THESIS

on

POTASSIUM AND CARBOHYDRATE METABOLISM - A STUDY OF POTASSIUM IN PHYSIOLOGICAL AND PATHOLOGICAL PROCESSES IN THE HUMAN ORGANISM.

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by

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"Without speculation there is no good or original observation." - Charles Darwin.
INTRODUCTION.

Among the mineral elements which have been studied extensively in relation to their physiological roles is the metal potassium. Blake in 1839 was apparently the first to investigate its properties; he injected potassium carbonate intravenously into a dog with a promptly fatal result. Much less crude were the investigations by Ringer of the action of potassium on the isolated frog heart in 1830-81 and on the frog gastrocnemius muscle in 1887. His experiments were perhaps the first to show the importance of potassium in experimental physiology; they initiated numerous studies of the effect of potassium on isolated tissue as well as on the intact animal and individual systems which are still being continued at the present time. As regards the biochemistry and the quantitative changes of potassium in blood or tissues the early methods of analysis were very laborious, unreliable and they required an excessive amount of material. (Dennis and Hobson 1922). Progress in this line was, therefore, slow and it was not until the advent of the micromethods for /
for potassium estimation, notably those of Kramer and Tisdall in 1921 and of Shohl and Bennett in 1923 that these changes could be investigated. It is, therefore, only within recent years that precise studies of potassium metabolism have been possible and, although much work has been done on this subject, many problems still remain to be investigated. Potassium, like the other alkaline metals, e.g. sodium, calcium and magnesium, is of great significance in biological processes. It is present in considerable quantity in all living matter and is essential for the wellbeing, growth and life sustenance of plants, animals and even of microorganisms. (Miller 1922 A.B.; Schrader, Prickett and Salmon 1937; McCance 1936). Although so closely related physically and chemically to sodium, biologically the two elements are only interchangeable to a small extent. They play, in fact, quite distinct and separate rôles; they may perhaps be described as complementary but on occasion they appear to be antagonistic as is evidenced clinically by their administration to patients with Addison's disease. Potassium has universally (except in the red /
red blood corpuscles of certain animals) been adopted as the main cellular base, whereas sodium, although to a small extent an intracellular ion, is the main base of extra-cellular tissue fluids. This accumulation of potassium with little or no sodium in cells living in a medium richer in sodium than in potassium can, therefore, be considered a general attribute of living matter, and it follows that cells must have a selective affinity for the potassium ion. (Osterhout 1930; Mitchell and Wilson 1921).

Potassium does not play an entirely passive part in tissues in the maintenance of osmotic equilibrium and the vital degree of alkalinity. It is concerned in active processes such as muscular contraction and the transmission of nerve impulses. It is closely related to the functions of endocrine organs and the autonomic nervous system which, in turn, are to a large extent responsible for the activity of cellular structures. In view of this connection between potassium and tissue activity and the fact that sugar is the main tissue fuel it is, perhaps, not surprising that there appears to be a close /
close relationship between potassium and the utilisation of sugar.

It is this relationship between potassium and carbohydrate metabolism which has been the subject of the present study. As will be seen, a relationship has been suggested on several occasions, but these suggestions have been based on little and incomplete original work, and there has been no attempt to correlate all the independent indirect data in evidence of such a supposition. Hill and Howitt (1936) and Jensen (1932) in their excellent monographs on insulin mention contradictory evidence for the effect of insulin on the plasma potassium level and offer no comment, nor is potassium mentioned in the sections on carbohydrate metabolism in any of the standard textbooks of Biochemistry (Bodansky 1938; Cameron 1939; Macleod 1935; Steel 1937); nor, in fact, has any article dealing exclusively with the association of potassium and carbohydrates so far appeared in literature. Yet, as I shall show, partly from my own experimental evidence, the two are intimately connected and it is my belief that no article on carbohydrate metabolism is in any sense complete unless due consideration is given /
given to the potassium ion. To add a point to this statement, plants are rich in sugars, particularly starch. They are also rich in potassium, in fact in the middle ages potassium was obtained for commercial purposes by burning plants (Holmyard 1933). White (1936) showed that a deficiency of potassium reduced the capacity of plants to hydrolyse starch and concluded that potassium regulated plant carbohydrate metabolism by controlling the starch-glucose balance. Gregory (1938) showed that a deficiency of potassium in plants resulted in a low total sugar content. The relationship between potassium and carbohydrate metabolism in plants does not perhaps come within the sphere of physiological processes as applied to animals. For instance, the starch of plants is not the same as glycogen in animals, but they correspond (Martin 1937) and inorganic phosphate is concerned in plant carbohydrate metabolism (Lohmann 1938) as is, of course, the case in animals. In spite of the discrepancies of comparative physiology this evidence would seem at least suggestive and is certainly not irrelevant. As regards carbohydrate metabolism itself, there is, perhaps, no branch in biology which has been the subject /
subject of such intense research.

The fate of ingested sugar, the association of blood sugar with the plasma inorganic phosphate and the formation of hexosephosphate and phosphate derivatives in muscle has been given special attention and has been established on a relatively sound basis: but the mechanism controlling the fate of ingested sugar still appears to be relatively obscure. On studying the literature concerning the effects of the endocrine glands on the metabolism of carbohydrate (generally apart from the blood sugar level) one is confronted with what is, in reality, a maze of confusing and contradictory conclusions. It follows, therefore, that the knowledge of the mechanism of carbohydrate metabolism is generally still sufficiently incomplete to make dogmatic statement difficult; it is, according to Jensen (1932) a subject which is still obscure and controversial. A few quotations from the literature will justify these statements. Martin (1937), from a survey of literature for a monograph on "glucose therapy" citing hundreds of original papers on carbohydrate metabolism, states that the animal organism is unable to utilise glucose without /
without insulin. Houssay (1936 B) in a brilliant lecture delivered at Harvard University mainly on a study of the relationship between the anterior pituitary gland and carbohydrate metabolism, and citing a similar number of references considered it proved that "even without the internal secretion of the pancreas the organism can utilise sugars."

Accordingly, there appear to be two theories regarding the processes at fault in diabetes. (1). The non-utilisation theory which explains diabetes as a condition in which carbohydrates cannot be oxidised. This theory cannot explain the more direct observations of numerous workers, e.g. Shorr, Richardson and Sweet (1936), Himwich and Nahum (1929, 1932), to the effect that the diabetic organism is able to utilise large amounts of sugar. (2). The over-production theory. This theory postulates the uncontrolled formation of glucose by the liver in excess of the amount which can be utilised by the muscles. This latter theory cannot explain the sub-normal use of sugar by isolated tissues or organs which, according to Soskin and Levine (1937) has been proved to occur in the diabetic animal. It has not been possible to decide between these two theories according to Hill and Howitt (1936) who also consider "that /
"that both may be true." Finally, Himwich (1933) states that insulin increases, but is not essential for the utilisation of carbohydrate which appears to be the modern interpretation of the part played by insulin in carbohydrate metabolism, at least as far as the tissues are concerned. As regards the liver, numerous observations according to Bodansky (1938) have shown that the mechanism regulating its retention and output of carbohydrates resides in the liver itself; insulin increasing its storage of glycogen either by promoting glycogen synthesis or by inhibiting the reverse process of glycogenolysis.

This then brings the action of insulin on the muscles and the liver into line with the other hormones in that it is an accepted fact (Kendall 1938) that the endocrine glands do not initiate new types of physiological processes, they merely modify the rates at which fundamental chemical changes can take place in the tissues.

I have already alluded to the fact that potassium is closely related to the functions of the endocrine glands, to a connection between potassium and tissue activity, and, in my association of potassium and carbohydrate metabolism, I can only hope /
hope that I have considered the latter in a manner which is in agreement with modern conceptions and present day theories. I venture to suggest that a direct study of the relationship between potassium and the utilisation of sugars in the experimental animal or in isolated tissues would solve many of the problems still confronting the research worker in his study of carbohydrate metabolism. Indeed, there are signs that this idea is beginning to appear as Jacob and Mond (1937) according to Lundsgaard (1938) point out that the utilisation of glucose in an artificially perfused muscle is dependent on the concentration of electrolytes in the perfusion fluid.

I do not wish to give the impression that I consider that the potassium is present in cells solely on account of its connection with carbohydrate metabolism. For instance, potassium represents practically all the fixed mineral base of human red blood corpuscles (Kramer and Tisdall 1922) containing approximately 425 mg. per 100 gm. (Kerr 1937). For comparison moist human skeletal muscle contains 349 mg. per 100 gm. (Norn 1929A). Yet, according to Hansen (1937) erythrocytes have no independent carbohydrate /
carbohydrate metabolism. Obviously potassium is here concerned with the regulation of osmotic tension and the alkali reserve, e.g. the wellknown Hamburger effect and the oxygen carrying capacity. Incidentally, this is perhaps the reason why sodium is predominant in the erythrocytes of certain animals, e.g. the cat, sheep and dog (Kerr 1937) the specificity of the alkali ion not being essential for these purposes. Similarly there may be variations in the plasma potassium level which have probably no direct connection with carbohydrate metabolism; as a few examples, may be mentioned the rise in the plasma potassium concentration occurring in post-transfusion haemolysis (Ilin and Vavzykovskaja 1936) or in severe burns. From the work of Mitchell and Wilson (1921), Fenn and Cobb (1933) and Baetjer (1935) it can be concluded that cells on disintegrating lose potassium and that there follows ionic equilibrium with the extracellular fluids. A rise in the plasma potassium concentration occurs in Bright's disease (Hoffman and Jacobs 1922), which fact does not appear to be related to carbohydrate metabolism. A reduction of the plasma potassium content occurs in spontaneous attacks /
attacks of familial periodic paralysis without any change in the blood sugar content. (Ferrebee, Atchley and Loeb 1938, Fudenz et al 1932). In this condition there may be a disturbed carbohydrate metabolism in spite of the absence of changes in the blood sugar level. This, however, will be discussed later.

As a brief summary, the evidence for the intimate relationship between potassium and carbohydrate metabolism is based on the following data.

(1). The effect of glucose on the blood sugar and the plasma potassium concentrations.

(2). The effect of insulin on the blood sugar and the plasma potassium concentrations.

(3). The parallelism of the effects of glucose and insulin on the plasma potassium and the plasma inorganic phosphate levels, and the incorporation of the latter in the metabolism of sugar.

(4). The effect of adrenaline on the plasma potassium level and the metabolism of sugar.
My own work is chiefly a study of the effect of glucose administration on the plasma potassium level. Initially glucose was administered to patients suffering from a variety of diseases, some of which were of uncertain or unknown aetiology. It was thought that there might be some alteration in the metabolism of potassium in these diseases, and that the administration of glucose would throw light on any such alteration since it was known that the administration of glucose lowered the plasma potassium level in health. It was also known that potassium metabolism was disturbed in such clinically different and, apparently, unrelated conditions as familial periodic paralysis and Addison's disease. It was thought that a disturbed potassium metabolism in such conditions as, for instance, progressive muscular atrophy or paralysis agitans would be within the bounds of possibility. This study was, however, rather unproductive. The fasting potassium levels and the curves obtained after glucose administration were in all respects so similar to each other and to the results recorded in the literature that one is justified in concluding that the results obtained were /
were from individuals with a normal potassium metabolism. These remarks hold for all the patients studied except, perhaps, for a patient with severe myasthenia gravis; the possibility of a disturbed potassium metabolism in this condition will be discussed later.

It will be seen that a great part of the evidence is based on variations in the plasma potassium concentration. Most workers (including myself) have estimated the potassium concentration in serum. I have used the word "plasma" in preference to the word "serum" throughout this thesis because physiological processes are being considered. There is, of course, no "serum" in the intact organism and, therefore, the word "plasma" is correct. As regards their inorganic constituents plasma and serum are identical in composition. (Kramer and Tisdall 1922). Quantitatively the terminology is immaterial and the two words are, therefore, interchangeable.

There is comparatively little published work on the variations in the plasma potassium level. This is undoubtedly due to the difficulties inherent in the technique of the estimation and the time involved. The method of Shohl and Bennett (1928) which I have employed is probably the most dependable. The method will be described briefly in the appendix.
The fasting plasma potassium level in health, like the other inorganic plasma components, is relatively constant. Kramer and Tisdall (1922) estimated the plasma potassium content of thirteen normal individuals and in each instance obtained the result of 19.5 mg. per 100 c.cm. of plasma. Whelan (1925) found a range of 17 to 20.8 in ten normals with a mean of 19. Hoffman and Jacobs (1933) found an average figure of 19.3 in 30 normal adults of both sexes. Laurent and Walther (1935) from ten observations give 15.2 to 22.5 as the range and 17.4 as the average. Hirschfelder and Haury (1938) incidental to a study of potassium in relation to epileptic convulsions found the plasma potassium content of 14 normal individuals to vary between 17.2 and 24.7 with a mean of 20.35. Pedersen, Maddoch and Winslow (1938) found a range of 20.3 to 22.1 in seven adults with an average of 21.4. My own studies on thirteen individuals give results varying between 16.3 and 21.4 with an average of 18.9. These results
do not include the values obtained in two patients with myasthenia gravis. In cases where repeated investigations were performed in the same patient the average fasting value for each individual is included. It will be seen from the above results that a relatively wide range is reported by several observers. It may be possible that in some of the investigations the specimens examined were not obtained from individuals in the strictly fasting state. Laurent and Walther (1935) showed that a rise in the plasma potassium level of 2-3 mg. per cent occurred after a mixed meal, the daily intake on a mixed diet being 2-6 g.; (Clark 1937) or as much as 40 g. daily on a vegetarian diet (Bunge 1873). A lower level would be found if carbohydrate were ingested prior to the taking of the specimen. Again Cloetta, Fisher and van der Loeff (1934) demonstrated that the potassium content of humans fell on an average by 15.3 per cent during sleep so that it is reasonable to assume that a low plasma potassium content would be found if blood were removed for analysis immediately on wakening. It is doubtful if these factors have always been taken into account by /
by the various investigators.

