Oral Hypoglycemic Agents

Panel Discussion

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PRESIDENT REED: The panel will discuss some of the new oral hypoglycemic agents. I take this opportunity to introduce Dr. Arthur R. Colwell, Sr., of Northwestern University Medical School, who will moderate the program.

DR. COLWELL: The release is imminent for general use of a sulfonamide compound which, when given by mouth, has unquestioned ability to lower blood sugar values both in normal and in many diabetic subjects. All are properly interested in several major points. How does the substance act? How should it be used in treatment? Are there risks in its use? What is its relationship, if any, to insulin? This panel will endeavor to provide answers to these and other questions. If there is disagreement among us it will reflect the difficulties which have been encountered in trying to find reliable answers to many important questions, particularly concerning mechanisms of action.

A great deal of experimental and clinical data has been accumulated during the last two years or so concerning the sulfonylurea compounds. The experts at my side are well-informed concerning them and have contributed generously to their study. To start the discussion, I will ask each of the panelists to give us a brief orientation on certain aspects of the subject. For the most part, this will concern the sulfonylurea compounds, and specifically tolbutamide, which is marketed under the trade name of Orinase, the only compound available now clinically in this country.

Dr. Root, will you give a brief historical background and identification of these compounds?

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DR. ROOT: You all have probably reviewed the history of these compounds. I will remind you that some years ago, Loubatières did work in France with an isopropyl thiodiazol and found it lowered blood sugar, but there were side effects which made it undesirable for clinical use. In more recent years, a German group, looking for soluble sulfonamides similar to Gantrisin, noticed reactions in some of their patients which appeared to be hypoglycemic in character. When they investigated further, it turned out that they were producing severe hypoglycemia in some patients. Therefore they started studying the compound in diabetic patients.

This was the compound BZ-55, or carbutamide. Since then Hoechst in Germany developed D-860 which we know as Orinase, and a great deal of work has been done on compounds of this type, studying the structure-activity relationship. There are a number of compounds related to carbutamide and Orinase which lower blood sugar in normal animals and in diabetic patients. About all that can be said at the moment is that the sulfonylurea part of the molecule seems to be necessary for any great degree of activity. It is possible to modify the structure at both ends of the molecule and still maintain some degree of activity.

DR. COLWELL: Dr. Levine, isn't it strange that sulfonamides should lower blood sugar? How do they exert this action?

DR. LEVINE: It is impossible to give all the available evidence in one or two minutes. The β cells of the islets of Langerhans are sensitive to the action of the sulfonylureas. There is some evidence that as a result of such action a small amount of insulin is ejected from the β cells under the influence of sulfonylureas. The presence of the pancreas appears to be necessary for the

drugs to show effects. The presence of the liver does not seem to be essential. There is some evidence that in the absence of the pancreas, but in the presence of exogenous insulin, some potentiating effect is present. The mechanism of this potentiation is unknown.

One thing that seems clear, however, is what the sulfonylureas do not do. They are not substitutes for insulin and do not operate in vitro on insulin-sensitive tissues by increasing their glucose entry or utilization. And they do not operate via the known endocrine antagonists of insulin. Sulfonylureas are still active in the absence of the hypophysis, the adrenals, the thyroid and the gonads. Either endogenous insulin or exogenous insulin at certain dosage levels is necessary for the action of the sulfonylureas. This is about as far as one can go at the moment.

DR. COLWELL: Thank you, Dr. Levine. You are always very lucid on this subject. Dr. Duncan, how are the sulfonylureas used in practice? Which patients are responsive? In which diabetics should they be used?

DR. DUNCAN: In general one can say that sulfonylurea compounds should not be used in patients whose diabetes can be controlled without drug therapy and yet maintain adequate nutrition. With rare exceptions these compounds are not effective in the younger age group, but they correct hyperglycemia and glycosuria in most patients who have developed diabetes in adult life and who are over forty years of age.

