 0.88±.03 (0.74±0); 120 minutes, 0.98±0.09 (0.75±.02). When 100 mg./kg. of the drug was given, there was an increase in forty minutes from 0.79 to 0.97. Thereafter the animals began to die of hypoglycemia. In eight diabetic patients, with much less accurate facilities available, we have found no change in the R.Q. or oxygen consumption with average daily doses of 150 to 200 mg. of PEDG.

In preliminary experiments on guinea pigs injected subcutaneously with PEDG, diaphragm, adipose tissue and liver slices, removed two hours later and incubated with glucose-C^{14}, were not found to have an increase in radioactivity in the protein or lipid fractions. The question now arising is what happens to the glucose after its rapid disappearance in the muscle?[9] Since PEDG causes lactic acid to accumulate in significant amounts in vitro and in vivo, and since it produces a decrease in CO_2 of diaphragm,[7] it is suggested that the compound promotes anaerobic glycolysis.

Thus, PEDG presumably produces hypoglycemia in two major ways: (a) by increasing anaerobic glycolysis and (b) by decreasing gluconeogenesis. It seems likely that isoamyl- and amyl-diguanide may act similarly.

As recently reviewed by Creutzfeldt,[9] decamethyldiguanidine (Synthalin) has been shown to have many actions like those we have observed with the diguanides (table 1) and, indeed, has been used effectively in the treatment of patients with diabetes. However, certain investigators demonstrated that it was toxic to the liver and kidneys. Such damaging effects have not been found with some of the other diguanides studied.[10,11,12,13] For example, p-chlorophenyl-iso-propyl-diguanide acetate (Paludrine) has been studied extensively and has been considered one of the safest of all the effective antimalarial compounds. Another diguanide, 1:6-di-4'-chlorophenyldiguanidohexane, given to rats for one year, was relatively nontoxic.[13] Moreover, the observations made with phenethyl-, isoamyl- and amyl-diguanide have not demonstrated significant toxic effects.[1-7,10,11] Because of special interest in the possible toxic effects of amyl-diguanide, the following studies are detailed.

We injected seven young guinea pigs subcutaneously twice daily for five and one-half weeks with 10 mg. (per kg. of body weight) of the drug in 1 per cent acacia.

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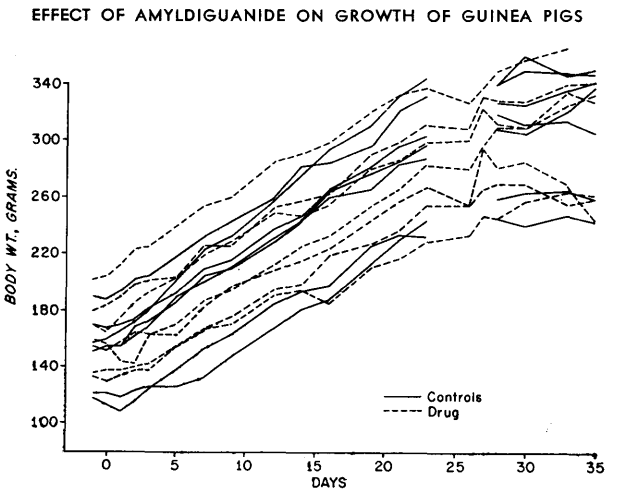

FIG. 3. The animals were weighed every two days. Note that the weight gain was comparable in the treated and the untreated animals.

This dosage is larger, on a per body weight basis, than that used clinically. Seven controls were injected with the same constituents, excluding the diguanide. As can be seen in figure 3, the drug-treated groups gained weight at the same rate as the untreated ones. Occasionally, certain of the treated animals developed the clinical picture of hypoglycemia but rapidly responded to food. No significant alteration was found at autopsy examination of all the abdominal and thoracic viscera, and histological examination kindly made by Dr. Paul Griffith (Assistant Professor of Pathology) of the liver, kidney, spleen, pancreas, adrenal and gastrocnemius revealed no toxic effect. However, after carefully weighing the liver, left kidney, both adrenals and the thyroid, it was found (table 2) that the adrenals of the drug-treated group were enlarged. This presumably was a response to the hypoglycemia. The livers showed borderline enlargement, but there was no increase in the weights of kidney or thyroid. Therefore, there was no evidence of anatomical damage.