From the above observations and from the values obtained by various other workers analysing the blood of smaller numbers of individuals, (Harrop and Benedict 1923; Bourdillon 1937; Crabtree and Maizels 1937; Aitken and associates 1938, and Greig 1938) I feel inclined to limit the normal fasting range of the plasma potassium to 19±3 mg. per 100 c.c. of plasma. These are the values given by Bodansky (1930) although the textbooks differ. The potassium level also varies within strict limits in the same individual on different days under identical conditions as regards fasting, rest, etc. This is evident from my own work and from the references quoted. One can also conclude that the plasma potassium content does not vary with age or sex, at least in adults. Furthermore, there is no quantitative relationship in normal fasting individuals between the potassium and other plasma metallic components on the plasma inorganic phosphate level, as can be inferred from the results of Briggs and co-workers (1923), Harrop and Benedict (1923), Takeuchi (1923), Aitken and associates (1937) and others.

Finally, there is no parallelism between the fasting potassium level in the plasma (or whole blood) and the fasting /
fasting blood sugar level. This is suggested by the figures given by Briggs and co-workers (1923), Harrop and Benedict (1923), Takeuchi (1928B), Aitken and associates (1937) and Greig (1933), and is supported by my own results. A few of my own figures will illustrate this. The blood sugar is given in mg. per 100 c.cm. of whole blood (Hagedorn Jensen method) and the plasma potassium values in mg. per 100 c.cm. of plasma.

<table>
<thead>
<tr>
<th>Blood sugar levels</th>
<th>Number of observations</th>
<th>Average potassium val.</th>
</tr>
</thead>
<tbody>
<tr>
<td>71-80 (average 76)</td>
<td>6</td>
<td>18.0</td>
</tr>
<tr>
<td>81.90</td>
<td>25</td>
<td>17.9</td>
</tr>
<tr>
<td>98-102</td>
<td>97</td>
<td>18.4</td>
</tr>
</tbody>
</table>

These results include those obtained in patients with myasthenia gravis. As will be mentioned later the fasting plasma potassium level is probably reduced in this condition - hence the low average potassium levels.

From repeated observations I would suggest that there is no parallelism between the fasting blood sugar and plasma potassium levels even in the same person at different time. For instance, in the same individual /
individual at intervals of four, eight and thirteen days respectively under identical conditions the following results were obtained.

<table>
<thead>
<tr>
<th>Blood sugar levels</th>
<th>Plasma potassium levels</th>
</tr>
</thead>
<tbody>
<tr>
<td>(1) 84</td>
<td>13.6</td>
</tr>
<tr>
<td>(2) 74</td>
<td>13.1</td>
</tr>
<tr>
<td>(3) 84</td>
<td>13.3</td>
</tr>
<tr>
<td>(4) 75</td>
<td>21.5</td>
</tr>
</tbody>
</table>

The high potassium content in the last sample was probably due to the daily administration of large doses of potassium chloride during the ten days preceding the withdrawal of the blood specimen.

The above observations are in keeping with the findings of Futer and Weiland (1929) that there is no relationship between the blood electrolytes and the two supposedly clinical types of negative tone (Vogotonic and sympatheticotonic) with the obvious implication as regards the fasting blood sugar and plasma potassium levels.

It is of interest to note that the figures provided by the various workers already quoted collectively indicate that there is no definite relationship between the fasting plasma inorganic phosphate /
phosphate level and the blood sugar content. This is contrary to the claim made by Florence and Zola (1927) that a high blood sugar is associated with a low plasma inorganic phosphate level, and vice versa.
THE FASTING PLASMA POTASSIUM LEVEL IN DIABETES AND ITS RELATIONSHIP TO THE BLOOD SUGAR CONCENTRATION.

The values of the fasting plasma potassium content in diabetes does not appear to be related to the raised blood sugar concentration. The following figures are given in the literature.

<table>
<thead>
<tr>
<th>Plasma pot. content in mg. per 100 c.cm.</th>
<th>Blood sugar in mg. per 100 c.cm.</th>
<th>Remarks</th>
<th>Source of information</th>
</tr>
</thead>
<tbody>
<tr>
<td>18</td>
<td>363</td>
<td>Harrop &amp; Benedict 1923</td>
<td></td>
</tr>
<tr>
<td>18.2</td>
<td>312</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>18.5</td>
<td>290</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>13.9</td>
<td>?</td>
<td>Diabetic coma</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>667</td>
<td>Kerr 1928</td>
<td></td>
</tr>
<tr>
<td>20.6</td>
<td>280</td>
<td>Greig 1933</td>
<td></td>
</tr>
<tr>
<td>21.3</td>
<td>121</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>16.5</td>
<td>107</td>
<td>&quot;</td>
<td></td>
</tr>
<tr>
<td>20.7</td>
<td>350</td>
<td>No acet-uria</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Own observation</td>
<td></td>
</tr>
</tbody>
</table>

These values suggest a slightly low plasma potassium content (but within normal limits) in severe diabetes. Perhaps this may be related to the associated /
associated acidosis and diuresis as Bodansky (1938) states that a diminished alkali reserve is accompanied by a definite reduction in the blood sodium and potassium. On the other hand, it has been reported that the plasma potassium level is characteristically elevated in diabetes. Rathery Bertolatti (1934), for instance, found values averaging 35 per cent above normal in seven cases of diabetes not on insulin therapy and 22 per cent above normal in seven insulin treated cases. As regards animal experiments the reports are also controversial. Takeuchi (1938) found an average increase of 25 per cent in the plasma potassium level in nine dogs after pancreatectomy (no acetonuria). Kerr (1928) found the same plasma potassium content before and after pancreatectomy in six dogs. His findings were confirmed by Houssay (1936) similarly using pancreatectomised dogs. It seems likely from these observations that there is no relationship between the plasma potassium level and the blood sugar content in diabetes. This, of course, is in line with the previous conclusion that no relationship exists between the levels of these two substances in the fasting blood in health. As regards the fasting blood /
blood sugar level in diabetes and the inorganic phosphate content of the plasma I can find no reference describing any parallelism between the two. Finally, no relationship between the plasma potassium and inorganic phosphate in diabetes has been described. The paucity of the concurrent estimations recorded in the literature invalidates any conclusion in this respect.

Owing to the absence of any relationship in health and in diabetes between the fasting blood sugar concentration and the plasma potassium, and inorganic phosphate levels the mechanism regulating the fasting levels will not be described.
THE EFFECT OF GLUCOSE ADMINISTRATION
ON THE PLASMA POTASSIUM LEVEL.

In tracing the fate of carbohydrates in metabolism we are primarily concerned with the chemical changes which glucose undergoes after absorption (Bodansky 1938). To initiate the relationship of potassium and carbohydrates it is, therefore, appropriate to begin with a study of the effect of glucose administration on the plasma potassium and the blood sugar levels. There are few references in literature.

Aitken and associates (1937) were the first to demonstrate that the administration of glucose lowered the plasma potassium level. Although Walker in 1935 demonstrated that a very marked fall occurred in the plasma potassium in a patient suffering from familial periodic paralysis during an attack induced by the ingestion of sugar, it has since been shown by Aitken and associates investigating the same patient and by Gammon (1938), Allott and McArdle (1938), Ferrebee, Atchley and Loeb (1938) and Fudenz et al (1938) that the potassium of the plasma is unduly labile in this condition and that familial periodic /
periodic paralysis is characterised by a disturbed potassium metabolism. Aitken and associates (1937) were, therefore, the first to show this particular effect in a normal individual. Their results will be tabled with my own experimental work.

Flock et al (1932) apparently in view of the above findings decided to investigate the same problem. They knew that a marked drop in potassium and inorganic phosphate of the plasma occurred coincidentally with the fall in blood sugar after insulin and that an intake of carbohydrate produced a decrease in the plasma inorganic phosphate content. They administered glucose intravenously into six dogs fasting over night and into two dogs fasted 12-14 days with hunger diabetes, at the rate of 1/2 to 2 g. per Kg. of body weight per hour, and found in each instance a decrease of approximately 20 per cent in the plasma potassium level 15 minutes after the commencement of injection. They found a rise to just above the fasting level three hours after cessation of the injections. Incidentally they found that laevulose had the same effect as glucose. Identical experiments were also carried out in four depancreatised dogs maintained for three days without insulin. In two of these dogs the plasma potassium responded /
responded to glucose as in the normal animals, whereas the other two responded with only a slight fall of the plasma potassium. Greig (1938) administered glucose to three patients suffering from disseminated sclerosis, diabetes mellitus and myotonia respectively and levulose to a patient with Wilson's disease (hepato-lenticular degeneration). His results will be recorded with my own. Aitken and his associates, and Greig suggested that potassium left the plasma with the blood sugar to enter the muscles. Greig suggested further that the potassium left the plasma, "being necessary for the formation of the intermediary carbohydrate phosphate compound in the metabolism of glucose to glycogen." As will be seen, similar suggestions were made as early as 1923 and have been made several times since from studies of the effect of insulin on the blood sugar and plasma potassium concentrations.

Own Experimental Work.

The effect of the administration of various amounts of glucose on the plasma potassium level.

Protocol No. 1.

All the patients investigated were kept in bed and fed on the ordinary hospital diet for a variable number /
number of days prior to the taking of the blood specimens. At 7 p.m. on the eve of the investigations a light meal was given; no food or water was subsequently allowed until the investigations were completed. In a few instances, however, medicine was given on the previous evening with no apparent influence on the results. Glucose was administered orally in quantities of 50 to 150 grammes, dissolved in water in a concentration of 16-30 per cent. It was given generally about 9 a.m. after a fasting specimen of blood had been drawn off. In some cases the glucose produced nausea and vomiting when the investigations were discontinued. Others became nauseated and administration was then interrupted; the quantity ingested was measured and the investigations allowed to proceed. Although a variable time was occupied by the process of glucose administration in the different individuals the variance was so slight (1.10 min.) that one would not expect this to have any appreciable effect on the results obtained. Following the ingestion of glucose, specimens of blood were drawn off at approximately half hourly intervals for 2-3 hours; the exact timing being shown on the curves. It was necessary,
necessary, however, for the sake of uniformity in the presenting of the results in tabular form to deduce from the curves the values of the blood sugar and the plasma potassium at identical time periods after glucose ingestion in each case. The tables and the curves have the same numbers and the reader is referred to the curves which show the changes more clearly.

Throughout the series of investigations occasional specimens of blood became haemolysed with, of course, a rise in the serum potassium content. This will be mentioned in more detail in the appendix. The loss of a specimen either by haemolysis or by an accident such as the breaking of a test tube is indicated in the curves by an interrupted dotted line. Two investigations in which two specimens of blood were lost in this way are not recorded. When duplicate analysis of individual specimens were performed the average result was taken in each case. Such duplicate analysis was performed sixteen times and the values obtained are indicated in the curves by two short horizontal lines, joined by a vertical line.

Owing to the fact that several of the patients had either a fasting blood sugar above the normal 80-90 mg. per 100 c.cm. (Stewart and Dunlop 1937) and /
and/or such poor sugar tolerance as to be borderline cases of diabetes (in the absence of other detectable endocrine involvement), I have found it necessary to consider the plasma potassium changes occurring in normals and diabetics at the same time. I have already discussed briefly the various pathological states of the patients under investigation. I would add that none had any febrile disturbance, cardiovascular or renal diseases, endocrine dysfunction (except where indicated) or clinically detectable liver deficiency. I have mentioned the possibility of the existence of a disturbed potassium metabolism in myasthenia gravis. This is based on:

(1) The finding of a low fasting plasma potassium level in six patients with myasthenia gravis by Laurent and Walther (1935). They found a variation 13.8 to 16.4 mg. per 100 c.cm. with an average of 15.34. Although this was several mg. less than the fasting plasma potassium level in health the authors did not attach much importance to it. In my own experiments the fasting plasma potassium level was estimated in two myasthenics on seven occasions. A range of 15.9 to 18.8 was obtained with an average of 16.8. This is again several mg. less than my average of 19 for other individuals under identical conditions. /
conditions.