I fear there will be a temptation to give these drugs to diabetic patients who are obese rather than reduce weight by food restriction. This would encourage the maintenance of obesity, which is known to contribute to the development of degenerative changes.

DR. COLWELL: Dr. Dolger, do you want to comment on this?

DR. DOLGER: There are two problems here. One is that the longer we use Orinase, the more difficult it is to anticipate which patients will respond clinically. Some with high insulin dosages do very well, while others with mild diabetes do not respond despite a maximum dose.

The second problem involves the selection of patients by the physician. The best candidate is the relatively mild diabetic who has insignificant glycosuria but who is unable to maintain weight on a limited diet. In order to raise the diet the physician will prescribe Orinase. When the physician gains experience with the drug he will expand its use to include persons taking insulin.

DR. DUNCAN: For clarification, a patient may take more than 100 units of insulin daily, but not necessarily have severe diabetes. An obese person who has mild diabetes may tolerate this amount of insulin. This does not mean that he should be given insulin. He should have his weight reduced instead, and not use either insulin or Orinase.

DR. COLWELL: To start the specific questioning period I suggest that we establish an objective. Suppose we first discuss what are the features which make a drug ideal for use by mouth in maintenance therapy of diabetes.

DR. LEVINE: I think the ideal agent would be one which is orally effective, does not irritate the gastrointestinal tract, does not have any toxic effects, and has the established actions of insulin.

DR. DUNCAN: It might be well to emphasize that insulin is dependable in patients with acute infections and ketosis, while the oral preparations are not.

DR. ROOT: Fundamentally the ideal is something with a controlled release factor that would be activated by rising blood sugar and deactivated by falling blood sugar.

DR. DOLGER: I should also like the ideal agent to prevent degenerative changes.

DR. COLWELL: It should be useful in all diabetics, also. Dr. Dolger, how do you think tolbutamide qualifies as an ideal substance?

DR. DOLGER: The answer is simple: it is not the ideal.

DR. COLWELL: Dr. Root, do you want to give us an idea of dosage? Let us take the animal evidence first. What is the effective range of dosage in animals, and how does this compare with human dosages?

DR. ROOT: The first thing to remember is that, in general, effective dosages of pharmacological agents in laboratory animals are usually larger than those used clinically. This is not true for every drug, but it certainly is true of many. Although there is some difference between carbutamide and tolbutamide, the dosage necessary to lower blood sugar in the normal animal is considerably higher than in man. If converted to man, the minimal dose which is effective in rabbits and rats would be equivalent to about 3 gm. in a 70-kg. man. Dog dosages are slightly lower, perhaps equivalent to 1.5 to 2 gm. for a 70-kg. man. Three times this dose in the dog and other animals can be used without toxic effects. These doses produce about the same blood levels as those considered desirable in patients.

There are some species differences in mechanism of action and rate of metabolism of the drug. The monkey tolerates these compounds very well. One can give as much as 150 mg. per kg. per day to a monkey without producing toxic reactions. This would be equivalent to

a dose of approximately 10 to 11 gm. for a 70-kg. man. There have been few signs of toxicity in normal animals until the dose and the blood level are much higher than any used clinically. In such situations the animals develop anorexia and usually die after several days. No tissue changes can be detected in most of the animals.

DR. COLWELL: Is there any distinction between carbutamide and tolbutamide in these respects?

DR. ROOT: There is no difference except for a slight difference in effective dosage.

DR. COLWELL: Dr. Dolger, will you discuss dosage in clinical treatment?

DR. DOLGER: There are three types of patients. In the mild diabetic on a diet a small dose of Orinase (0.5 to 1.0 gm. daily) may be effective. The patient with untreated diabetes who is desirous of not using insulin can be given a dose of 3 gm. This is reduced as results warrant. The patient taking insulin should begin with a 3-gm. dose daily. Insulin is reduced accordingly, depending on the dose. If it is 10 units, we would stop it. Anything over about 10 units is cut down in steps of 10 to 20 per cent daily. A patient taking 100 units of insulin would drop 10 units per day, or 20 units every two days, as a trial. At the first sign of failure, best indicated as increasing glycosuria, Orinase should be abandoned and the original insulin dose resumed.

