include only leukopenia in thirteen cases, but without agranulocytosis. In no instance did clinical symptoms or signs appear. There were no cases of anemia or thrombocytopenia. The skin changes were of varied nature with tolbutamide, usually of short duration, and often clearing in the face of continuing administration of the drug. Exfoliative dermatitis did not occur. There were no reports of hypothyroidism or of drug fever. The one fatality was associated with hypoglycemic coma in an eighty-four-year-old man who apparently took an unknown amount of tolbutamide during a period of six days when he was not under direct medical supervision. Obviously the same precautions and supervision are as essential with these new oral hypoglycemic agents as with insulin.

These comparisons indicate that tolbutamide so far has not exhibited the same type of serious toxic reactions found with carbutamide. Consequently, it is only fair to predict that the former drug will have some place in the management of the older, stable-type patient whose diabetes is not too severe and who does not develop ketosis when deprived of insulin. Dietary control of the obese individual will remain as essential as before and the fact that the sulfonylurea drugs seem to exert their effect primarily on endogenous glucose formation also emphasizes the need to avoid dietary excesses. Patients taking the drug must be kept under continuous observation in order to detect quickly the possible appearance of any new type of toxic reaction. The physician must also be aware that stress situations, such as trauma or infection, may worsen the diabetic state and ketosis may develop, with resulting ineffectiveness of the oral drugs. Under such circumstances the physician must be on the alert to step in with insulin to avoid disaster.

CHAIRMAN GRAEF: Thank you, Dr. Miller.

We come to our last presentation. I think I probably speak for most of you here when I say that we need a long view from the bridge. Are we on a bridge to a new form of therapy of diabetes, to an entirely new approach to the selection of patients for control? Can we now envisage a degree of control or prevention of the vascular complications?

Incidentally, you all, I am sure, noted that no reference was made, presumably because of the lack of long-range observations, on the effectiveness of the oral compounds in inducing cessation or recession of nephropathy, retinopathy or neuropathy.

I don't think I have to say any more about why we need Dr. Best, and it is a pleasure to welcome him here again to give us a "long view" perspective on this subject.

Closing Discussion

CHARLES H. BEST, M.D., D.Sc., (*Toronto, Canada*): I regret that another meeting in New York this morning prevented my attending the earlier session. I was particularly sorry to miss the presentation of Dr. Lazarow. My imagination has always been stimulated and my understanding increased by his contributions to our knowledge of the pancreas and of insulin. I suppose, however, that all recent evidence has confirmed and strengthened our opinions, formed many years ago, that insulin is a respectable physiological hormonal agent. It possesses all the qualifications of a hormone, which I need not discuss in detail here.

Certainly the work on glucagon has not yet reached the stage when the same can be said about it although great strides have been made. I have read the excellent paper that Dr. Bromer presented. This is a triumph indeed. We now know in detail the structure of glucagon.

I am sorry that I did not hear my friend, Dr. Anderson, discuss the interrelationship of insulin and glucagon, but I have to insist that we are on much stronger grounds when we study variations in insulin effect, using all available procedures, than we are when we investigate what may be the effects of glucagon. It has been inferred that the variations in blood sugar which are caused under certain circumstances when growth hormone is given, are due to glucagon liberation. There is little evidence for this as I will discuss in a moment.

Dr. Salter presented our recent work on the effects of an excess of glucagon, and he feels very strongly, as I do, that these are good observations but not physiological ones. Both Dr. Salter and I agree with Dr. Herbert Evans, that the evidence does not indicate that the effects of these large doses of glucagon represent a physiological action, but the findings are extremely stimulating and may be of some physiological interest.

We wish to press ahead, to give smaller doses, and

to see if any aspect of these new findings can be co-ordinated with physiological processes.

The effects of injection of growth hormone on blood sugar in dogs are extremely interesting. You will perhaps remember the paper by Bornstein, Reid and Young and the communications by Dr. Foa which demonstrated that a substance producing hyperglycemia was liberated into the pancreatic duodenal vein of rats and dogs after administration of growth hormone.