(2) The improvement occurring in the condition of myasthenia gravis through the raising of the plasma potassium level by the therapeutic administration of potassium salts. This has been reported by Laurent and Walther (1935), Laurent and Walker (1936), Minski and Stokes (1936) and others, and is now an accepted form of treatment.

(3) One of my patients with severe myasthenia was made worse by the administration of 105 g. of glucose. Muscular power as shown by the hand dynamometer was reduced roughly parallel to the fall in the plasma potassium level induced by the glucose. This is shown in curve No. 17. Subjectively the patient also felt weaker and was more dyspnoeic. The plasma potassium curve after glucose also differs in one respect from those obtained in other patients. This will be discussed later.

(4) The similarities between this condition and familial periodic paralysis in which the potassium metabolism is known to be disturbed. This will not be considered in detail. It is sufficient to point out that one is a chronic progressive type of muscular asthenia; the other an acute type with a low plasma potassium level during an attack and a normal /
normal level during intervals. In both, potassium administration is of benefit, particularly in familial periodic paralysis. Prostigmine and allied urethanes are specific in the treatment of myasthenia gravis. An excellent paper on this subject is that of Fraser, McGeorge and Murphy (1937). Recently Pudenz et al. (1938) have demonstrated a similar specificity in the treatment of familial periodic paralysis by the same choline esters. These observations, although they do not prove the existence of a faulty potassium metabolism in myasthenia gravis, are, nevertheless, suggestive. It has been necessary to consider this possibility as part of the evidence, for the effect of glucose administration on the plasma potassium level has been drawn from observations on several patients suffering from this condition. The results obtained in the patients with myasthenia will be tabulated together.

Similarly, Greig (1938) studied the same changes in a patient with myotonia, a condition etiologically the opposite of myasthenia (Russell 1939) and involving the possibility of a disturbed potassium metabolism. This /
This possibility need, however, not be discussed as the values obtained are only used as additional evidence.

Experimental Results.

The plasma potassium is expressed in milligrammes per 100 c.cm. of plasma. Sugar was estimated by the Hagedorn Jensen method and is given in milligrammes per 100 c.cm. of whole blood. The values recorded are those obtained from blood specimens withdrawn immediately before the ingestion of glucose (zero) and at \( \frac{1}{2}, 1, 1\frac{1}{2}, 2 \) and 3 hours after the completion of ingestion. Sometimes a specimen was also taken four hours after glucose administration.

(1).

P.N.M., aged 26. Peptic ulcer. 11.11.32.

<table>
<thead>
<tr>
<th>Time</th>
<th>Zero</th>
<th>( \frac{1}{2} )</th>
<th>1</th>
<th>1( \frac{1}{2} )</th>
<th>2</th>
<th>3</th>
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</thead>
<tbody>
<tr>
<td>Potassium</td>
<td>18.1</td>
<td>18.8</td>
<td>18.8</td>
<td>18.5</td>
<td>18.5</td>
<td>19.2</td>
</tr>
<tr>
<td>Sugar</td>
<td>79</td>
<td>108</td>
<td>105</td>
<td>85</td>
<td>73</td>
<td></td>
</tr>
</tbody>
</table>

50 g. of glucose given at zero.

(2)

W.D., aged 53. Progressive muscular atrophy. 15.11.33.

<table>
<thead>
<tr>
<th>Time</th>
<th>Zero</th>
<th>( \frac{1}{2} )</th>
<th>1</th>
<th>1( \frac{1}{2} )</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium</td>
<td>17.7</td>
<td>17.4</td>
<td>15.8</td>
<td>20.3</td>
<td>17.7</td>
<td>19.1</td>
</tr>
<tr>
<td>Sugar</td>
<td>107</td>
<td>126</td>
<td>112</td>
<td>105</td>
<td>103</td>
<td></td>
</tr>
</tbody>
</table>

50 g. of glucose given at zero.

(3). /
(3).

W.B., aged 27. Paralysis agitans. 21.11.38.

<table>
<thead>
<tr>
<th>Time</th>
<th>0</th>
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<th>1</th>
<th>1 3/4</th>
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</thead>
<tbody>
<tr>
<td>Potassium</td>
<td>18.6</td>
<td>18.3</td>
<td>18.9</td>
<td>17.5</td>
<td>17.7</td>
<td>18.8</td>
</tr>
<tr>
<td>Sugar</td>
<td>88</td>
<td>146</td>
<td>154</td>
<td>146</td>
<td>109</td>
<td></td>
</tr>
</tbody>
</table>

50 g. of glucose given at zero.

(4).

J.C., aged 29. Progressive muscular atrophy. 24.11.38.

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Potassium</td>
<td>18.4</td>
<td>18.4</td>
<td>17.9</td>
<td>17.9</td>
<td>16.5</td>
<td>18.4</td>
<td>15.8</td>
</tr>
<tr>
<td>Sugar</td>
<td>93</td>
<td>116</td>
<td>139</td>
<td>110</td>
<td>95</td>
<td>87</td>
<td></td>
</tr>
</tbody>
</table>

50 g. of glucose given at zero.

(5).

H.K., aged 60. Progressive muscular atrophy. 13.12.38.

<table>
<thead>
<tr>
<th>Time</th>
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<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium</td>
<td>20.4</td>
<td>20.5</td>
<td>18.8</td>
<td>18.6</td>
<td>18.8</td>
<td>19.4</td>
</tr>
<tr>
<td>Sugar</td>
<td>93</td>
<td>153</td>
<td>177</td>
<td>250</td>
<td>203</td>
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</tr>
</tbody>
</table>

50 g. of glucose given at zero.

(6).


<table>
<thead>
<tr>
<th>Time</th>
<th>0</th>
<th>1/2</th>
<th>1</th>
<th>1 3/4</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium</td>
<td>20.7</td>
<td>19.9</td>
<td>18.7</td>
<td>17.8</td>
<td>18.3</td>
<td>19.4</td>
</tr>
<tr>
<td>Sugar</td>
<td>351</td>
<td>470</td>
<td>533</td>
<td>532</td>
<td>524</td>
<td></td>
</tr>
</tbody>
</table>

50 g. of glucose given at zero.

(7). /
(7).

T.L., aged 43. Disseminated sclerosis. 20.2.39.

<table>
<thead>
<tr>
<th>Time</th>
<th>0</th>
<th>1</th>
<th>1½</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium</td>
<td>20.6</td>
<td>20</td>
<td>19.5</td>
<td>18.7</td>
<td>20</td>
</tr>
<tr>
<td>Sugar</td>
<td>82</td>
<td>112</td>
<td>92</td>
<td>82</td>
<td>76</td>
</tr>
</tbody>
</table>

100 g. of glucose given at zero.

(8).

D.A., aged 34. Disseminated sclerosis. 10.1.39.

<table>
<thead>
<tr>
<th>Time</th>
<th>0</th>
<th>1</th>
<th>1½</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium</td>
<td>20.3</td>
<td>18.2</td>
<td>17.4</td>
<td>16.8</td>
<td>16</td>
</tr>
<tr>
<td>Sugar</td>
<td>74</td>
<td>121</td>
<td>122</td>
<td>110</td>
<td>81</td>
</tr>
</tbody>
</table>

118 g. glucose given at zero.

(9).


<table>
<thead>
<tr>
<th>Time</th>
<th>0</th>
<th>1</th>
<th>1½</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium</td>
<td>16.3</td>
<td>16</td>
<td>13.8</td>
<td>12.8</td>
<td>13.2</td>
</tr>
<tr>
<td>Sugar</td>
<td>80</td>
<td>147</td>
<td>161</td>
<td>175</td>
<td>150</td>
</tr>
</tbody>
</table>

150 g. of glucose given at zero.

(10).


<table>
<thead>
<tr>
<th>Time</th>
<th>0</th>
<th>1</th>
<th>1½</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium</td>
<td>19.1</td>
<td>17.5</td>
<td>14.1</td>
<td>15.7</td>
</tr>
<tr>
<td>Sugar</td>
<td>74</td>
<td>122</td>
<td>99</td>
<td>95</td>
</tr>
</tbody>
</table>

150 g. of glucose given at zero.

(11). /
(11).


<table>
<thead>
<tr>
<th>Time</th>
<th>0</th>
<th>1</th>
<th>1½</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium</td>
<td>17.3</td>
<td>17</td>
<td>16</td>
<td>15.4</td>
<td>15.3</td>
</tr>
<tr>
<td>Sugar</td>
<td>86</td>
<td>125</td>
<td>146</td>
<td>136</td>
<td>112</td>
</tr>
</tbody>
</table>

150 g. of glucose given at zero.

Two patients with myasthenia gravis.

(12).

Mrs. R., aged 29. 3.11.38.

<table>
<thead>
<tr>
<th>Time</th>
<th>0</th>
<th>½</th>
<th>1</th>
<th>1½</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium</td>
<td>18.8</td>
<td>15.8</td>
<td>15.6</td>
<td>16.7</td>
<td>18.8</td>
<td>19.2</td>
<td>18.6</td>
</tr>
<tr>
<td>Sugar</td>
<td>94</td>
<td>130</td>
<td>138</td>
<td>106</td>
<td>88</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

50 g. of glucose given at zero.

(13).

Mrs. R., aged 29. 3.11.38.

<table>
<thead>
<tr>
<th>Time</th>
<th>0</th>
<th>½</th>
<th>1</th>
<th>1½</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium</td>
<td>16.1</td>
<td>14.6</td>
<td>14.3</td>
<td>14.8</td>
<td>15.1</td>
<td>17.2</td>
<td>16.4</td>
</tr>
<tr>
<td>Sugar</td>
<td>102</td>
<td>161</td>
<td>169</td>
<td>130</td>
<td>110</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

50 g. of glucose given at zero.

(14).

A.B., aged 43. 22.11.38.

<table>
<thead>
<tr>
<th>Time</th>
<th>0</th>
<th>½</th>
<th>1</th>
<th>1½</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium</td>
<td>13.1</td>
<td>17.3</td>
<td>17.2</td>
<td>18.4</td>
<td>16.8</td>
<td>18</td>
</tr>
<tr>
<td>Sugar</td>
<td>79</td>
<td>145</td>
<td>175</td>
<td>126</td>
<td>88</td>
<td></td>
</tr>
</tbody>
</table>

50 g. of glucose given at zero.

(15). /
(15).

A.B., aged 43. 28.11.32.

<table>
<thead>
<tr>
<th>Time</th>
<th>0</th>
<th>1</th>
<th>1½</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium</td>
<td>15.9</td>
<td>15.7</td>
<td>16.6</td>
<td>16.8</td>
<td>17.3</td>
</tr>
<tr>
<td>Sugar</td>
<td>85</td>
<td>103</td>
<td>145</td>
<td>99</td>
<td>75</td>
</tr>
</tbody>
</table>

50 g. of glucose given at zero.

(16).

A.B., aged 43. 1.12.35.

<table>
<thead>
<tr>
<th>Time</th>
<th>0</th>
<th>1</th>
<th>1½</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium</td>
<td>16.9</td>
<td>16.5</td>
<td>15.8</td>
<td>16.1</td>
</tr>
<tr>
<td>Sugar</td>
<td>83</td>
<td>102</td>
<td>127</td>
<td>127</td>
</tr>
</tbody>
</table>

50 g. of glucose and 2.5 mg. of Prostigmin (Roche) subcutaneously at zero.

(17).

A.B., aged 43. 13.1.39.

<table>
<thead>
<tr>
<th>Time</th>
<th>0</th>
<th>1</th>
<th>1½</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium</td>
<td>16.3</td>
<td>13.3</td>
<td>13.3</td>
<td>13.4</td>
<td>14.0</td>
</tr>
<tr>
<td>Sugar</td>
<td>71</td>
<td>180</td>
<td>224</td>
<td>235</td>
<td>197</td>
</tr>
</tbody>
</table>

105 g. of glucose given at zero.

Before drawing any conclusions from the results it must be pointed out that the technique of potassium estimation is very difficult. About a month was spent practising the method before the results became sufficiently accurate to be accepted. In /
In spite of this it seems obvious that occasional results are not to be relied on. The general trend in at least thirteen of the seventeen tables is for a fall in the plasma potassium curve to occur after glucose administration. The results in the literature show clearly that this does occur. In Table 1 a definite rise of the plasma potassium appears to take place following the ingestion of glucose. This is probably due to an error in the estimation of the fasting potassium level. In Tables 2 and 14 the values obtained 1½ hours after glucose administration are probably too high. Similarly in Table No. 15 the results seem to be at variance. No explanation can be given for these errors or presumptive errors in the technique of the estimation. It should be realised that the actual amount of potassium in 2 c.c. of plasma - the quantity used for analysis - is approximately 0.4 mg. An error of 1 mg. per 100 c.c. represents one fiftieth part of an mg. in the actual estimation. Fenn, Cobb and Marsh (1934) and Fenn and Cobb (1934A) using the same method of analysis found occasional large errors which they state is inherent in the method. In view of these difficulties most of the conclusions will be drawn from /
from average results incorporating my own work and the results recorded in literature. These have already been referred to and are now presented in tabular form.