DR. COLWELL: We will come back to the question of transition from insulin to the drug a little later on. Coming now to toxic reactions and side effects, I should like to be quite practical. Dr. Root, why was carbutamide withdrawn from clinical testing?

DR. ROOT: In clinical trials with carbutamide in about 10,000 cases, the incidence of side effects appeared to be at least 5 per cent. This would not be important if the side effects had been mild, but they ranged from mild skin rashes to agranulocytosis, exfoliative dermatitis, one case of interstitial myocarditis, and two cases of apparent liver damage.

DR. COLWELL: I should like to supplement this with a little information on tolbutamide (Orinase), which Dr. O'Donovan of The Upjohn Company was kind enough to give me a short time ago. Apparently tolbutamide is less toxic than carbutamide. It causes fewer side reactions and they are less serious. This is generally attributed to the fact that the benzene ring has a CH_3 group in the initial position instead of an NH_2 group.

O'Donovan has data on about 5,000 cases collected as of April 1957, from physicians making clinical trials of tolbutamide. The longest any patient had used the drug was about eighteen months. About 170 of these 5,000 cases had had reactions of some kind, an incidence of about 3 per cent. The largest number, about 1 per cent of the total, showed nausea, vomiting and anorexia. Nausea and vomiting due to diabetic acidosis which followed withdrawal of insulin were included. This may well be the chief danger, now that the drug is going into widespread use. Some sixty patients had mild skin reactions. There was no exfoliative dermatitis. Thirty-three had miscellaneous reactions such as headache, weakness and paresthesia. There were eleven leukopenias, with white counts of 1,800 to 3,000 but without any severe depression of granulocytes. A good many of the milder reactions subsided even though the drug was continued.

There have been two good studies of hepatic function, one by Dr. Marble in Boston and the other by Dr. Sherry in St. Louis. Both agree that there were virtually no functional signs of hepatic damage within the limits of the experimental conditions. When there were changes, they most often appeared as BSP retention and increased alkaline phosphatase. They were not striking, were inconstant, and very often temporary.

Dr. Duncan, it was reported yesterday that degranulation of the beta cells occurs, at least in experimental animals. What about this? What is the possibility of islet-cell exhaustion?

DR. DUNCAN: In Allen's work, and later that of Lukens in which animals were made diabetic by removing a large portion of the pancreas and then overfed, there were opportunities to observe the decrease in islet cell function precipitated by overfeeding. This would be a good type of experimental study with the sulfonylurea compounds. We have seen a few patients in whom glycosuria actually increased following the use of these drugs. Two belong to the group which probably produce little or no insulin of their own, namely the juvenile type. Hence it is unlikely that the increased glycosuria was due to exhaustion of the islets of Langerhans.

What has concerned me more is that an increasing number of patients on oral therapy have had to return to insulin, despite an apparently favorable effect from the drug, after four to ten months. One wonders if those patients could not tolerate stimulation of the islets. One can picture reserve islet function that may stand stimulation and produce sufficient insulin to do the job without harm. In other cases continuous stimulation might cause islet cell exhaustion. Of course, clinic patients might do well with oral therapy, and then be careless with the diet. Yet, I have followed several private patients in whom I have complete confidence. In each of three patients we had proved the need for insulin to control the diabetes at a satisfactory state of nutrition. Tolbutamide was shown to be equally effective. Each of

these patients now has had to resume insulin to keep the diabetes under control.

DR. COLWELL: How about the concurrent use of the sulfonylureas with other sulfonamides, with barbiturates or with alcohol?