Some time ago Dr. Sirek and I showed in dogs that the abrupt rise obtained in blood sugar after growth hormone could be prevented by dihydroergotamine. The action of glucagon is not prevented by this drug. Therefore, this effect was probably due, in small part, if at all, to glucagon.

More recently Dr. and Mrs. Sirek have shown that one can dispense with the pancreas completely. If you take blood from the preserved pancreaticoduodenal vein you get exactly the same effects as if the pancreas were there. The hyperglycemic material therefore does not come exclusively, if at all, from the pancreas.

Recently, Dr. Anna Sirek has experimented with 5-hydroxytryptamine (Serotonin). She has shown, for the first time, that this substance causes a very pretty rise in blood sugar in depancreatized dogs. Perhaps this is the substance liberated, and not glucagon at all. Her data show some respectable rises in blood sugar when you give 5-hydroxytryptamine to depancreatized dogs. There are many points to be worked out and there is yet no proof whatever that 5-hydroxytryptamine is liberated by growth hormone. We hope to explore this possibility.

I find myself quite undecided about the physiological role of glucagon. The chemistry has been advanced and there are many, many opportunities to add to our knowledge of the physiological action. When we attempt this, we must be certain that we *are* studying the effects of glucagon.

Now we come to the sulfonylureas, and I must not recapitulate statements which have been made by so many authorities this afternoon. I have listened with great pleasure to Dr. Goldner, Dr. Cox, Dr. Miller and Dr. Levine, and those who discussed their papers. There are many indications from these and other communications that the production of sugar in the liver is inhibited by these sulfonylureas. The activity of a rapidly increasing list of enzymes which function in liver tissue has been shown to be decreased by administration of the sulfonylureas.

Dr. Berson reviewed this particular field extremely well. There is no doubt that in many species, as Dr. Levine emphasized, there is a stimulation of insulin liberation. I think, as Dr. Dolger pointed out, that there probably is a stimulation of insulin liberation in some human patients — presumably the group in which Dr. Gerald Wrenshall has demonstrated residual pancreatic insulin. This may be very small, however, and under some circumstances, I think the evidence indicates that it is very small indeed. I am thinking only, of course, of the cases in which the drugs produce an effect.

In answer to Dr. Lazarow's question, Dr. Ashworth, working with Dr. Haist, has given BZ-55 over a long period of time and has seen a definite increase in the islet volume of the rat pancreas.

It may be that the safe therapeutic action of the sulfonylureas has to do with the liberation of insulin and perhaps with the stimulation of the insulin-producing apparatus. In depancreatized dogs, there is a very slim margin between the amount of sulfonylurea which exerts an antidiabetic effect and the amount which is very definitely toxic. A dose which exerts no antidiabetic effect may be toxic. I think it was Dr. Izzo who referred to a publication from our laboratory in which it was stated that a depancreatized dog on BZ-55 was receiving no insulin at all. The effect of the sulfonylurea on the blood sugar was very definite. Mrs. Sirek has now studied a number of these dogs. The adult dogs may go on for several months before signs of toxicity appear. Mrs. Sirek has also treated depancreatized puppies. Two of these puppies have died suddenly with degeneration of the liver and widespread signs of hemorrhage. The histological picture of the liver indicated a very definite toxicity. In the two depancreatized puppies and in two adult dogs the prothrombin levels were reduced.

This effect on the clotting mechanisms was also drawn to my attention by Dr. Hallas-Møller and a paper from his laboratory by Dr. Per Schambye is now on press.* Before this, however, as we have reported in the *Journal of the Canadian Medical Association,* a depancreatized dog had been maintained on BZ-55 without insulin. This was the first finding which alerted us to the possibility of liver damage. Somewhat later, actually before I received word of Schambye's findings, Mrs. Sirek had observed signs of generalized bleeding in her depancreatized dogs. There were, of course, other possible explanations but the evidence is now becoming quite definite that liver injury plays a role in the effect of BZ-55 in depancreatized dogs.