One normal person. Aitken and Associates (1937).

<table>
<thead>
<tr>
<th>Time</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium</td>
<td>21</td>
<td>21.6</td>
<td>17.9</td>
<td>16.1</td>
<td>15.9</td>
</tr>
<tr>
<td>Sugar</td>
<td>78</td>
<td>94</td>
<td>109</td>
<td>92</td>
<td>81</td>
</tr>
</tbody>
</table>

260 g. of glucose given orally at zero.

One patient with disseminated sclerosis, aged 23. Greig (1938).

<table>
<thead>
<tr>
<th>Time</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium</td>
<td>15.7</td>
<td>16.0</td>
<td>14.6</td>
<td>14.6</td>
<td>15.7</td>
</tr>
<tr>
<td>Sugar</td>
<td>102</td>
<td>131</td>
<td>116</td>
<td>99</td>
<td>102</td>
</tr>
</tbody>
</table>

50 g. of glucose given at zero.

One patient with diabetes mellitus, aged 58. Greig (1938).

<table>
<thead>
<tr>
<th>Time</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium</td>
<td>20.6</td>
<td>20.2</td>
<td>16</td>
<td>17.4</td>
<td>20.2</td>
</tr>
<tr>
<td>Sugar</td>
<td>280</td>
<td>395</td>
<td>368</td>
<td>340</td>
<td>279</td>
</tr>
</tbody>
</table>

50 g. of glucose given at zero.

One patient with myotonia, aged 25. Greig (1938).

<table>
<thead>
<tr>
<th>Time</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>1.5</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium</td>
<td>17.7</td>
<td>13.8</td>
<td>16.6</td>
<td>15.7</td>
<td>21.9</td>
</tr>
<tr>
<td>Sugar</td>
<td>90</td>
<td>183</td>
<td>160</td>
<td>129</td>
<td>92</td>
</tr>
</tbody>
</table>

50 g. of glucose given at zero.

One /
One patient with Wilson's disease, aged 12.
Greig (1938).

Time   zero  ½  1  1½  2
Potassium   16.5  14.7  10.8  15.9  14.8
Sugar    107    147   162   152   146

50 g. of Laevulose given at zero.

Note:-- It will be seen that in this patient a marked fall of the plasma potassium occurred after a relatively small dose of carbohydrate. The patient had a liver deficiency as indicated by the laevulose tolerance curve and the result will, therefore, not be used in making conclusions. It is the only report of such an investigation in a patient with hepatic cirrhosis and the marked fall of the plasma potassium cannot be commented upon. The result is included only to illustrate the general effect of the ingestion of sugar in the plasma potassium content.

It is then obvious that the administration of glucose produces a drop in the plasma potassium level. It is possible to make certain other conclusions. These have been made from the values given in the curves rather than from the tables, the former being more accurate as regards the timing of the withdrawal of blood specimens. It can be accepted that:

(1). The larger the amount of ingested glucose the more marked is the fall in the plasma potassium level. This is illustrated in the following table.

Amount of glucose

given.
Amount of glucose given. | Average maximum fall of potassium, (in any specimen after glucose administration) | No. of investigations.
---|---|---
50 g. | 2 mg. | 14
100-118 g. | 3.1 mg. | 3
150 g. | 3.6 mg. | 3
250 g. | 5.1 mg. | 1

(2). The maximum rise in the blood sugar following glucose administration occurs earlier than the maximum fall in the plasma potassium level. This is illustrated as follows.

| Time of max. rise of blood sugar | Time of average max. fall of potassium | No. of investigations.
---|---|---
30 mins. | 64 mins. | 10
60 mins. | 130 mins. | 8

These values are only approximate as the blood samples were taken only at approximately half hourly intervals. The apex of the rise in the blood sugar curve was for that reason missed in many cases. As regards individual results, only in one case did the maximum fall of the plasma potassium precede the apex of the rise of the blood sugar. This was in a patient with severe myasthenia gravis (curve 17). His condition was at that time rapidly deteriorating. (His dynamometer readings, for example, were 150 and 60 /
60 for the left and right hand respectively as compared to 190 and 100, 34 days previously). I have already referred to the possibility of a disturbed potassium metabolism in this condition. In other seven of the total of twenty-one series recorded, the maximum fall in the plasma potassium and the apex of the rise in the blood sugar appears to occur at approximately the same time. This includes four investigations in the patients with myasthenia gravis and the results obtained by Greig (1938) in the patient with myotonia. There are, therefore, left only two curves (Nos. 5 and 9) obtained from patients with a normal potassium metabolism which show this variation. It will be seen from these curves that the differences between the plasma potassium level at the time of the maximum rise of the blood sugar and the next specimens analysed are relatively slight. This brings in the possibility of an error in the estimation. It would seem, therefore, that the maximum rise of the blood sugar after glucose administration tends to occur earlier than the maximum fall in the plasma potassium content. It is /
is obvious, therefore, that the maximum fall in the plasma potassium content occurs when sugar is rapidly being removed from the blood for metabolism in the tissues.

(3). The raising of the blood sugar level by the administration of glucose does not per se cause the removal of potassium from the plasma. This is a corollary of the previous conclusion. On the ten occasions in which the maximum rise of the blood sugar occurred in half an hour (an average of 53 mg. of sugar) the average fall of the plasma potassium was 1.3 mg. when the blood sugar concentration was at its height. This includes two results obtained in a patient with myasthenia and one from a patient with myotonia in whom the maximum rise of the blood sugar and the maximum fall of the plasma potassium coincided. The reduction in the plasma potassium content in these three cases of 3.4, 1.7 and 3.9 mg. per cent considerably raises the average values. For comparison the average maximum fall in the plasma potassium level occurring on an average thirty-seven minutes after the apex of the rise of the blood sugar was 2.8 mg. in the same ten curves. It seems from these observations that the drop in the plasma potassium /
potassium content is not compensatory to a raised blood sugar concentration.

(4). The fall in the plasma potassium concentration after glucose administration depends on the removal of sugar from the blood. This fact is indicated by (a) the maximum fall of the plasma potassium occurs later than the maximum rise of blood sugar - as has been shown above. (b) The extent of the drop increases steadily as the mechanism for the removal of sugar from the blood comes into action. The following tables illustrate this clearly. (The results are expressed as mg. per 100 c.cm. increase (+) or decrease (-) of the pre-glucose levels of the blood sugar and the plasma potassium.

(1). The cases in which the maximum rise of the blood sugar occurred in approximately thirty minutes. Average values for nine investigations are given. The figures obtained in a severe diabetic are not included.

<table>
<thead>
<tr>
<th>Hours after glucose administration</th>
<th>Time</th>
<th>Fasting</th>
<th>1/2</th>
<th>1</th>
<th>1 1/2</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium</td>
<td>18.2</td>
<td>-1.3</td>
<td>-2</td>
<td>-1.3</td>
<td>-0.4</td>
<td></td>
</tr>
<tr>
<td>Sugar</td>
<td>39</td>
<td>+44</td>
<td>+23</td>
<td>+16</td>
<td>+3</td>
<td></td>
</tr>
</tbody>
</table>

(2). Investigations in which the maximum rise of the blood sugar occurred in sixty minutes (approximately); average values for seven investigations are given - /
given - the results obtained in a severe diabetic are again excluded.

<table>
<thead>
<tr>
<th>Time</th>
<th>Fasting</th>
<th>½</th>
<th>1</th>
<th>1½</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium</td>
<td>13.0</td>
<td>-0.1</td>
<td>-1.0</td>
<td>-1.0</td>
<td>-1.7</td>
</tr>
<tr>
<td>Sugar</td>
<td>76</td>
<td>+43</td>
<td>+66</td>
<td>+43</td>
<td>+14</td>
</tr>
</tbody>
</table>

It will be seen from these two tables that (a) the later the rise of the blood sugar, the later does the fall in the plasma potassium begin. (b) The slower the rate of removal of the blood sugar, the later does the maximum fall in the plasma potassium level occur. This is also illustrated on page 37. In other words, the more delayed the passage of sugar from the blood into the tissues the slower the removal of potassium from the plasma and the slower the return to the initial level. It, therefore, seems that there is a parallelism between the variations in the plasma potassium concentration and the blood sugar tolerance. This statement could be accepted as a fact if it could be shown that the administration of a large amount of glucose to individuals with a high sugar tolerance produced a rapid and marked fall in the plasma potassium concentration.
concentration with a rapid return to the pre-sugar level. Such an effect is illustrated in Curve 10 from an investigation in a patient with asthma. Asthmatics are recognised vagotonics (Price 1937) which implies a high sugar tolerance (Hill and Howitt 1936). A comparison of the results in Curves 12 and 13 obtained from a patient whose sugar tolerance varied on the two occasions also illustrates this effect. Insufficient work, however, has been done to consider this a conclusion.

As a brief summary these conclusions and suggestions indicate that there is a close relationship between the removal of sugar from the blood and the fall in the plasma potassium concentration after glucose administration. The removal of the two substances from the circulation appears to be so intimate as to support the view that potassium accompanies glucose into the muscles. There must be some reason for this relationship and it seems likely that potassium accompanies the glucose to take part in the active utilisation of the latter. Moreover, the results indicate that when this phase of the metabolism of glucose has passed potassium returns to the plasma.

As /
As regards the results obtained in the two patients suffering from severe diabetes mellitus, it will be seen that here also a drop in the plasma potassium level took place after glucose administration. The two curves are very similar except that in one patient the maximum drop occurred 1½ hours after the glucose ingestion (Curve 6), while in the other the maximum fall occurred in 1 hour (page 36). These results correspond to those obtained by Flock et al (1938) in four depancreatized dogs. Their findings have been mentioned previously. Hill and Howitt (1936) from a view of the literature state that the absorption of glucose by a normal person causes the secretion of insulin. As the fall in the plasma potassium level also occurred in the diabetics it would seem that the removal of the potassium from the plasma is not necessarily due to the secretion of insulin caused by the ingestion of sugar. I have already stated the modern view that carbohydrate can be, and is, utilised in the entire absence of insulin. The diabetic organism requires only a higher glycoemic level before utilisation of glucose can take place (Soskin and Levine 1937). The /
The finding that the plasma potassium falls in severe diabetes after glucose administration is, therefore, quite in keeping with the suggestion that the potassium leaves the plasma because it is required in the utilisation of glucose. Conversely, if potassium is utilised in the metabolism of glucose, the fact that the plasma potassium level falls after glucose administration in the diabetic as well as in the healthy individual supports the modern view that insulin is not essential for the occurrence of sugar utilisation.

The Effect of Insulin Administration on the Plasma Potassium and Blood Sugar Levels.

The fact that the injection of insulin is followed by a fall in the plasma potassium content has been known for many years. Harrop and Benedict (1922 and 1923) investigating the changes in the concentration of the inorganic plasma constituents produced by insulin were the first to demonstrate this effect. Their work regarding potassium was limited to several diabetics and to two healthy rabbits.
rabbits. Their results will be recorded in full.
The values for plasma potassium and blood sugar are
expressed in mg. per 100 c.cm. of plasma and whole
blood respectively.
   Fasting sugar 363.
   Ten units of insulin given 5 minutes later and
twenty-five units after another 4 hours.
   4½ hours after the last injection the following
results were obtained:
   Potassium 13.9  Sugar 110.
   3 hours later another ten units of insulin were
given with the following values from a blood
specimen obtained after 1/2 hour.
   Potassium 16  Sugar 119.

   Fasting sugar 312.
   Thirty units of insulin given 5 minutes later
and fifteen units after another 4 hours.
   4½ hours after the last injection when the
patient showed hypoglycoemic symptoms the
figures obtained were:
   Potassium 13.6  Sugar 81.

3. Severe diabetes. Fasting potassium 18.5
   Fasting sugar 290.
   Thirty units of insulin given 5 minutes later.
   8½ hours later when the patient had hypogly-
coemic /
hypoglycoemic symptoms the values obtained were:

Potassium 13.9  Sugar 52.

   Sugar not given.
   Thirty units of insulin given in 15 minutes.
   2\(\frac{1}{2}\) hours later the values obtained were:
   Potassium 9.7  Sugar 226.
   Another thirty units of insulin were given \(\frac{1}{2}\)
   hour after the withdrawal of the blood specimen.
   2\(\frac{1}{2}\) hours later the plasma potassium and the
   blood sugar levels were 9.4 and 114 respectively.

5. hours after the last injection the values
   found were:
   Potassium 10.5  Sugar 310.

5. Healthy rabbit fasted 48 hours.
   Plasma potassium 18.5  Blood sugar 138.
   Ten units of insulin given immediately after
   of the blood sample.
   55 minutes later: - Plasma potassium 14.2
   Blood sugar 25.