DR. DOLGER: Everything is compatible with Orinase except alcohol. Following its ingestion some of our patients have developed a cerise color of the skin. The administration at the same time of other sulfonamides, antibiotics, tranquilizers, or barbiturates has not interfered with the effectiveness of Orinase or vice versa.

DR. DUNCAN: I would be interested to know if any of Dr. Dolger's patients have had to return to insulin therapy after having had initially a satisfactory response to oral therapy?

DR. DOLGER: Between 5 and 10 per cent of our group using Orinase showed signs of relapse after four or six months. Mounting glycosuria and hyperglycemia justified discontinuance of Orinase and return to insulin. In these instances the subsequent insulin dose was no higher than that used originally. The explanation for such a relapse eludes us. In only a few people does it seem to be related to an increased diet or gain in weight. In many diabetic patients there is a rising need for insulin, of course, with passage of time.

DR. COLWELL: Do we know anything about the use of sulfonamides in renal disease? How about their use in pregnancy?

DR. LEVINE: You have touched upon two subjects about which there is very meager information. In the Kimmelstiel-Wilson syndrome the drug might accumulate in the blood due to renal insufficiency and lead to side reactions not manifested otherwise. Pregnancy usually occurs in diabetes of juvenile onset which has been treated with insulin until the fertile period. In those instances one would not expect responsiveness to the drug.

DR. COLWELL: It should be pointed out that in contrast to carbutamide it is very difficult to follow blood levels with Orinase. The methods are difficult to establish in the ordinary laboratory.

How about the effectiveness of the sulfonamide compounds in experimental diabetes?

DR. ROOT: Much of this was covered by Dr. Ricketts and in the discussion of his paper this afternoon. The sulfonamides are not effective in the totally depancreatized animal. That goes for the dog and also for the monkey. If alloxan diabetes is severe the drugs are not effective in a variety of animals. Our experience with the use of a sulfonylurea plus suboptimal insulin dosage has given results similar to those reported by Dr. Ricketts in the dog. The same thing happens in the alloxan diabetic dog, and there is some indication that it occurs, also, in the depancreatized monkey.

The type of toxic reaction described by Dr. Ricketts has been found in Dr. Best's laboratory, by Dr. Schambye in Denmark, and by our group. It occurs with carbutamide, with tolbutamide and with several other similar compounds. It seems to be inherent in all of the compounds that we have looked at so far. I didn't get a chance to reply earlier to Dr. Williams' comment that it may be due to a lack of exocrine secretion from the pancreas. The same type of toxic reaction occurs in the alloxan diabetic dog as in the depancreatized dog.

The damage seems to be in the liver. There is a gradual increase of serum alkaline phosphatase and glutamic-oxalacetic transaminase, together with a gradual decrease in serum proteins, especially in the albumin fraction. Although we have not seen it very early, in the later stages there is prolongation of prothrombin time, with capillary bleeding in the intestinal tract.

DR. COLWELL: How about the clinical counterpart of experimental diabetes in which the drugs are ineffective, Dr. Levine?

DR. LEVINE: They are ineffective in the juvenile cases. The major reason for believing that the main activity is exerted on the beta cell is the almost perfect correlation of the degree of effectiveness with the age of onset of diabetes. This may be correlated with Wrenshall's studies in Best's laboratories, which show a similar correlation between the insulin content of the pancreas at death and the age at onset of diabetes. The sulfonylureas are not active in the depancreatized human, either with or without insulin. There is some potentiation of insulin in dogs. This may be a question of species difference. I hate to invoke species difference, because that is always the easy way out.

DR. COLWELL: There has been a good deal of comment about screening tests for the selection of these drugs. Dr. Duncan, is there a good routine method of selection?

DR. DUNCAN: Three groups can be ruled out at once as not being suitable candidates for such therapy. First, patients with acute complications, infections, fever ketosis, and many surgical conditions; second, those who do not need insulin under ordinary circumstances to control the diabetes; and third, juvenile diabetics. More than 70 per cent of uncomplicated diabetes occurs in patients who are overweight. That reduces greatly the number of patients for whom this drug might be indicated, if you agree that diabetes in the obese should be controlled by reducing weight.