Dr. Per Schambye has used somewhat higher doses

* This paper and one from our laboratory covering a similar field have now been published in DIABETES 6, 146 and 151, 1957.

than Mrs. Sirek and he has seen more advanced liver degeneration with the profound bleeding tendency. Liver involvement has been suspected in some human cases but I know of no record of such definite effects as those observed in depancreatized dogs.

I would think, from everything that I have heard and read, that there are probably two actions of these sulfonylureas: (1) the liberation of small amounts of insulin with perhaps a stimulation of insulin production, and (2) a mild or chronic toxic effect on the liver. This may prove to be so mild that it can be ignored therapeutically. But the signs in these depancreatized puppies are reminiscent of what we saw years ago with Synthalin, which was certainly a potent liver poison. The sulfonylureas have a much more subtle action and of course one may be found which is acceptable therapeutically in certain cases. I have to emphasize that our observations are with carbutamide only*—and only in the dogs. The story may well be quite different with other compounds and many of these will certainly be studied. A great deal of what was said today should encourage chemists and clinicians to find a safer and more effective stimulant of insulin production in the cases which still have the mechanisms for this process available in their pancreas.

We may be unduly impressed by findings in depancreatized dogs. Similar toxic effects have not been clearly seen with doses equivalent to those used therapeutically in other species. But the dogs have helped us many times. I am no authority on clinical matters, but I do not think it would be in the best interest of diabetics to recommend widespread general use of any of the sulfonylureas at present available.

There are already a number of experimental studies, as yet unpublished, which suggest that Orinase also may be exerting at least a part of its effect on the liver. The absence of toxic effects of this substance in the patients, who have not, I believe, been observed as long as those on BZ-55, should also be stressed. I predict that the next year will reveal many new facts about the agents now being studied and, I hope, that new and even safer adjuvants will be developed. There is certainly a place for the perfect one.

* Dr. A. Sirek, in confirmation and extension of the findings of Dr. Schambye, has now observed that Orinase, given in amounts comparable to those recommended for clinical use, produces in depancreatized puppies treated with insulin, raised serum alkaline phosphatase and prothrombin times and a lowering of plasma proteins. These effects are similar but less severe and slower in onset than those produced by BZ-55 in depancreatized dogs.

What is Obesity?

The specification of "optimal" or "ideal" weights, as well as diets, is a hazardous business. For body weight and relative obesity, at least, the only point on which there will be full agreement is that major departures from the population average should be avoided. There is no doubt that there is an excess mortality penalty in later life associated with marked overweight at the time of application for life insurance. However, the primary data are for major degrees of overweight, from 20 to 75 per cent above the standard average body weight at given height and age, the majority apparently being something like fifty pounds heavier than the average of the population. But to suggest that the major national health obstacle in the United States is obesity because perhaps a tenth of the population may be 10 per cent or more above the average body weight[1] is more than can be sustained from present evidence. Is there actually any serious health hazard necessarily associated with 10 per cent overweight? From what causes? At what ages? And can we disregard the question of obesity versus overweight? Much more research is needed before scientifically acceptable answers to these questions will be at hand. One thing seems certain. The elimination of gross overweight among Americans cannot, by itself, be expected to bring our adult mortality experience to a level to compare favorably with that in such countries as England and Wales, the Netherlands, Italy and the Scandinavian countries.[2] A more penetrating analysis of obesity, rather than mere body weight, might reveal more scope for improvement.

From the book *Modern Nutrition in Health and Disease* edited by Michael G. Wohl, M.D., and Robert S. Goodhart, M.D. Philadelphia, Lea & Febiger, 1955, Chapter "Body Weight, Body Composition and Calorie Status" by Ancel Keys, Ph.D., pp. 29-30.

[1] Armstrong, Dublin, Wheatley, and Marks: J.A.M.A. *147*:1007, 1951.

[2] ————: Am. J. Pub. Health *43*:1399, 1953.