6. Healthy rabbit fasted 48 hours.
   Plasma potassium 15.6  Blood sugar 128.
   Ten units of insulin given immediately after
   withdrawal of the blood sample.
   55 minutes later: - Plasma potassium 12.6
   Blood sugar 31.
These results suggest that the larger the fall in the blood sugar following insulin administration, the greater the fall in the plasma potassium. In no cases, however, did the plasma potassium drop to more than half the initial level so that there is no absolute proportionality between the extent of the removal of the two substances from the circulation. Their own conclusions will be considered later. Briggs and co-workers (1923) apparently investigated the same problem independently using fasting dogs. They were, however, able to conclude that not only did insulin reduce the plasma potassium content but the extent of the fall was proportional to the amount of insulin injected. Their work was confirmed by Häusler and Heesch (1925) and Kerr (1926B). Kerr (1928) observed a drop in the plasma potassium content of six healthy dogs a variable time after a variable dose of insulin. He also found a fall in the plasma potassium level to 7.2 mg. 2.5 hours after the injection of forty units of insulin in a severe diabetic with a fasting blood sugar and plasma potassium of 667 and 17 mg. respectively. Takeuchi (1928B.C.) studied the effect of insulin on the plasma potassium level /
level much more completely and in a more systematic manner. He experimented with fasting, normal and pancreatectomised dogs and gives the following results.

1. Normal dogs - average of 5 experiments.

<table>
<thead>
<tr>
<th>Time</th>
<th>0 hr.</th>
<th>3 hrs.</th>
<th>5 hrs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium</td>
<td>22.3</td>
<td>25.2</td>
<td>24.8</td>
</tr>
<tr>
<td>Sugar</td>
<td>96</td>
<td>49</td>
<td>47</td>
</tr>
</tbody>
</table>

Insulin given at zero.

In a control experiment in a normal dog under identical conditions no appreciable change in the blood sugar or plasma levels were found.

2. Pancreatectomised dogs - average of 6 experiments.

<table>
<thead>
<tr>
<th>Time</th>
<th>0 hr.</th>
<th>3 hrs.</th>
<th>5 hrs.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium</td>
<td>33.4</td>
<td>31.2</td>
<td>33.3</td>
</tr>
<tr>
<td>Sugar</td>
<td>311</td>
<td>235</td>
<td>116</td>
</tr>
</tbody>
</table>

Insulin given at zero.

It will be observed that in the diabetic dogs little change in the plasma potassium content was produced in spite of twice as much insulin being injected as in the case of the normal animals, and I am unable to explain this discrepancy. He further demonstrated (Takeuchi 1928D), again using normal dogs, that insulin in large quantities caused a fall in the potassium content of lymph, that the fall in the /
the lymph potassium was directly proportional to the drop occurring in the plasma and that the extent of the drop in the lymph was proportional to the amount of insulin injected. D'Silva (1936B) found that insulin lowered the plasma potassium level of cats only when administered in large doses. He, however, used cats under chloralose anaesthesia which brings in an unnecessary complication as chlorose itself lowered the plasma potassium level.

Aitken and associates (1937) incidental to their observations on familial periodic paralysis studied the effect of insulin on the plasma potassium of one normal individual and report as follows. (Fasting plasma potassium and blood sugar levels at zero, the other values are timed in hours after the injection of insulin).

<table>
<thead>
<tr>
<th>Time</th>
<th>0</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium</td>
<td>21.9</td>
<td>22.1</td>
<td>18.3</td>
<td>16</td>
<td>17.4</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>Sugar</td>
<td>82</td>
<td>79</td>
<td>56</td>
<td>82</td>
<td>79</td>
<td>.77</td>
<td>.76</td>
</tr>
</tbody>
</table>

20 units of insulin given at zero.

From these results and from the fact that a similar fall of the plasma potassium occurred after glucose administration (page 36) they pointed out that the fall occurred independently of the hypo-glycoemia produced by insulin and that it was unlikely /
unlikely to be part of a compensatory physiological response to hypoglycoemia. They described the fall as one accompanying the passage of sugar into the tissues. Kendall (1933) from unpublished results states that the influence of insulin on the potassium ion may be of significance equal to its better known action on the concentration of the blood sugar - "indeed, the two may be inseparable."

Before summarising the effect of insulin on the plasma potassium level I must mention for the sake of completeness that there is one reference in the literature to the effect that insulin in large doses causes an increase in the blood potassium in both normal and diabetic animals. This reference (Staub Guenther and Fröhlich, 1923) constitutes the only contradictory report in the literature. Their results might be related to the use of impure insulin which, according to Hill and Howitt (1936) was so frequent in the early days of insulin therapy. In any case, they can be neglected in view of the preceding evidence. The reference is, however, cited by Hill and Howitt (1936) and Jensen (1938) and is probably the reason why these authors fail to comment /
comment on what I believe is of significance in the metabolism of carbohydrates.

From the data available then it is possible to conclude that the administration of insulin lowers the plasma potassium level. Furthermore, the data indicates the following:-

1. The greater the amount of insulin given the more marked is the drop in the plasma potassium level and the slower its return to the previous level.

2. The fall of the plasma potassium begins when the insulin commences to influence the carbohydrate metabolism and is maintained during the action of the insulin on the metabolism (as shown by the blood sugar values).

One can, therefore, conclude that the fall in the plasma potassium occurring after insulin administration corresponds closely to what one would expect if the potassium were removed from the plasma to take part in the utilisation brought about by the insulin. I have suggested previously that the effect of administered insulin is merely to modify the rate at which chemical changes take place in the tissues. The effect of increased utilisation of carbohydrates /
carbohydrates on the plasma potassium content is, therefore, very similar or perhaps identical whether produced by an increased intake of carbohydrate or insulin. I have mentioned that Takeuchi (1923D) found that insulin caused a fall in the potassium content of lymph closely parallel to the fall of the plasma potassium. Such an alteration would be expected as Meyer, Bisch and Günther (1925) showed the potassium content of lymph and plasma to be identical. Similarly, Drinker and Field (1933) state that the salt content of lymph and tissue fluids is identical. These facts indicate that, not only after insulin but also after glucose administration potassium leaves the lymph and extracellular fluids of the body and that the change is not confined to the plasma.

Before accepting that the fall in the plasma potassium following the administration of glucose or insulin is due to the passage of potassium into the tissues (especially the muscles which are the main seat of sugar utilisation, Hill and Howitt 1936) - to take part in the metabolism of sugar, it must be mentioned that no one has yet demonstrated an increase in the total muscle potassium content after the /
the administration of glucose or insulin. This has apparently never been attempted probably because of experimental difficulties. Again, no one has yet investigated the plasma potassium level in arterial and venous blood drawn off simultaneously following glucose or insulin administration. It is, therefore, necessary to consider the various alternative possibilities. Insulin or glucose might lower the plasma potassium by causing its excretion by the kidneys, the plasma level subsequently being restored by the release of potassium from some tissue or organ. Glucose was given in aqueous solution probably in all the cases reported in literature; in my own investigations as much as 500 c.c. of water (with 150 glucose) was ingested. It might, therefore, be suggested that the fall in the plasma potassium might be due to haemodilution or to a disturbance in the ionic equilibrium in the plasma. It is, therefore, necessary to consider the other plasma metals and to discuss at the same time whether the change is specific for potassium. It must also be shown that the potassium ion is able to penetrate into muscle cells and that it does not pass into cells which are not concerned in the metabolism of carbohydrates - especially the red blood corpuscles. These various problems will now be considered.
Miller (1922a) fed several pigs on a strict starch diet and found that the daily small quantities of the urinary excretion of potassium did not exceed the small quantities present in the starch. Harrop and Benedict (1923) administered insulin to a moderately severe diabetic whose potassium excretion during the previous 24 hours was constant. They found that when the plasma potassium level was low the urinary excretion of potassium was reduced. An increase in the amount of potassium excreted occurred "during the following night when the effect of insulin had ended." Kendall (1932) similarly demonstrated that insulin retarded the excretion of potassium in normal rats. Allot and McArdle (1933) Gammon (1933) and Pudenz et al (1933) found a decreased amount of potassium in the urine during attacks of familial periodic paralysis induced by the administration of glucose, other carbohydrate or insulin. A subsequent compensatory increase in the urinary potassium excretion occurred when the paralysis had passed off and the plasma potassium level had returned to its initial level. Flock et al (1938) in their studies on the plasma potassium content /
content of dogs following the intravenous injection of glucose solution found that the urinary output of potassium was inconsistent. They do not mention the concentration of the solution of the solution used but their inconsistent results were possibly due to large quantities of water being used. Gammon (1938) found that the ingestion of large quantities of water with resultant diuresis caused a slightly increased excretion of potassium.

These observations, in my opinion, are sufficiently comprehensive to justify the conclusion that the fall in the plasma potassium level after glucose or insulin administration is not due to the excretion of potassium by the kidneys. There is, therefore, no need to describe any possible release of potassium from any source in the body to compensate for any loss of potassium by urinary excretion. The question of excretion of potassium by other channels such as in the sweat (Freyberg and Grant 1937) hardly necessitates any consideration.
THE PROBLEM OF HAEMODILUTION.

The possibility of diluting the blood by the administration of watery solution of glucose with a resultant fall in the plasma potassium content has been suggested already. The ingestion of water by itself even in very large amounts leads only to a very trivial dilution of the blood. Thus, according to Wright (1937) if 2 litres are drunk in fifteen minutes the blood water content is found scarcely to alter at all. If the haemoglobin is taken as an index of haemodilution there is a fall of 2% only (after two litres). Szeloczey (1930), Bruger and Mosenthal (1932) found that the administration of sugar subcutaneously, intravenously or orally induced diuresis. McClelandon (1931), on the other hand, found a marked retention of water when 400 g. of glucose were taken in 2,400 c.cm. of water. Similarly, Bachmann, Haldi, Ensor and Wynn (1933) found that the amount of urine excreted after large amounts of sugar and water was less than the amount excreted after the same quantity of water alone. In my own investigation the maximum amount of water ingested /
ingested (with 150 g. of glucose) was 500 c.cm., any resultant dilution of the blood, if any, would, therefore, appear to be very slight. Flock et al (1933) administered continuous intravenous glucose solution into dogs. Accompanying the fall in the plasma potassium they found a fall in the plasma sodium; the percentage fall of the sodium, however, was small compared to the fall of potassium. This latter fact indicates slight haemodilution because, as will be seen later, the effect is specific on the plasma potassium. I can find only one reference in the literature stating that the administration of glucose definitely causes dilution of the blood. Fisher and Wishart (1922) found that the ingestion of large amounts of glucose caused a haemodilution which succeeded the state of hyperglycaemia. The fact that the haemodilution was delayed, however, would seem to indicate that the plasma was for some reason diluted by the advent of tissue fluids rather than by the extrinsic addition of water. As already pointed out, the potassium content of lymph and tissue fluids is identical with the blood plasma. A fall in the potassium level of the plasma could, therefore, hardly be due to intrinsic dilution. Further confirmation /
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confirmation comes from the fact that no reduction in the plasma potassium content occurs after bleeding (Kerr 1926A; Baetjer 1935; Houssay, Marenzi and Gerschman, 1936 A.B.C.) in which condition, as is well known, intrinsic haemodilution occurs. It is further of interest that the injection of adrenaline causes haemoconcentration and, as will be seen, it lowers the plasma potassium level. From these observations it seems obvious that the oral administration of glucose water solution in the quantities used could not account for the drop in the plasma potassium level due to any resultant dilution of the blood.

As regards insulin Kerr (1922) found a slight increase in the water content of the plasma of normal dogs three hours after over-dosage with insulin. Similarly, he found a noticeable increase in the water content of the blood of a diabetic after insulin. The dilution in each instance was, however, "not sufficient to account for the changes in the plasma potassium level." Hill and Howitt (1936) from a general review of the literature state that the administration of insulin does not cause haemodilution either in the normal person or in the diabetic.
diabetic. If it did it would in any case be intrinsic haemodilution. Further comment would, therefore, appear unnecessary.
THE QUESTION OF SPECIFICITY.

The question whether the fall in the plasma potassium level after glucose administration is specific for this component among the plasma metals is one which has received little attention. Fudenz et al (1933) found that no fall in the plasma concentrations of sodium and calcium occurred in attacks of familial periodic paralysis induced by glucose administration. The plasma potassium and the plasma inorganic phosphate levels alone were affected. Flock et al (1938) using dogs found a slight fall of the plasma sodium as well as a more marked fall of the plasma potassium after the intravenous administration of glucose. This was mentioned in the previous chapter when I suggested the reduction of the plasma sodium was due to haemodilution. There are no other references in the literature regarding any simultaneous investigation of the plasma changes regarding these two metals after glucose administration. I have been unable to find any other papers dealing with any effect of glucose administration on the plasma sodium calcium or /
or magnesium. For that reason and from the two references quoted I believe that potassium alone among the plasma metals is reduced by the administration of glucose. This conclusion is further supported by the specificity of insulin on the plasma potassium content. This specificity will now be discussed in detail.