We went through three different phases in screening our patients. First, we wanted to find out how quickly and to what degree the drug acted, and the duration of its blood-sugar lowering effect. We divided the diet into twelve equal liquid formula feedings and gave one of these every two hours around the clock. This is not to be considered a form of treatment. After having reduced the insulin sufficiently to allow hyperglycemia and glycosuria, we were then able to observe the rate and degree to which the drug reduced the blood sugar and the duration of its effect. The chief handicap of this method was that it entailed several days.

In the second method the insulin was also reduced to provoke glycosuria and hyperglycemia—a reduction of 10 or 15 units was usually adequate. A blood sugar determination was then done before each meal and after bedtime for one control day. These tests were repeated the following day when tolbutamide was given. By contrasting the two curves an approximate effect of the drug could be estimated.

Recently we have used a more satisfactory test for identification of patients who do not respond favorably to tolbutamide. Such patients need insulin, of course. The dose is reduced by one-half or even omitted if the patient comes into the hospital. (That is desirable in questionable cases.) Following the sharp reduction or omission of insulin and the simultaneous administration of tolbutamide (1 gm. with each meal on the day of the test) each successive urine specimen is tested for sugar and ketones. If a severe grade of glycosuria appears and does not subside it is unlikely that a favorable response will be seen with prolonged therapy. If acetone appears in the urine in increasing amounts within twelve hours, it is a danger sign. Such a patient will not be benefited by tolbutamide and must return without delay to his former insulin therapy. If ketones do not appear, it does not necessarily mean that the patient will be benefited.

The potential danger of abrupt withdrawal of insulin deserves emphasis. Patients who have a real need for large amounts of insulin will be exposed to less risk if they are admitted to the hospital for initial precautionary testing.

DR. COLWELL: Does anyone want to add anything concerning the transition from insulin to sulfonylurea?

DR. DOLGER: I am against hospitalizing patients for initiation of Orinase therapy, because when it becomes available to everybody there will not be enough hospital beds. Secondly, it entails unnecessary expense, besides the trauma of hospitalization. Yet, an uncooperative patient is one that we can not trust. We have had three serious episodes of ketosis in patients who deliberately misled us regarding their symptomatology when we were reducing the insulin to a lower level. These are patients whose eagerness to go off insulin is such that they will give false statements as to their symptoms, and deny the existence of glycosuria. The key to success is close cooperation with the patient when the transition is made, since there is no way of judging which patient may go into ketosis rather rapidly.

DR. COLWELL: Dr. Levine, except for the brief transitional period in which the transfer is made, is there any point in the combined use of insulin with Orinase?

DR. LEVINE: No. At first there was the thought that one might smooth out the labile diabetic by a combination of a smaller dose of insulin with Orinase. This has not been confirmed.

Since the major advantage of the drug is its oral effectiveness, I can see no point in giving one hypodermic injection and one oral pill instead of giving one hypodermic injection alone.

DR. COLWELL: We have two related questions. Do high doses cause hypoglycemia as with insulin? Is there any relationship between increasing dosage and response?

DR. DUNCAN: Yes. I think that the best response is obtained with a relatively small dose. We do not like to give more than 2 gm. daily to start with, and not more than 1 gm. daily in continued treatment. It has been shown that if the dosage is increased, as we might increase insulin to a very large dose, it may actually intensify the hyperglycemia rather than alleviate it.

DR. COLWELL: Will Orinase make labile diabetes more stable?

DR. LEVINE: I would say no. What do you say?

DR. DUNCAN: No, but an open mind should be kept on this aspect.

DR. DOLGER. No.

DR. LEVINE: We agree on one thing.

DR. ROOT: I am sorry, but my patients are all animals.