TABLE 1

Comparisons of some hypoglycemic compounds

	PEDG	Synthalin	Insulin	Tolbutamide
Hypoglycemia				
without pancreas	+	+	+	0
without liver	+	+	+	+
Glucose uptake*	inc	inc	inc	0
Muscle glycogen*	dec	dec	inc	0
Liver glycogen	dec	dec	±	inc
Liver glucose output	dec	dec	dec	dec
Glucagon hyperglycemia	0	0	+	+
Epinephrine hyperglycemia	0	0	+	+
Glucose oxidation	0	?	inc	inc
Respiratory quotient (man)	0	—	inc	0
Lactic acid†	inc	inc	inc	±
Permanent damage (man)‡	0	+	+	0
Alpha cell damage	0	+	0	0

*Diaphragm in vitro.
†Presumably by anaerobic glycolysis in muscle.
‡No permanent damage has been demonstrated to occur in man from PEDG or tolbutamide therapy, but some may appear with extended studies. Synthalin has caused hepatic and renal alterations. The most severe permanent damage from insulin is found in the central nervous system and is associated with severe hypoglycemia. Of course, the other compounds presumably could cause the same type of damage if they caused as severe and as prolonged hypoglycemia, but so far they have not shown this inclination.
+ signifies a positive response.
0 signifies a negative response.
inc signifies an increased response.
dec signifies a decreased response.

Many of these changes occur only under certain special conditions. The conditions for study of the various phases differed, but those for any one phase were relatively comparable. Except where indicated differently, the studies were with intact animals.

TABLE 2

Effect of amyl-diguanide on organ weight*

	Adrenals mg.	Thyroid mg.	Left kidney mg.	Liver gm.
Control	34.4±5.6	13.3±1.8	500±37	3.0±0.3
Amyl-diguanide	50.2±6.9	14.2±2.3	550±54	3.7±0.3

*All organ weights are indicated per 100 gm. body weight.

CLINICAL STUDIES

Details concerning our investigations on the use of phenethyl-, isoamyl- and amyl-diguanide in diabetic patients will be reported later. The present general comments are based on preliminary observations made while treating twenty-six patients with PEDG, twenty-five with isoamyl-diguanide and fifteen others with amyl-diguanide. For certain patients, each of these compounds has been more effective in controlling diabetes than either tolbutamide or insulin. In other instances, however, control has been less successful. Our own experiences, as well as those of others,[3,11] indicate that the diguanides are more effective in juvenile diabetes than is tolbutamide. In some cases the combined use of insulin and a diguanide has given smoother control than either one alone.

The chief untoward effects of the diguanides are anorexia, nausea and/or vomiting. These symptoms have occurred, so far, in approximately one-third of the patients and are related somewhat to the size of the dose. Few patients experience such symptoms with 100 mg. daily, or less of PEDG or amyl-diguanide, or with less than 200 mg. daily of isoamyl-diguanide. However, doses

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larger than these are required in most subjects for control of the diabetes, and the higher the dosage, the greater the percentage of those who will experience side effects. There is a significant individual variation in susceptibility to these effects; some patients can take with impunity doses several times the amount which would cause unbearable nausea in others. Upon cessation of therapy, the ill effects subside within a day or two, and no further sequelae are observed. Isoamyl-diguanide is less satisfactory than either of the other agents in that it causes nausea and/or vomiting more frequently and exerts less complete control of diabetes. Whether or not amyl-diguanide will prove to be superior to PEDG, which we consider a possibility, depends upon the results of further studies; these are now under way.

Frequent evaluations of liver and kidney function in these diguanide-treated patients, and careful observations of the patients during the course of treatment, have failed to demonstrate any other significant untoward reactions. However, much more extensive investigations will be required to determine the net usefulness as well as the hazards which may be involved in this type of therapy.

SUMMARY

Studies are reported suggesting that phenethyl-diguanide lowers blood sugar by (a) promoting anaerobic glycolysis, with increased glucose utilization and (b) by causing decreased gluconeogenesis, with a decrease in the output of glucose from the liver.

In preliminary investigations using phenethyl-, isoamyl- and amyl-diguanide in the treatment of diabetes, each has appeared preferable to tolbutamide or insulin in some patients. Nausea and/or vomiting occur relatively frequently and, when they do, cessation of diguanide therapy may be indicated. No other significant ill reactions from these drugs have been observed. Some patients have never experienced side effects in spite of relatively large doses. Isoamyl-diguanide appears less satisfactory than the other diguanides.

Much more extensive investigation will be required to determine the net usefulness as well as the hazards of this type of therapy.

SUMMARIO IN INTERLINGUA

Le Actiones Hypoglycemic De Phenethylo-, Amylo-, E Isoamylo-Diguanido

Es reportate studios que pare indicar que phenethylo-diguanido reduce le sucro del sanguine per (a) promover glycolyse anaerobi—con le effecto de un augmentate utilisation de glucosa e (b) causar un retardo del gluconeogenese—con le effecto de un reducite rendimento hepatic de glucosa.

