THE ÆTIOLOGY AND TREATMENT OF DIABETES MELLITUS.

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SINCE there is at present no unanimity of opinion as to the ætiology of diabetes mellitus—the disease characterised by the appearance of dextrose in the urine over weeks, months, or years, accompanied by increase in the amount of urine, increased thirst, abnormal appetite, and, as a rule, by wasting and exhaustion—I propose first to discuss the ætiology of the disease and then the treatment employed which follows logically from the ætiological conclusions arrived at.

Glycosuria is an essential feature of the disease, but there can be no doubt that, besides carbohydrate, protein and fat metabolism are also frequently deranged, and in the worst cases derangement of the metabolism of all three classes of metabolites is present.

The sugar found in the blood and tissue juices is dextrose, in which form it is absorbed from the intestine. It occurs in any quantity up to 0.2 per cent. If it rises above this it is excreted by the kidneys, and glycosuria results. When during digestion a large amount of dextrose is being absorbed from the intestines the amount in the arterial blood does not normally rise above .2 per cent., because the liver and tissue cells (*e.g.*, the muscle cells) take up the surplus and store it in the form of

glycogen, which is reconverted into dextrose to keep up the normal percentage of dextrose in the blood during fasting. Cohnheim and others have demonstrated experimentally that the oxidation of the dextrose molecule by the tissue cells depends on the interaction of two substances forming a compound ferment, one part produced by the tissue cells is heat-labile being of the nature of complement, the other part is heat-stable is of the nature of immune-body, and is produced by the pancreas. The absence of either element of the compound ferment would prevent the oxidation of the dextrose, and so lead to the excretion of the unmetabolised sugar.

Fat is also metabolised in a similar way by the tissue cells by the interaction of the heat-labile and heat-stable elements of a compound ferment, the complement-like part being produced by the tissue cells, the immune-body-like part by the pancreas. These facts have been recently demonstrated by Shaw-Mackenzie and Rosenheim, who call the heat-stable part "co-ferment."

Practically nothing definite is known as to the form in which protein food substances are passed into the blood from the alimentary canal. We know that the intestinal cells take them up as amino-acids, but whether they build them up into large protein molecules such as serum-globulin and serum-albumin, and secrete these into the blood, and the tissue cells break these large molecules down again into amino-acids, before using them as food, or whether the amino-acids are passed into the blood stream as such and the tissue cells absorb them direct, is not known. We do know from the facts of hæmolysis and bacteriolysis that the tissues can break down a large protein molecule. As is well known, hæmolysis and bacteriolysis are brought about by the interaction of two substances, one heat-labile, complement, the other heat-

stable, immune-body or co-ferment; so that the breakdown of the large protein molecules of which the stroma of red corpuscles and the body of microbes is composed is similar to the process by which the molecule of fat and carbohydrate is broken down, and the pancreas alone has been shown to produce the immune body or co-ferment part of these compound ferments. It seems to me, therefore, quite likely that the pancreas produces the immune body for protein metabolism, and is at any rate the chief source of these essential factors in anti-bacterial immunity.

Certain clinical observations point in this direction. (1) It is well known that diabetics have a much lowered resistance to microbial invasion, which may be due to the patient's pancreas having a reduced capacity for turning out immune bodies.

And (2) in a diabetic the "negative phase" after an injection of vaccine is almost invariably accompanied by an increase of the amount of urine and sugar excreted. I think it is quite possible to explain this by supposing that the cells that produce the carbohydrate co-ferment also produce the protein co-ferment, and that the lowering of their vitality by the injection of a foreign protein which they are not able to digest, and which, therefore, interferes with their metabolism, causes a reduction of the output of carbohydrate co-ferment, which, of course, leads to a reduction of the amount of dextrose metabolised, and, therefore, to increased glycosuria.

The pancreas is stimulated to secrete both its intestinal and tissue ferments by means of a hormone, "secretin," formed in the mucous membrane of the upper part of the intestine from a precursor prosecretin under the influence of the acid gastric content when it passes into the intestine from the stomach.

From the above considerations of tissue metabolism it

is easy to understand the profound derangement of it that must take place when the co-ferments are suddenly and completely withdrawn, as they are when the pancreas is entirely removed under experimental conditions in dogs. The animal soon develops a complete picture of an acute severe case of diabetes mellitus; sugar appears in the urine within twenty-four hours, the animal becomes abnormally hungry and thirsty; there is increase in the amount of urine; later β -oxybutyric acid, &c., appears in the urine, and there is a large increase in the ammonium-urea ratio.

Glycosuria has also been produced experimentally by puncturing the floor of the fourth ventricle between the nuclei of the eighth and tenth nerves. This glycosuria lasts only as long as there is glycogen in the liver, and does not occur if the vagi have been previously cut.

Phloridzin and phloretin cause glycosuria. They act on the kidney cells, most probably stimulating their dextrose excreting powers. Another view is that they dissociate the dextrose from a normal combination with a protein, and that then the kidneys excrete the uncombined sugar. At any rate they produce a hypoglycæmia, and the glycogen from the liver, muscles, &c., is converted into dextrose to keep up the normal percentage in the blood. When the glycogen is exhausted sugar continues to be excreted, being formed from the proteins of the body as it frequently is in diabetes.

