the strictest observance of the methods of modern archaeology.

Through this discovery we now know definitely that the Boskop race preceded the Strandlooper race historically. They perhaps owed their extinction to the latter, the Solutrian culture of which (so ably examined by Dr. L. Perinquey,³ the Director of the South African Museum) indicates familiarity with the uses of the bow. We know further that the Boskop specimen was no human freak, but a type representative of a race once widely distributed in South Africa from

³ "The Stone Ages of South Africa," etc. *Annals of the South African Museum*. Vol. viii. July 5, 1911.

the Transvaal to the remotest south-eastern corner of the continent.

The implements, culture, and æsthetic achievements of these big-brained men of pre-history still remain to be discovered. Their employment of ochre in their burial rites indicates their familiarity with pigments and the artistic and symbolical uses to which they might be put. The remarkable parallelisms between the so-called "Bushman" art and that of Cro-magnon man in Europe was insisted upon by Sollas many years ago, and the evidence may yet be forthcoming which will conclusively solve the fascinating yet elusive problem of their correlation.

Insulin and its Value in Medicine.¹

By Prof. J. J. R. MACLEOD, F.R.S.

CARBOHYDRATES are essential in the chemical processes upon which life depends. Not only is the glucose, the form in which they are mainly absorbed into the blood, the source of muscular energy, but it is also in some way necessary in the oxidation of fats. Preceding its oxidation, glucose undergoes a series of preliminary changes which proceed step by step in such a manner that a long series of intermediary substances is formed; and when anything interferes with the process at any stage, as in diabetes, glucose accumulates in the blood and tissue fluids, causing the main early symptoms of the disease, hyperglycæmia and glycosuria. Later involvement of the oxidation of fats results in the accumulation of the ketone bodies in the organism, and these, by their toxic action, cause the often fatal condition of coma.

The control of this process of carbohydrate metabolism has for years been assumed to be the function of a hormone derived from the Isles of Langerhans of the pancreas. Although the existence of this hormone was fairly certain, little success resulted from attempts to extract it in potent form from the pancreas, probably because it was destroyed by the powerful digestive enzymes also present in such extracts. Banting and Best circumvented these by making extracts of the degenerated residue of pancreas following ligation of the ducts, it having previously been shown that in this residue the islet cells are more or less intact but the external secretory cells are largely degenerated. The extracts were found to remove the two chief symptoms of diabetes in depancreatized dogs. Alcoholic extracts of adult beef pancreas were also found to contain the hormone, and by their continued use it was possible considerably to prolong the life of the diabetic animals. J. B. Collip then succeeded by fractional precipitation with alcohol in ridding these alcoholic extracts of irritating substances, so that they could be repeatedly injected into diabetic patients.

With larger supplies of insulin available, it was now possible to show that it removes all of the observable symptoms of diabetes in depancreatized dogs. Thus, not only did it cause glycogen to become deposited in large quantities in the liver when sugar was fed to the animals,

the first analysis giving more than 20 per cent. of this substance (J.B.C.), whereas without insulin traces only are found, but it also caused the respiratory quotient (ratio between CO₂ and O₂ in respired air) to become raised. These results were soon confirmed on diabetic patients. In more recent work, in which depancreatized dogs were given insulin daily along with considerable quantities of carbohydrate, life has been prolonged for over four months, and by careful comparison of the sugar balance of the animals it has been found, by F. N. Allen, that a small amount of insulin is capable of causing relatively much more glucose to be metabolised than when a large amount is given. Or, in other words, the glucose equivalent per unit of insulin is much higher with small than with large doses.

Although there can be no doubt of the high therapeutic value of insulin in the treatment of many cases of diabetes, its value as a new instrument for the investigation of problems of metabolism other than those relating to this disease is also high. Evidence for this belief is founded, among other things, on the striking effects of insulin on normal animals. When it is administered to rabbits, for example, the first effect is a very rapid lowering in the percentage of sugar of the blood—first observed by J. B. Collip—and when this reaches a certain level symptoms of a peculiar nature supervene. These consist usually of violent convulsive seizures each lasting for a minute or so, and of a gradually increasing state of coma, with fall in body temperature, ending often in death from respiratory failure. Symptoms of a similar character occur also in other animals, including man, after large doses of insulin.

The symptoms were found to be dependent on the lowering of blood sugar; thus, they usually supervene in normally fed animals when the blood sugar has fallen to about 0.045 per cent., and they are removed immediately by the addition of glucose to the blood either by administering this sugar subcutaneously or by causing it to be liberated in the body from glycogen, as by the injection of adrenalin (epinephrin). It was found, moreover, that, of all the sugars, glucose alone has an immediate and lasting effect, even leavulose and galactose, which are its nearest neighbours, having only a slight and transitory action.