Investigationes preliminari con phenethylo-, isoamylo-, e amylo-diguanido como medicationes anti-diabetic ha monstrate que omne iste compositos es a preferer a tolbutamido e a insulina in certe patientes. Nausea e/o vomito occurre con relativemente alte frequentias. In lor presentia, cessation de diguanido es possibilemente indicate. Nulle altere significative reactiones adverse ha essite observate in le uso de iste drogas. Il ha patientes qui ha nunquam experientiate ulle effectos lateral in despecto de relativemente alte doses. Isoamylo-diguanido pare esser minus satisfactori que le altere diguanidos.

Multo plus extense investigationes es requirite pro determinar le utilitate nette como etiam le riscos de iste typo de therapia.

ACKNOWLEDGMENTS

We are very grateful to Dr. Georges Ungar and Dr. Louis Freedman of the U. S. Vitamin Corporation for the generous supply of the compounds and for other aid. We also appreciate the kind assistance given by Dr. Paul Hyde, Dr. Hiromichi Narahara, Dr. Henry Tomizawa, Dr. Jean Tyberghein and Miss Maureen O'Connell.

These investigations were aided by grants from the Atomic Energy Commission, the U.S. Public Health Service, the Warren Orr Fund and the U. S. Vitamin Corporation.

ADDENDUM

Additional studies have revealed that approximately two-thirds of our patients have experienced untoward reactions to diguanide therapy. Slightly more than one-half observed the gastrointestinal complaints that have been mentioned. Approximately one-third of the patients taking this therapy for more than one month lost a few pounds in body weight, but this was regained rapidly upon substituting insulin for the diguanide. No permanent ill-effects of any type have been observed.

Continued observations are necessitated for the most accurate appraisal of this type of therapy. At present it appears that it has a very limited field of usefulness, but it has exhibited significant merit in certain subjects, particularly brittle diabetics. An important objective is to determine whether some of the untoward effects can be eliminated while preserving the benefits—such is a possibility.

Steiner et al. have recently found that phenethyldiguanide significantly inhibits cytochrome oxidase. This could account for many of the biochemical changes described in this paper.

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GROUP DISCUSSION OF THE PRECEDING PAPER AND OF "CLINICAL TRIALS WITH DBI, A NEW (NON-SULFONYLUREA) ORAL HYPOGLYCEMIC AGENT," BY LEO P. KRALL, M.D., AND RAFAEL CAMERINI-DAVALOS, M.D.

JULIUS POMERANZE, M.D., (*New York City*): Our problem, as the first clinical investigators with phenylethylbiguanide (DBI), was to establish a proper clinical dose and indicate absence of toxicity. Oral and intravenous glucose tolerance curves in normal and diabetic subjects established that 100 mg. of DBI orally had a sugar lowering effect. They also showed some evidence of increased peripheral utilization of glucose. (*Proc. Soc. Exp. Biol. & Med.* 95:193-94; Scientific Exhibit, AMA Annual Meeting, June, 1957.)

We have had more than fifty patients under study for eleven months. A young male diabetic was the first patient started with the drug. He was poorly controlled with 70 to 80 units of insulin per day. Two hundred fifty milligrams of DBI and 20 units of insulin effectively controlled the diabetes.

During the course of treatment, this patient on two occasions experienced severe hypoglycemic reactions with nausea and vomiting. He rapidly recovered following glucose therapy and readjustment of insulin and DBI dosage. Repeated liver function studies and renal and hematologic studies showed no evidence of any damage having been done during these severe episodes, or by the continuation of the drug for a period of eleven months.

We have two other young diabetics who are receiving 150-200 mg. per day of this drug for periods up to six months without insulin. This drug is effective in the juvenile type of diabetic, although exogenous or endogenous insulin is probably required. We also have patients who have had diabetes for as long as twenty-eight years and have responded satisfactorily to the drug without insulin.

I think it is important at this time to enumerate both the disadvantages and advantages of the drug. The disadvantages, of course, are the side effects, the occasional severe hypoglycemic reaction and the ketosis following the vomiting incurred by the use of the drug.

The advantages, of course, are the oral administration of the drug, its effective hypoglycemic effect without any evidence of toxicity to date, its effectiveness in the young diabetic patient, especially in helping to smoothen their course. The labile patient, who is not easily controlled with insulin dosage, can be better controlled with supplemental use of the drug. It has always been my hope that in the treatment of diabetes, something may become available to control the degenerative as well as the biochemical aspects of the disease. This may not be such a drug, but studies such as this may develop a drug which will have this desirable effect on the degenerative changes.