DR. COLWELL: When does a single dose of Orinase reach its maximum effectiveness during the day? When is the maximum action in the average diabetic patient as distinct from the normal?

DR. LEVINE: Probably between four and six hours; at most eight. Therefore, it might be most rational to divide the daily dose into two equal parts.

DR. COLWELL: Is there general agreement on this point?

DR. DOLGER: I could not demonstrate the difference between 3 gm. once a day and the same amount given in divided doses. Most of our patients take it as a single dose in the morning.

DR. DUNCAN: By dividing the day's nourishment into twelve equal amounts given at two-hour intervals, the greatest effect of a single dose of tolbutamide can be shown to occur between four and six hours. We have abandoned single in favor of divided doses for this reason.

DR. COLWELL: Suppose I am a doctor in practice who does not know much about this subject. Should I prescribe the drug for any and all diabetics? Only for those who use insulin? How much insulin? Only for those who do not?

DR. DUNCAN: Patients for whom oral therapy should be prescribed are those who, under usual circumstances, would require insulin and yet respond favorably to the oral medication. To this degree the drug is a substitute for insulin.

DR. DOLGER: I can think of many specific instances where Orinase can be prescribed. There is no doubt that for handicapped diabetic patients, those visually impaired, those whose problems of intelligence preclude taking insulin properly, in the socio-economic situation that exists in a fairly significant part of our population—if such diabetics can be taken off insulin and put on Orinase safely a great boon would be achieved. When it works, it is of great value to patients suffering from recurrent hypoglycemia due to insulin. Where getting meals or snacks on time is difficult, Orinase is more than a convenience; it improves the whole life situation.

DR. COLWELL: What contraindications are there to the use of the drug, Dr. Levine?

DR. LEVINE: The first is juvenile diabetes; the second is diabetes following pancreatectomy or pancreatic disease; the third is diabetes during pregnancy, because we do not know anything about it; the fourth might be renal complications; the fifth are those severe diabetics who may have been adults at onset of the disease, but who behave like juveniles. In other words, all juveniles are not young.

DR. DUNCAN: I would add to this rather complete list those patients having acute infections and ketosis.

DR. COLWELL: There has been some confusion about albuminuria in people taking Orinase. Dr. Dolger, do you want to say something about that?

DR. DOLGER: The administration of Orinase produces a flocculent precipitate when ordinary albumin tests of the urine are made. This precipitate is due to the excretion of a carboxylated product of Orinase. This will make it appear that the patient has albuminuria. The brochure distributed by the manufacturer describes the technic for distinguishing between pseudo and actual albuminuria. A simpler and accurate method for detecting albuminuria in the presence of a confusing precipitate of Orinase excretory product is the Albutest tablet of the Ames Company.

DR. COLWELL: We might use the last five minutes for each member of the panel either to discuss the papers on "DBI" which were given this afternoon, or else to answer some of the questions which are before them. There are a few which cover items that we have not discussed.

DR. ROOT: I am not competent to say anything about the "DBI" work. We probably have heard today all that has been done with it.

I would like to point out one more thing about the sulfonylureas. One sees it in animals as well as in patients. The drug's major effect seems to be on the fasting blood sugar. The effect on the postprandial blood sugar is less than one sees with insulin.

DR. LEVINE: I have a question here which is interesting. "Is there any indication that a classification of patients responsive to the sulfonylureas might serve to divide the syndrome of diabetes mellitus into further component entities?" In a way, yes. Indication can be found in the work on sulfonylureas, on the inhibitors of insulin action, and on the carriers of insulin in the plasma. Insulin assays indicate that the syndrome of diabetes mellitus, which we divide roughly into juvenile and adult onset varieties, might be classified instead into groups of individuals who do not manufacture insulin; those who manufacture insulin but do not easily release it in response to the normal stimulus; those who release it but have a substance in the plasma that inhibits its action; those who release it and have an inhibitor only during ketosis; and perhaps other varieties. We are approaching an era of classification on biochemical grounds. If the sulfonylureas do nothing else they have stirred up everybody concerned with diabetes.