Harrop and Benedict (1922, 1923) administered large doses of insulin to four severe diabetics and found no change in the concentration of the plasma sodium or calcium. Briggs and co-workers (1923) confirmed these findings in normal dogs and extended the observations to include the magnesium ion. As regards calcium the majority of investigators (Davies, Dickens and Dodds 1926, Brougher 1927, Ellsworth 1928, Raiha 1932) have actually observed a slight increase in its plasma concentration following insulin administration. Takeuchi (1928B) found no change in the plasma sodium or magnesium after insulin, and Rathery and Sigwald (1931) found no change in the plasma sodium and magnesium after insulin. There is, therefore, a remarkable constancy in health as well as in diabetes in the plasma inorganic elements apart /
apart from this specific effect on the potassium ion. It is well known that a lowering of the alkali reserve occurs in diabetes - this has already been discussed as regards the plasma potassium ion. This tendency towards acidosis is, of course, rectified by insulin and from the above considerations it is obvious that the alteration of the alkali reserve of the blood is not brought about through any influence on the metallic components of the plasma. Again, the carbon dioxide combining power in hypoglycoemia induced by insulin is, of course, normal (Gigon 1925, Stewart and Dunlop 1937) and, as already pointed out, the potassium of the plasma is specifically lowered by insulin in normals as well as in diabetes. It might be argued that this specific fall in the plasma potassium level following insulin (or glucose) administration might be related to an attempt at equilibrium of the pH in the blood and tissues. As will be seen later, however, the inorganic phosphate among the plasma anions is similarly specifically affected. It seems unlikely, therefore, that potassium leaves the plasma to adjust any alteration of the Muscle pH due to the administration of those substances. The significance of the specificity will be discussed later.
From the previous considerations it is, of course, obvious that the potassium leaving the plasma as a result of the administration of glucose and insulin must of necessity penetrate into the cells of the body. As already stated, however, no one has yet demonstrated that this actually does occur after the administration of glucose or insulin. Positive evidence for the permeability of cells to the potassium ion will, therefore, serve to confirm this assertion.

Lévy (1923) injected potassium chloride intravenously into human beings and concluded that the potassium passed quickly into the tissues. Whelan (1925) injected potassium chloride intravenously into dogs and found that the potassium left the circulation rapidly and that it was not excreted to any marked extent. Norn (1929C) in similar injection experiments using nephrectomised rabbits found that the increase in the plasma potassium concentration was so low that the great part of the injected potassium must have left the extracellular fluids, the only /
only path of exit being the tissue cells. These findings were later confirmed by D'Silva (1934B) in experiments with normal cats and by Bourdillon and Page (1937) similarly using rabbits but with both ureters ligated. Houssay and Marenzi (1937 A.B.) injected adrenaline into dogs and found that a brief period afterwards the plasma potassium concentration of the Femoral vein was less than in the Femoral artery. Houssay and Marenzi (1937A.B.) again using dogs injected potassium in large doses intravenously and found a constant rise of potassium in the muscles. The plasma potassium curve was not modified by bilateral nephrectomy removal of the liver and the whole of the digestive tract "from the cardia to the anus." They concluded from their experiments that the muscles were the important place for "fixation" of potassium. There is also corroborative evidence in that various investigators (Bunge 1873, Miller 1922A, Blum, Aubel and Hausknecht 1921A.B., Bourdillon 1937) and others have found that the administration of potassium salts causes the excretion of salts of sodium as well as salts of potassium. Winkler and Smith (1938) from their study of the volume of the fluid of the body through which /
which any substance is distributed state that the behaviour of potassium in entering and leaving cells readily is unique among all ions and that exogenous potassium enters some and probably most of the cells of the body. Fenn and Cobb (1933, 1934b) found that potassium left the extracellular fluids and entered the muscle fibres when the carbon dioxide tension of the latter was increased. They further state that potassium is the only cation apart from the H⁺ ion which is able to penetrate. It seems, however, a remarkable fact as pointed out by Osterhout (1930) and various of the authors quoted above that potassium possesses this great ability to penetrate cells in spite of the fact that cells already contain relatively large quantities of potassium. This property of potassium is sometimes described as the ability to diffuse into the cells against a concentration gradient. Fenn and Cobb 1933 quote Mond and Netter (1930, 1932) as stating that potassium in muscle is 30-40 times as concentrated in the muscle fibres as in the tissue spaces. I shall suggest later that this phenomenon is perhaps not so surprising considering the quantity of potassium and its physical properties in muscle cells. This will be /
be discussed later. However, this is an adequate consideration of the penetrative powers of the potassium ion.
THE QUESTION OF THE RED BLOOD CORPUSCLES
AND ITS PERMEABILITY TO POTASSIUM.

The potassium content of human red blood corpuscles according to Kramer and Tisdall (1922) is 410 to 440 mg. per 100 c.c. of corpuscles with an average value of 423 mg. These figures are similar to those given by Bodansky (1938) and Kerr (1937) and others, and need not be discussed. Without considering whether the potassium of the cells is in an ionised or organically combined state or both, it is apparent that the membranes of the cells suspended in plasma with a low but ionised potassium content would be peculiarly subjected to the remarkable penetrative powers of potassium both from within and without. I have stated earlier that the erythrocyte has no independent metabolism. Any such penetration occurring as a result of the administration of glucose or insulin would, therefore, largely invalidate any conclusions that potassium is concerned in the utilisation of carbohydrates. Several studies have been made on the permeability of red cells in vitro. Hamburger (1916A.B.) showed that red blood corpuscles washed with /
with glucose solution subsequently yielded potassium to a potassium free Ringer solution. Ashby (1924) found red corpuscles permeable to potassium in aqueous solution. Kerr (1926B) added serum containing an excess of potassium chloride to washed erythrocytes and found no increase in the cell potassium content after an hour. He later (Kerr 1929) washed red blood corpuscles in strong hypertonic saline solution and found that potassium entered the cells but only when a great part of the serum was washed away. He also found that red cells washed with isotonic serum sodium chloride mixtures lost potassium when the proportion of serum fell to 25%, and that on adding potassium chloride crystals to the serum up to a concentration of 200 mg. per cent the potassium content of the red cells increased. It would, therefore, seem that the membrane of the erythrocyte in vitro is permeable to the potassium ion only under conditions which can hardly be termed physiological.

As regards in vivo experiments the results are more uniform. Collip (1921) and Doisy and Eaton (1921) found no shift of potassium from the plasma into the corpuscles on saturating the blood with CO₂. They concluded
concluded from their experiments that the red blood cells are permeable to anions (chloride shift, etc) but impermeable to both sodium and potassium. Similarly Fenn and Cobb (1934B) concluded that the osmotic equilibrium across the cell membrane of the erythrocyte was maintained by its impermeability to ions. Whelan (1925), using dogs, injected potassium chloride intravenously and found that potassium did not enter the red blood corpuscles. Gerschman and Marenzi (1932) in similar experiments and Houssay and Marenzi (1937B) in identical experiments arrived at the same conclusion.

Briggs and co-workers (1923) from their few analyses of whole blood concluded that the effect of insulin was to lower the potassium of the corpuscles as well as of the plasma. Kerr (1926B) found that the fall in the plasma potassium level induced by insulin was accompanied by an increase in the red cell potassium by as much as 250%! He later (1928) repeated these experiments, found that the potassium content of the red cells was not increased and cancelled his previous report. From these findings and from his in vitro experiments as described above he /
he again later (Kerr 1929) concluded that the impermeability of the red cell membrane under physiological conditions seemed to be well established. Similarly, van Slyke (1926) and Steel (1937) state that the red corpuscle is not ordinarily permeable to either potassium or sodium but becomes so under extraordinary conditions. Does then the administration of insulin or glucose or, for that matter, adrenaline, constitute an extraordinary or unphysiological condition? An example of what is meant is perhaps well illustrated by the experiments of Henriques and Oerskov (1936 A.B.) who showed that red cells can become permeable to cations in vivo. They produced a toxic anaemia in rabbits by injections of phenylhydrazine and showed that the potassium content of the red cells fell, to rise again as the anaemia improved after cessation of injections. They believe that the permeability to potassium was raised by toxic influence on the cell membranes. In the same way addition of distilled water in large quantities to the circulation caused a fall in the potassium content of the red cell which, however, rose again quickly (c.f. the in vitro experiments of Kerr above). As Hansen (1937) states regarding these findings, one can still maintain that the normal red cells is impermeable to the potassium ion.
It is, of course, well known that during physical exertion large amounts of carbohydrate are metabolised in the tissues, particularly in the muscles. Muscle glycogen is rapidly used up when they contract (Macleod 1935) and is subsequently replenished by glycogenolysis in the liver and the passage into the muscles of sugar from the blood (Martin 1937). If then potassium is required in the metabolism of carbohydrate one would expect potassium to leave the plasma during exercise to take part in the utilisation of sugar. As there is no recognised storehouse for potassium in the body (D'Silva 1934B) a fall in the plasma potassium level would be expected. There is no reference in literature stating that this actually does occur, in fact, some observers find an increased plasma potassium concentration during exercise. To explain this discrepancy it is necessary to consider (1) the quantity and physical state of potassium in resting muscle. (2) The changes as regards potassium brought about by muscular activity.

1. /
1. The Quantity and Physical State of Potassium in Resting Muscle.

The potassium content of human skeletal muscle is given by Norn (1929A) as 349 mg. per 100 g. of moist muscle. He gives very similar values for the potassium content of the muscles of various animals. His figure corresponds closely with those of Steel (1937) and Bodansky (1938) and need not be discussed. As regards the physical state of potassium in resting muscle the literature is, to a small extent, controversial. Loeb, as early as 1906, stated "We may take it for granted that potassium forms a non-dissociable constituent of the protoplasm of a number of tissues of animals and plants." Norn (1929C) from extensive observations concluded that part of the potassium administered to rabbits and humans passed into undissociated organic combination in the cells of the body and that it was gradually dissociated and excreted. Hill and Kupalov (1930), on the other hand, concluded from their studies on cellular osmotic tension that the potassium inside the muscles must be in solution if the osmotic pressure inside is
is to equal that outside.

Fenn and Cobb (1934B) investigating the migration of the potassium ion in relation to changes in the pH of muscles concluded that their results were compatible with the theory that potassium is immobilised in the tissues because it is combined with an indiffusible anion. They refer to the work of Hill and Kupalov (above; in a previous paper) (Fenn and Cobb 1933) and must have been aware of their findings! From these observations and from the investigations of the changes in the state of muscle potassium during muscular contractions (which are described below to avoid repetition) it can be concluded that the potassium in muscle is, at least mostly, in a combined undissociated state. A muscle cell then is not a sac containing an ordinary solution, but an intimate colloidal arrangement of complex chemical bodies in water. In my opinion it is, therefore, not such a remarkable fact as suggested previously that potassium is able to enter muscle cells against the so-called potassium concentration gradient. Again, the potassium leaving the plasma following glucose or insulin administration must necessarily be in an ionised state. If that potassium
potassium is concerned in the metabolism of sugar it would seem to be so in virtue of this ionised state. It is obvious that the amount of potassium leaving the plasma and extracellular fluids after glucose or insulin is not sufficient to alter materially the total quantity of the potassium in muscle. In any case, inorganic phosphate leaves the plasma in a similar manner as will be shown later, to take part in the utilisation of sugar and there is already an appreciable amount of inorganic phosphate in muscle. Bodansky (1938) gives the total phosphate of muscle ash as 0.17 to 0.25% of which 80% is inorganic. For comparison, the values he gives for the potassium content of muscle ash are 0.25 to 4.0%. Quantitatively there is, therefore, no reason why potassium leaving the plasma following glucose or insulin administration should not be concerned in the utilisation of sugar.

2. The Changes in the Plasma Potassium Concentration and in the Physical State of Muscle Potassium as a Result of Muscular Activity.