THOMAS H. MCGAVACK, M.D., (*Martinsburg, West Virginia*): In connection with the use of DBI I would like to emphasize the word of caution that was implied in the data on one of the slides shown by Dr. Krall. We have followed about twenty patients to whom this drug has been given. It was quite difficult to determine the effective dose in any given subject, without running the chance of hypoglycemia on the one hand, or acidosis on the other. In other words, the toxic and therapeutic

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dosages seem very close together.

Our second objection to DBI is the high incidence of side effects; three-fourths of our patients developed one or more toxic symptoms, chiefly of a gastrointestinal nature.

In the third place, we have seen acidosis occur in the presence of normoglycemia and aglycosuria. This occurred without warning in one individual. I think we must proceed with the utmost caution in the clinical use of this drug.

HENRY T. RICKETTS, M.D., (*Chicago*): Despite the very interesting clinical and experimental observations that have been presented, I have not heard enough yet to satisfy me concerning extensive animal experimentation with these drugs, with a better delineation of long-term toxicities, MLD's and so on. I wonder if those who have been using this drug have any background in this respect, and if so, would they please give it.

GARFIELD G. DUNCAN, M.D., (*Philadelphia*): I am especially interested in the results of DBI therapy in the case of one of the juvenile patients reported by Dr. Krall. It is not rare to see all detectable evidences of diabetes disappear temporarily in adequately treated young patients only to find the diabetes return in a more severe and permanent form after a short period. I would like to ask whether or not DBI had been discontinued. If so, did hyperglycemia and glycosuria appear promptly? If this were not done, proof of the effectiveness of DBI would be lacking in this case. Furthermore, if DBI therapy was uninterrupted and hyperglycemia and glycosuria recurred, this might be interpreted as an indication of decreased effectiveness of the drug when in fact it would probably indicate the end of the short remission sometimes seen in these patients when no drug therapy was involved.

GEORGES UNGAR, M.D., PH.D., (*New York City*): I would like to answer Dr. Ricketts' question since I have been doing most of the animal work with DBI, besides Dr. Williams' group.

We have tried DBI in the following species: guinea pigs, rats, mice, rabbits, Rhesus monkeys, cats and dogs. With the exception of the dog, all species responded with hypoglycemia. Monkeys and guinea pigs are the most responsive animals.

There are great difficulties involved in evaluating the toxicity of a hypoglycemic drug. Like insulin, DBI could be considered as a highly toxic material since both kill the animals by hypoglycemic shock. This, however, is not a truly toxic effect since it is inherent in the pharmacological action itself.

The best we could do was to give DBI at dose levels which lower blood sugar by about 30 per cent. We have done this in guinea pigs, rats and monkeys for varying periods of time without producing any toxic symptoms or any biochemical, hematological or histological changes. At the end of this year, when the results of a six months' toxicity test are available, we can make a more definite statement.

ROBERT H. WILLIAMS, M.D., (*Seattle*): With regard to Dr. McGavack's comment relative to ketosis, I wish to state that even after prolonged observation we have observed no ketogenic effect of PEDG in any patient. Ketosis was observed in two subjects but this apparently occurred in spite of therapy rather than due to it. Guinea pigs kept fasting for four days and injected with large doses of PEDG did not develop any more acetonuria than the controls.

With respect to Dr. Duncan's comment relative to stopping and starting the PEDG therapy periodically, I wish to state that we have done this many times and have frequently switched to other oral compounds. It is clear that the biguanides significantly lower the blood sugar in many patients.

LEO P. KRALL, M.D., (*Boston*): Dr. McGavack, I agree perfectly that it is a very difficult drug to use. It certainly has many uncertainties that occur quite suddenly. I also agree that the therapeutic dose and that level which causes side effects are fairly close. As yet, we have no proof that the therapeutic dose is anywhere near the toxic dose, if any.

Dr. Ricketts, I regret there is no more information available concerning the animal experimentation, which has been under study for some two years by Dr. Georges Ungar. Dr. Julius Pomeranze has liver function studies on patients receiving DBI for ten to twelve months with no abnormal findings.

Dr. Duncan is correct about the juvenile diabetes, of course. No one can disagree with that. This case cited was given placebo during which period the blood sugar became elevated. She received insulin when she came into the hospital for three or four days. For all practical purposes, you might assume that she is relatively an untreated diabetic and certainly not the severest type. At this time we cannot fully evaluate this drug nor can we compare this with other drugs. It is far too early for that. We merely limited ourselves to watching patients, trying to work out dosage schedules, observing the blood sugar lowering effect, and trying to follow the earliest possible evidence of toxicity.

You must remember that these observations have been taking place for only six months and with only fourteen patients.

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