Although the symptoms commonly occur in well-fed

¹ A Lecture delivered in the Section of Physiology of the British Association at Liverpool on September 17.

animals when the blood sugar is about 0.045 per cent., they may fail to be observed until a much lower level has been reached. This is particularly the case when a large dose of insulin is given some time after food. The liability of symptoms to occur at the above percentage of blood sugar has served as a useful basis for measurement of the dosage of insulin, one unit being defined as the amount which can lower the blood sugar to the convulsive level of 0.045 per cent. within four hours in rabbits weighing about 2 kilogrammes. Since this "physiological" unit, as it is called, is said to be stronger than is necessary for certain clinical purposes, it has been decided for the present to use, as the "clinical" unit, one that is one-third the above strength. This question of the physiological assay of insulin is receiving much attention at present.

These observations clearly pointed the way to the next problem, namely, the cause for the lowering of blood sugar. At first it seemed as if this should soon be solved, for, as already mentioned, it has been found that insulin not only causes glycogen to be deposited in the liver of diabetic animals, when sugar is given, but also causes the respiratory quotient to become raised in a manner to indicate that there is increased combustion of carbohydrate. It seemed likely that stimulation of the same processes in the normal animal under insulin must be responsible for the disappearance of glucose from the blood. But the experimental evidence goes to show that the mechanism of action is much more complex. It has recently been found that glycogen is not formed when insulin is given along with sugar to normal animals (McCormick, O'Brien, and E. C. Noble); indeed, when given to those that are well fed it is decreased in amount (Dudley and Marriam), and no certain evidence can be obtained from respiratory experiments that more active combustion of glucose is a necessary accompaniment of the lowering of blood sugar. The consumption of oxygen greatly increases in dogs preceding the onset of symptoms, and the respiratory quotient usually becomes somewhat raised (Dixon, Eadie, and Pember), but in mice changes of an opposite character occur (Dudley, Laidlaw, Trevan, and Boock); in rabbits the symptoms are at first like those in dogs, though less marked, and subsequently like those in mice.

The glucose which disappears is apparently neither oxidised to carbon dioxide and water nor polymerised into glycogen. For the present the problem is unsolved, but we must not lose sight of the possibility that insulin changes both glucose and glycogen into some intermediary product which we fail to identify with our present methods of analysis, either because it does not give the reducing reactions upon which the detection and estimation of sugars depend, or because it is not precipitated by alcohol after treatment with strong alkali, which is the characteristic property of glycogen. That such substances may exist in the tissues is indicated by the fact that it is impossible after injecting large amounts of sugar into animals to recover much more than one-half by chemical analysis of the entire body.

Whatever may be the nature of the mechanism by which the blood sugar becomes lowered, there is no doubt that it acts in the tissues and not in the blood itself (Eadie). Thus, the addition of insulin to blood

incubated outside the body does not alter the rate at which the sugar disappears from it, and when the isolated heart is perfused with a suitable saline solution containing sugar the addition of insulin to the solution causes this to lose its sugar more rapidly (Hepburn and Latchford). The hypoglycæmic effect of insulin lasts for a period which varies in different animals. In rabbits the blood sugar often begins to rise again in about an hour after the injection, but this depends very largely on the amount of glycogen which is stored in the liver. This becomes converted into glucose to replace that lost from the blood, so that well-fed animals show much quicker recovery and can withstand much larger doses of insulin, without the development of symptoms, than those previously starved. This mobilisation of the carbohydrate reserves would appear to depend on the transmission to the liver through its nerve supply of messages set up by the hypoglycæmic condition, for Burn has shown that if the nerve pathway (splanchnic) be locked by the drug ergotamine, insulin causes, in well-fed animals, a more profound degree of hypoglycæmia than otherwise.

Another important effect of insulin is on the hyperglycæmia due to other causes than removal of the pancreas. So far as it has been investigated, insulin is capable of preventing the development of hyperglycæmia in all these conditions. Most attention has been paid to its effect on the hyperglycæmia due to epinephrin, partly because of the possibility that insulin may be assayed by determining the amount necessary to antidote a known amount of epinephrin, which itself can be accurately assayed, and partly because an investigation of the physiological antagonism between these two hormones may throw some light on the mechanism of the action of insulin. One example may be given to illustrate this. We have seen that insulin causes the glycogen stored in the liver to become less in amount, acting in this regard like epinephrin, although probably much less quickly. When insulin is given along with epinephrin, however, glycogen disappears from the liver much more slowly than with epinephrin alone, indicating that under certain conditions the pancreatic hormone arrests rather than stimulates the breakdown of glycogen. When these two hormones are in excess in the body, one prevents the other from causing glycogen to disappear. Another curious result of a somewhat similar nature has been obtained by Burn with pituitrin, a hormone derived from the pituitary gland. When it is given along with epinephrin it also prevents hyperglycæmia, and when it is given with insulin it prevents hypoglycæmia. These results indicate the very puzzling nature of the problem of the action of insulin, and they show that this action may possibly be linked with that of other hormones in the animal.

Chemically, insulin usually gives the biuret test, and it behaves in its general properties not unlike a proteose. It may, however, be a much simpler substance, since active preparations have been obtained from the pancreas of the skate, in which no biuret test could be obtained. Its chemical identity being unknown, it is of course out of the question that it could at present be prepared synthetically.