The reports in the literature regarding the changes /
changes in the plasma potassium level and the loss of potassium from muscle as a result of muscular contractions are somewhat contradictory. Rakestraw (1921) found a moderate increase of the plasma potassium during recovery following exercise. Harrop and Benedict (1923) injected strychnine into rabbits and found an increase of approximately 60% in the plasma potassium concentration. They attributed this change to a loss of potassium from the muscles. Mitchell and Wilson (1921) found that frog muscles bathed in Ringer solution lost potassium only when fatigued beyond physiological limits. Drill, Talbot and Edwards (1930) found no change in the plasma potassium level of men during exercise. Cloetta, Fisher and van der Loeff (1934) found that mammalian skeletal muscle exercised by electric stimulation lost potassium. The plasma potassium level was also increased in animals whose muscles were rhythmically stimulated. Similarly, stimulation of the central nervous system produced a rise in the plasma potassium level. This latter effect was prevented by curare and it was concluded that the potassium came from the muscles. Fenn (1936) stimulated /
stimulated muscles of cats "sufficiently to make them lose potassium." He found that the rise of the plasma potassium was "minimal." Norn (1929A) experimenting on himself found that intensive muscular exercise did not influence the amount of potassium excreted. Fenn (1937) exercised rats with one leg denervated by making them swim and found that there was slight loss of potassium from the active muscles as compared to the denervated muscles. Houssay, Marenzi and Gerschman (1937A.B.) report a rise in the plasma potassium level in dogs by stimulating the sciatic nerves with an intense Faradic current. The rise was of the nature of 1.6 to 2 mg. per cent, and they concluded that the potassium came from the liver. Keys (1937) investigated six normal persons and found (like Rakestraw) that at the end of brief violent exercise the potassium in the plasma was as much as 25% above the resting level. These reports have been recorded in some detail because they show conclusively that no fall in the plasma potassium level occurs during exercise. As I have stated already this is what one might /
might expect if potassium is required in the utilisation of sugar. Also most of the reports suggest that potassium is lost from muscle during muscular contraction which tends to confirm that potassium is liberated in muscles during contraction.

The Changes in the Physical State of Muscle Potassium during Activity.

Ernst and Schiffer (1922) stated that a perfused muscle when stimulated lost large amounts of potassium. They believed that the loss of potassium was not related to fatigue or to an increased permeability of the cell membrane. Only an increase in the ionised potassium content of the muscle during contraction could explain this phenomenon. Ernst and Fricker (1934) concluded that during rest potassium in muscle is mainly in combined form and that during muscular activity potassium is liberated in diffusible form. Reginster (1937, 1938A.B.) confirmed these findings in a series of investigations. He found that the ratio of combined to ionised potassium was markedly increased by both direct and indirect
indirect muscle stimulation. He concluded that the quantity of potassium liberated in muscles by nerve stimulation was proportional to the number of stimuli and suggested that the potassium was liberated by the secretion of acetylcholine at the nerve ending. If then ionised potassium is required in the utilisation of carbohydrate during muscular activity it would appear as if nature had provided for sufficient dissociation of potassium to take place without the necessity of the drawing of potassium from the plasma. The extent of the dissociation appears to be just sufficient for some to leak out of the muscle into the extracellular fluids. During attacks of familial periodic paralysis, as I have mentioned already, potassium leaves the plasma and passes into the tissues. Allott and McArdle (1938) suggest that in this condition there is a periodical demand for potassium. The administration of potassium salts by mouth rapidly relieves the paralysis which suggests a deficiency of ionised potassium. Might it not be that during attacks there is an insufficient amount of ionised potassium in the muscles resulting in an inability to utilise sugar (energy) with resultant paralysis? /
paralysis? The fall in the plasma potassium level or the periodical demand as mentioned above might quite well be a **compensatory** change in an attempt to raise the ionised muscle potassium content.
INORGANIC PHOSPHATE AND CARBOHYDRATE
METABOLISM. THE ASSOCIATION OF
POTASSIUM AND INORGANIC
PHOSPHATES.

The fact that inorganic phosphate takes part in
the utilisation of sugar in muscle has been well
established. The standard textbooks in biochemistry
(Bodansky 1932, Cameron 1933, Macleod 1937, Steel 1937)
al describe the formation of hexosephosphate and
other intermediary phosphorus compounds in the
metabolism of glycogen to lactic acid. Hill and
Howitt (1936) from a survey of the literature state
that phosphorus compounds play an essential part in
the utilisation of sugar, although its exact role
has not yet been clearly established. Perhaps the
incorporation of potassium would help to clarify the
interpretation of the processes taking place. Apart
from the formation of phosphate compounds the
acceptance of the fact that inorganic phosphate
is concerned in the metabolism of sugar is based on
the following data. (The plasma inorganic phosphate
content /
content is expressed in all cases as phosphorus in mg. per 100 c.cm. of plasma).

1. **The Reduction in the Plasma Inorganic Phosphate Content accompanying the Passage of Sugar from the Blood into the Tissues Following Glucose Administration.**

This has been shown to occur by numerous observers (Jensen 1932). The effect is illustrated particularly well by Harrop and Benedict (1923). They administered glucose to three persons with very similar results in each case. One of their tables will serve to illustrate.

<table>
<thead>
<tr>
<th>Time</th>
<th>Blood sugar in mg. per cent.</th>
<th>Plasma inorganic phosphate</th>
</tr>
</thead>
<tbody>
<tr>
<td>zero</td>
<td>108</td>
<td>3.52</td>
</tr>
<tr>
<td>20 minutes</td>
<td>180</td>
<td>3.04</td>
</tr>
<tr>
<td>30</td>
<td>133</td>
<td>2.63</td>
</tr>
<tr>
<td>120</td>
<td>123</td>
<td>2.62</td>
</tr>
<tr>
<td>220</td>
<td>79</td>
<td>3.13</td>
</tr>
</tbody>
</table>

200 g. of glucose was given at zero.

There are no tables in the literature showing the effect of glucose administration simultaneously on the plasma potassium and inorganic phosphate levels.
levels. Aitken and associates (1937) give the following values during an interval and during an attack of familial periodic paralysis induced by glucose administration. The attacks, of course, come on when glucose is being withdrawn from the blood.

<table>
<thead>
<tr>
<th></th>
<th>During interval</th>
<th>During attack</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma potassium</td>
<td>13.3 mg.%</td>
<td>10 mg.%</td>
</tr>
<tr>
<td>Plasma inorganic phosphate</td>
<td>3.2</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Flock et al (1938) injected glucose intravenously into dogs and found that the plasma potassium level fell parallel to the fall in the inorganic phosphate except that the potassium fell rather more rapidly. The changes observed as regards the plasma potassium have been demonstrated previously, they give no values for the plasma inorganic phosphate levels. No suggestion is given in their paper that potassium is concerned in the utilisation of sugar. It is, however, obvious from their findings and from the fact that potassium leaves the plasma when the inorganic phosphate passes into the tissues, that the reductions in the plasma concentration of the two substances /
substances correspond very closely. It seems likely, therefore, that following glucose administration, potassium and inorganic phosphate are both utilised in the metabolism of sugar.

2. The Effect of Insulin of Lowering the Plasma Inorganic Phosphate Level and of raising the Total Phosphate Content of Muscle.

The reader is referred to the numerous references quoted by Takeuchi (1923A), Martin (1937) and Jensen (1933) describing these changes. As an example, Martin (1937) from a survey of the literature states that the reduction in the blood sugar content in health and in diabetes is accompanied by a reduction of the plasma inorganic phosphate content. This, he states, indicates the formation of hexose phosphate during the combustion of glucose. It is, of course, obvious that most of the phosphoric acid required for the synthesis of hexose phosphate must originate in the muscles themselves. There is also a marked parallelism between the removal of inorganic phosphate and potassium from the plasma following insulin administration.
administration. This has been demonstrated by Harrop and Benedict (1923), Briggs and co-workers (1923), Kerr (1926), and Takeuchi (1923A,B.) and applies to man and animals whether normal or diabetic. Of these observers Harrop and Benedict (1923) alone concluded that potassium was concerned in the utilisation of sugar. This deduction was based on (1) the parallelism just mentioned; (2) That the excretion of potassium was reduced during the action of insulin in the one case studied; (3) That inorganic phosphate was required in the utilisation of sugar. They suggested that potassium was concerned in the formation of a phosphate carbohydrate compound in the muscles. It seems remarkable that this suggestion originating as early as 1923 has received so little attention. In any case, the parallelism between the removal of potassium and inorganic phosphate after insulin is striking. As it is accepted that inorganic phosphate is concerned in the resultant metabolism of sugar it would seem likely that potassium is also utilised for the same purpose.

3./
3. **The Effect of Adrenaline in Lowering the Plasma Inorganic Phosphate Content and of raising the Muscle Inorganic Phosphate Content.**

This effect and the association of potassium and inorganic phosphate after adrenaline will be described in the next chapter.
ADRENALINE, POTASSIUM AND CARBOHYDRATE METABOLISM.

The antagonistic effect of insulin and adrenaline in the blood sugar concentration is, of course, well known. There is, however, no such antagonism in their action on the utilisation of sugar in the muscles. Several observers (Kerr and Bisk 1932; Cori and Cori 1933) claim that insulin accelerates the peripheral sugar metabolism because it causes the secretion of adrenaline. The reverse process, namely the secretion of insulin by adrenaline, has also been claimed by various workers (Jensen 1933). It, therefore, appears that adrenaline and insulin have what may be described as a complementary effect on muscle sugar utilisation. If potassium is concerned in this process one would expect that adrenaline (like insulin and glucose) would lower the plasma potassium level. This is precisely what happens in humans. In animals, on the other hand, the literature is unanimous in that adrenaline has the opposite effect. I believe that this effect in animals /
animals can be explained so as to support the incorporation of potassium in the utilisation of sugar. This will, therefore, be discussed in some detail.

The Response of the Plasma Potassium Level in Man to the Administration of Adrenaline.

Keys (1937) injected 0.05 to 0.2 mg. of adrenaline intravenously into several healthy adults. He found that the plasma potassium level fell by 4 to 15% within the first few minutes and gradually rose to reach a value 5 to 15% above the initial level after about an hour. He later repeated these investigations (Keys 1938) and found that the plasma potassium level fell in two minutes by 11 to 12%. It rose to normal in twenty minutes and to 5% above the initial level 50 minutes after the injection. He found "the same general picture" after the intramuscular injection of adrenaline but gives no figures. Allott and McArdle (1938) injected 0.6 mg. of adrenaline subcutaneously into a normal individual and found a fall in the plasma potassium level of 3-4 mg. The maximum fall occurred in \( \frac{1}{2} \) hour and the initial level was regained in 1 to 2 hours. They /
They also injected a dose of 1 mg. of adrenaline every twenty minutes until 5 mg. had been given and found that the plasma potassium level fell to 10.5 mg. per cent. The first injection caused a more marked fall than the second, the other three injections caused no appreciable fall. They also found that the amount of potassium excreted was reduced during the action of adrenaline and that the plasma inorganic phosphate fell parallel to the plasma potassium level. Castleden (1938) injected 1 mg. of adrenaline intramuscularly into several normal individuals. Potassium began to leave the plasma in three minutes and fell from 13.2 mg.\% to 12.2 mg.\% in ten to twenty minutes. It then rose slowly but had not quite regained the initial level in seventy-five minutes. He confirmed that the amount of potassium excreted was reduced during the action of adrenaline. There was no constant corresponding change in the blood sugar concentration but often a rise in the blood sugar was found at the same time as the potassium fell. There are no other reports in the literature regarding the effect of adrenaline on the plasma potassium concentration in health. The investigations mentioned were in most cases performed /
performed because it had been shown previously by Aitken and associates (1937) that adrenaline lowered the plasma potassium level in familial periodic paralysis with a resultant attack. In no instance was the investigation performed with a view to associating potassium and carbohydrate metabolism.

It can be concluded from these observations that one of the effects of adrenaline, whether injected intravenously, intramuscularly or subcutaneously is to cause a very rapid removal of potassium from the plasma. The changes as regards the plasma potassium as well as the blood sugar level are well illustrated in the following table which constitutes one of my own investigations. Sufficient duplicate analyses were performed to justify this single report. (The blood sugar and the plasma potassium are expressed in mg. per 100 c.cm. of whole blood and plasma respectively).

(18).

W.B., aged 28. Asthma.

<table>
<thead>
<tr>
<th></th>
<th>Zero</th>
<th>16 min</th>
<th>30 min</th>
<th>44 min</th>
<th>60 min</th>
<th>132 min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma potassium</td>
<td>19.6</td>
<td>16.4</td>
<td>19.2</td>
<td>17.9</td>
<td>18.4</td>
<td>18.2</td>
</tr>
<tr>
<td>Blood sugar</td>
<td>84</td>
<td>102</td>
<td>122</td>
<td>124</td>
<td>113</td>
<td></td>
</tr>
</tbody>
</table>

0.6 mg. of adrenaline injected subcutaneously at zero.

It /
performed because it had been shown previously by Aitken and associates (1937) that adrenaline lowered the plasma potassium level in familial periodic paralysis with a resultant attack. In no instance was the investigation performed with a view to associating potassium and carbohydrate metabolism.

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(18).

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<table>
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<th>Time</th>
<th>Plasma Potassium</th>
<th>Blood Sugar</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zero</td>
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<td>102</td>
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<tr>
<td>30 min</td>
<td>19.2</td>
<td>122</td>
</tr>
<tr>
<td>44 min</td>
<td>17.3</td>
<td>124</td>
</tr>
<tr>
<td>60 min</td>
<td>19.2</td>
<td>113</td>
</tr>
<tr>
<td>132 min</td>
<td>18.8</td>
<td></td>
</tr>
</tbody>
</table>

0.6 mg. of adrenaline injected subcutaneously at zero.
It will be seen that the plasma potassium level was reduced by 3.2 mg. per cent sixteen minutes after the injection with a return to approximately the initial level in thirty minutes. These values are similar to those given by Allott and McArdle (above) whose report is the only one in the literature dealing with the effect on the plasma potassium level of adrenaline injected subcutaneously. There is one difference in that in my case the fall and the return to the initial level occurred more rapidly. This might be due to different rates of absorption of the adrenaline. On the other hand, it might be related to the fact that in my case the patient had a very high blood sugar tolerance. One would expect that adrenaline metabolises sugar more quickly in a person who is able to utilise sugar very rapidly. If potassium is concerned in this process it would leave the plasma more rapidly in such an individual.