DR. COLWELL: No one has pointed out yet today that the mechanism by which these substances act may be of even more importance than the drugs themselves.

DR. DUNCAN: I have several questioners to answer. The first asks "How do you correlate the following: Following glucose, given in a glucose tolerance test, there is a rise in the blood sugar. On Orinase therapy there is a fall following one-twelfth of the diet?"

In the glucose tolerance test, there is rapid absorption of a large amount of glucose, whereas the small feeding is absorbed more slowly and more uniformly. Furthermore, no blood-sugar lowering agent is given prior to the glucose tolerance test.

"Is not allergy to insulin an indication for Orinase?"

It is not particularly an indication for Orinase, but

rather a reason to find out to which insulin the patient is allergic, and whether he is allergic to the added protein or to the insulin molecule itself. If he is allergic to regular insulin, by all means desensitize him so that, if acute complications occur, he will not be deprived of its use. To use Orinase in place of insulin and do nothing more about insulin allergy would mean avoidable exposure to future difficulties.

"In a patient who has a blood sugar relapse after several months of therapy when do you discontinue Orinase?"

Discontinue it as soon as you decide Orinase is having no effect.

"How do you persuade the patient it is necessary to stop Orinase?"

By pointing out that his regimen is not adequate to control the diabetes.

"In resuming insulin therapy after failure with an oral agent, do you encounter sensitization to insulin?"

We have not had this experience. Such cases must be exceedingly rare.

"Are there other difficulties to be anticipated in the resumption of insulin?"

There are no difficulties. If oral therapy is inadequate, the insulin taken previously by the patient can be resumed promptly.

DR. DOLGER: In the light of this morning's conference and this afternoon's presentation, is it not logical to assume that a drug whose disadvantage is supposed to be that it works only via endogenous insulin may be superior to exogenous insulin?

DR. COLWELL: We must close now. On behalf of Dr. Marble, the Chairman of the Program Committee, and of the audience, I would like to thank the panelists for their interesting comments, and on behalf of the panel, to thank the audience for their attention and interest.

A Thirty-fifth Anniversary of Insulin Therapy and a Sixty-fifth Wedding Anniversary

H. I. Burtness, M.D., Santa Barbara, and E. F. Cain, M.D., Anaheim, California

The January 1956 issue of DIABETES commemorated the thirty-fifth anniversary of the discovery of insulin. Appropriate tribute was paid to the discoverers of insulin in Toronto, Sir Frederick G. Banting and Prof. Charles H. Best, and to Leonard Thompson, the first patient to receive insulin in Canada. We would like to supplement that report this year by reporting the case of Charles E. Cowan of Anaheim, California, a patient of the late Dr. William D. Sansum. According to our information, he is the first patient in the United States to receive insulin made here, and in May 1957 he celebrated his thirty-fifth year of insulin therapy. Mr. and Mrs. Cowan celebrated their sixty-fifth wedding anniversary on April 12, 1957. Such a celebration was an event in itself, but of greater significance was the fact that Mr. Cowan had lived to make it possible.

Mr. Cowan came to the Potter Metabolic Clinic in Santa Barbara on Nov. 8, 1920, the same day that Dr. Sansum arrived from Chicago to be director of the clinic. A brief history of this clinic may be of interest. It was established in 1919 by Dr. Nathaniel Bowditch Potter of New York City for the purpose of studying metabolic disorders, particularly diabetes, from the research and clinical viewpoints. Dr. Potter was a diabetic patient himself. Because of failing health, he had come to Santa Barbara and was unable to return to New York. Contributions, including funds for the project from the Carnegie Corporation, were transferred to Santa Barbara. With the financial assistance of friends here the Potter Metabolic wing of the Cottage Hospital was built. Dr. Potter died in July 1919, before the building was completed. In 1928 the Potter Metabolic Clinic be-