It will be evident that the plasma potassium level drops much sooner after adrenaline than after insulin. This is compatible with the well known fact that adrenaline is a much more rapidly acting drug than insulin. I do not propose to discuss the exact part played by adrenaline on the metabolism of /
of sugar as the literature is very confusing. Jensen (1932) from a general survey, states that adrenaline causes a decrease in the muscle glycogen content. Cori and Cori (1929) showed that the mobilisation of muscle glycogen is a constant as well as an early effect of adrenaline. They later demonstrated (Cori and Cori 1931) that adrenaline caused a breakdown of muscle glycogen and the accumulation of hexosephosphoric acid and lactic acid in muscle. If it is true that insulin accelerates sugar metabolism in muscle by causing the secretion of adrenaline it is obvious that the injection of adrenaline will act more rapidly than the injection of insulin. The rapid fall of the plasma potassium level after adrenaline is, therefore, quite compatible with the incorporation of potassium in the utilisation of sugar. As regards the plasma inorganic phosphate level I mentioned above that Allott and McArdle (1932) found that the fall occurring after repeated injections of adrenaline was parallel to the fall of the plasma potassium. This is the only report in the literature of any concurrent investigation of the effect of adrenaline on these two plasma constituents. The /
The fact that adrenaline lowers the plasma inorganic phosphate level has, of course, been demonstrated repeatedly (Jensen 1932). This author also states that the effect of insulin of lowering the plasma inorganic phosphate level is probably a secondary effect and the result of an increased output of adrenaline caused by the hypoglycoemia. One would, therefore, expect that inorganic phosphate like the potassium would leave the plasma earlier after adrenaline injection than after insulin. Peters and van Slyke (1932), however, state the effect of adrenaline on the plasma inorganic phosphate concentration is similar to that of glucose and insulin. This is substantiated by the figures given by Cori and Cori (1933) from experiments on rabbits. I am unable to explain this discrepancy. It seems, in my opinion, that if potassium as well as inorganic phosphate is required in the utilisation of sugar the changes in the plasma potassium level after adrenaline are more typical than the changes in the inorganic phosphate.

It will be seen from Curve No. 18 that after the injection of adrenaline a secondary fall in the plasma potassium /
potassium level took place. This "after fall" occurred when the blood sugar was returning to its initial level. Cori and Cori (1929) showed that less sugar passes into the tissues during adrenaline hyperglycoemia than during hyperglycoemia produced by glucose. It would appear that the "after fall" was due to the removal of sugar into the tissues and that the observation of Cori and Cori explains the small drop observed. These remarks further support the intimacy of the changes in the plasma potassium concentration and the metabolism of sugar.

The Effect of Adrenaline on the Plasma Potassium Concentration in Animals.

The fact that the administration of adrenaline causes a rise of the plasma potassium concentration in animals has been shown repeatedly. Bachromejew (1932A.B.) injected adrenaline intravenously into cats and found that the plasma potassium content rose within two minutes to 20.5-50% above the resting level. The effect was transient and passed off more or less parallel to the return of the blood pressure to normal. Schwartz (1935) and Keys (1938) using rabbits /
rabbits obtained similar results. D'Silva (1934A) using cats injected adrenaline intravenously and found that the plasma potassium level rose in one minute to 12 mg per cent above the initial level and returned to the initial level in four minutes. This was followed by a fall of 4-5 mg per cent ten minutes after the injection with a slow recovery to the normal level occupying 15-30 minutes. He concluded that the "after fall" was due to the secretion of insulin occasioned by the high blood sugar caused by the adrenaline. He later showed (D'Silva 1936A) that adrenaline had no effect on the plasma calcium level and that the changes as regards potassium was not due to variations in the corpuscle potassium content. He further showed conclusively in an extensive series of investigations (D'Silva 1936A.B.C. 1937) that the liver was the source of the raised plasma potassium concentration and that the liver potassium content was independent of its glycogen store. Marenzi and Gerschman (1936) found that the intravenous injection of adrenaline raised the plasma potassium level of dogs. The increase occurred in thirty seconds and reached its maximum in 30 to 60 seconds.
seconds, with a rapid fall to normal in 2-3 minutes. There was then a further fall occurring 5-10 minutes later. They found no variation in the plasma calcium, sodium, magnesium or chloride. They confirmed the findings of D'Silva that the liver was the source of the potassium. As the effect of adrenaline was to lower plasma potassium concentration of the blood in the femoral veins as compared to that in the femoral artery they concluded that potassium was retained in the muscles. The loss of potassium from the liver and its retention in the muscles after adrenaline administration were confirmed by Houssay, Marenzi and Gerschman (1936 A.B.C.) and Houssay and Marenzi (1937 B). Flock et al (1938) again using dogs administered a continuous intravenous adrenaline solution and found a fall in the plasma potassium concentration as after glucose and insulin. They concluded that the fall was more important than the transient rise reported in the literature but give no further comment. It can be accepted from these observations that the injection of adrenaline into animals causes a transient rise of the plasma potassium due to the liberation of potassium from the liver. The rise is followed by a fall which appears to be due /
due to the passage of potassium from the blood into the tissues. It is, therefore, evident that the effect of adrenaline in animals is similar to its effect in humans in that in both cases potassium is removed from the plasma. The only difference appears to be that in animals additional potassium is liberated from the liver. The transient rise in animals in no way precludes the conception that potassium is required in the utilisation of sugar. The evidence presented, in my opinion, rather supports this theory.
SUMMARY AND CONCLUSIONS.

The fasting plasma potassium level in health has been established and its relationship to the fasting blood sugar level, and the plasma inorganic phosphate concentration has been discussed.

The fasting plasma potassium level in diabetes mellitus and its relationship to the fasting blood sugar level and the plasma inorganic phosphate concentration in this condition has been considered as far as is possible.

The effect of the ingestion of varying amounts of glucose on the plasma potassium level has been studied in detail in a series of seventeen investigations. It has been shown that after the administration of glucose or insulin potassium leaves the plasma pari passu with the removal of sugar from the blood for metabolism in the tissues. The fall of the plasma potassium level is not due to the excretion of potassium, to the passage of potassium into the corpuscles, or to haemodilution. Following the administration of glucose or insulin there is a fall in the plasma inorganic phosphate content. This change /
change is specific for the inorganic phosphate among the plasma anions, it being involved in the utilisation of sugar. The reduction in the concentration of the potassium of the plasma is similarly specific as regards the plasma Kations and is parallel to the fall in the inorganic phosphate level. It is, therefore, concluded that after the administration of glucose or insulin, potassium like sugar and inorganic phosphate passes from the plasma into the tissue cells. It is suggested that the potassium is involved in the resultant metabolism of sugar in the tissues.

The effect of the injection of adrenaline on the plasma potassium concentration has been discussed. Although investigations show that the effect of adrenaline on the potassium ion is different in animals and in man, in both cases the results obtained are in accordance with the theory that potassium plays a part in the metabolism of sugar.

The effects of severe exercise on the utilisation of carbohydrates and the metabolism of potassium have been considered. The absence of a fall in the plasma potassium concentration during such exercise is compatible with the theory propounded.
The estimation of the serum potassium content was performed according to the chloroplatinate titration method of Shohl and Bennett (1928) as modified by Peters and Van Slyke (1932). This is the routine method used in the Clinical Laboratory of the Royal Infirmary of Edinburgh and as it was described in detail by Greig (1938) in a previous thesis no repetition is necessary. This method does not give exact analytical values, the experimental error according to the originators giving a range of ±4%. My own duplicate analysis, as will be seen from the curves, gives results generally agreeing well within this limit, although they are not as good as those of Keys (1937) whose estimations agreed within ±1%.

As the red corpuscles contain a large concentration of potassium it is essential to avoid any trace of haemolysis. This can be prevented by:

1. Using a dry syringe, sterilised in water.
2. /
2. The use of methylated ether for sterilising the skin and performing the venepuncture when the skin is perfectly dry.

3. The rapid transference of the blood from the syringe into the test tube so as to prevent the blood clotting in the syringe.

4. Preventing the formation of air bubbles on the surface of the blood in the test tube. Such bubbles cause faint haemolysis during the subsequent centrifugalisation.
Mr. P.N.M. AET. 26.

Peptic Ulcer.

11-11-38.
Mr. W.D. Aet. 53.

Progressive Muscular Atrophy.

15.11.38

After 50g. of glucose orally.
Mr. W. B. Aet. 27.

Paralysis Agitans.
(Post Encephalitic).

21.11.38.

(Time in Hours
After 50 G. of Glucose Orally.)
MR. J.C. AET. 29.

PROGRESSIVE MUSCULAR ATROPHY.

24. 11. 38.

Curve 4.

POTASSIUM IN MG. PER 100CC.

SUGAR IN MG. PER 100CC.

TIME IN HOURS

AFTER 50G. OF GLUCOSE ORALLY.
Mr. H.K. Aet. 60

Progressive Muscular Atrophy.

13.12.38.

POTASSIUM IN MG. PER 100 C.C.M.

TIME IN HOURS

AFTER 50G. OF GLUCOSE ORALLY.
Mr. T.S. Aet. 18

Diabetes Mellitus.

19.12.38

Time in hours after 50 g. of glucose orally.

Sugar

Potassium in mg. per 100 cc. cttv.

SUGAR.

POTASSIUM.

560

540

520

500

480

460

440

420

400

380

360

340

320

300

280

260

240

220

200

180

160

140

120

100

22
MR. T.L. AET. 48

DISSEMINATED SCLEROSIS

20-2-39.

POTASSIUM IN MG. PER 100CCMT.

SUGAR IN MG. PER 100CCMT.

TIME IN HOURS

AFTER 100 G. OF GLUCOSE ORALLY.
Mr. D.A. Aet. 34.

Disseminated Sclerosis.

10·1·39

POTASSIUM IN MG. PER 100 C.C.M.

SUGAR IN MG. PER 100 C.C.M.

TIME IN HOURS

AFTER 118 G. OF GLUCOSE ORALLY.
Mr. H. Mei, Aet. 18.

Epilepsy

16.12.38.

POTASSIUM IN MG. PER 100 CC.

SUGAR IN MG. PER 100 CC.

AFTER 150G. OF GLUCOSE ORALLY.

TIME IN HOURS

1.0 1.2 2 4 5 6
Mr. WB. Aet. 28.

Asthma.

24.1.39.

Curve 10.

POTASSIUM IN MG. PER 100 C.C.M.

SUGAR IN MG. PER 100 C.C.M.

TIME IN HOURS

AFTER 150 G. OF GLUCOSE ORALLY.
Mr. J. W. Aet. 39.

HUNTINGTON'S CHOREA.

10-2-39.

AFTER 150 G. OF GLUCOSE ORALLY.
MRS. R. AET. 29

MYASTHENIA GRAVIS.

3.11.38.

POTASSIUM IN MG. PER 100 C.C.M.

SUGAR IN MG. PER 100 C.C.M.

TIME IN HOURS

AFTER 50G. OF GLUCOSE ORALLY.
MRS. R. AET. 29.

MYASTHENIA GRAVIS.

8.11.38.

POTASSIUM IN MG. PER 100 C.CML.

SUGAR IN MG. PER 100 C.CML.

CHART 13.

TIME IN HOURS

AFTER 50 G. OF GLUCOSE ORALLY.
MR. A.B. AET. 43.

MYASTHENIA GRAVIS

22.11.38.

POTASSIUM IN MG. PER 100 C.F.V.

SUGAR IN MG. PER 100 C.F.V.

TIME IN HOURS

AFTER 50 G. OF GLUCOSE ORALLY.
Mr. A.B. Aet. 43.

Myasthenia Gravis.

28.11.38
Mr. A.B. Aet. 43.

Myasthenia Gravis.

1.12.38.

POTASSIUM IN MG. PER 100CCM.

SUGAR IN MG. PER 100CCM.

TIME IN HOURS AFTER 50G. OF GLUCOSE ORALLY,
2.5 MG. OF PROSTIGMIN SUBCUTANEOUSLY.
Mr. A. B. Aet. 43.

Myasthenia Gravis.

13.1.39.

Dynamometer Readings
Potassium in mg. per 100 c.c.m.

Sugar

Time in hours
After 105 g. of glucose orally.
Mr. W. B. Aet. 28.

Asthma.

20.1.39.

TIME IN HOURS
AFTER 0.1 cc. OF ADRENALINE SUBCUTANEOUSLY.
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