Another drug that produces glycosuria is adrenin, both when injected into circulation and when painted over the pancreas. It thus seems to act directly on the co-ferment forming cells of the pancreas. It is important to note that oral administration is less likely to produce glycosuria.

Glycosuria sometimes appears after ether narcosis, and it is interesting to note that ether precipitates the carbo-

hydrate co-ferment from its solutions. Many other drugs produce glycosuria, but I need not mention them here.

Lastly, dextrose may appear in the urine as a result of too large an ingestion of carbohydrate; the amount that can be given to a healthy animal without the appearance of glycosuria varies somewhat with the individual, and no doubt varies in the individual at different times.

This so-called alimentary glycosuria is probably due to the liver being able to store only a certain quantity of glycogen at a certain rate, a sudden flooding of it with an excess of dextrose leads to a greater amount than normal passing into the circulation, and so to glycosuria.

Turning now to the clinical aspect, it thus appears that glucose may appear in the patient's urine as a consequence of—

(1) An overdose of carbohydrate. The upper limit of the amount that can be given without sugar appearing lies between 150 and 200 grammes. If a dose under 150 grammes produces glycosuria something is wrong. It is subnormal in certain diseases of the liver, such as cirrhosis.

(2) A condition corresponding to puncture-diabetes has been associated with brain lesions, such as tumours and hydatid disease in the neighbourhood of the medulla.

The transitory glycosuria in individuals who are suffering from neurasthenia from overwork may be due to a nervous cause.

(3) That glycosuria may be caused by adrenin is of interest, because Rogers suggests that the diabetes, which sometimes occurs as a terminal event in exophthalmic goitre, when the thyroid becomes sclerotic and the patient myxœdematous, may be due to the unbalanced action of the adrenals. It is interesting in this connec-

tion to note that manipulation of the adrenals has produced glycosuria.

It is possible that in the later stages of diabetes the kidneys, owing to fatty degeneration, &c., may have a reduced power of keeping back sugar just as they have in phloridzin glycosuria.

(4) Failure of the tissue cells to produce the heat-labile part of the co-ferment. There is no experimental evidence that this occurs, but there is some evidence that it does not, for Baumgarten has shown that certain partly oxidised carbohydrates can be completely oxidised in the tissues of pancreatectomised dogs. Such a carbohydrate is d. glycuronic acid, which represents the first stage in the oxidation of dextrose. The difficulty that the tissues of diabetics seem to have, therefore, is the breaking of the long hexose chain. Another point against the glycosuria in pancreatectomised dogs being due to absence of complement is that it is only the source of co-ferment that has been removed, and that, therefore, in experimental diabetes the complement is intact, at any rate in the early stages of the condition. Very possibly in the later stages, owing to malnutrition of the cells, the complement may be diminished. It ought not to be difficult to devise experiments to determine this point.

(5) Lastly, the glycosuria may be due to functional or organic disease of the pancreas with its consequent diminution or absence of the co-ferment.

Taking the organic diseases first—

Pancreatic lesions have been frequently found in diabetes. They are various, such as interstitial fibrosis—that is, the fibrosis is intralobular and interacinar; various degenerations of the islands of Langerhans, such as round-celled infiltration, sclerosis, hyaline degeneration, &c. I do not propose to go into the vexed question as to

what relation the islands of Langerhans bear to the rest of the secreting epithelium, or whether they alone furnish the co-ferment. I will mention only the following facts :—

In 90 cases of diabetes Cecil, of the Presbyterian Hospital, New York, found sclerosis or degeneration of the “islands,” plus interstitial fibrosis, in 67. In these arterial sclerosis was common. The parenchyma normal, and lesions of the “islands” alone in 12, while the pancreas was normal in 11. Of these 11, five had marked diminution in number of the islands, while in two others the pancreas was abnormally small.

Others have found interstitial fibrosis in 50 per cent. of cases.

Cecil found also that in some diabetic pancreases, while the islands were for the most part degenerate, some had undergone enormous adenomatous hypertrophy. He suggests that this was compensatory.

Now, what is the origin of the interstitial inflammation that occurs in the pancreas? It is probably two-fold; firstly, it may spread up from the ducts, and secondly, it may begin in the connective tissue of the gland. In the first class the inflammation may be due to obstruction by a gall-stone or by calculi in the duct of Wirsung, or to infection with micro-organisms from the intestine or bile ducts. The diabetes in these cases is a terminal event in chronic pancreatitis.

When the inflammation is intralobular it is very probably due to infection through the blood stream.

When the islands alone are diseased it may be due to a microbial infection by way of the blood-stream; to toxæmia, just as the kidneys undergo amyloid degeneration in chronic suppuration (the removal of a gangrenous limb has been known to diminish the amount of sugar

excreted), or the islands may undergo disuse-atrophy owing to the absence of sufficient stimulus.

This brings me to the consideration of those cases in which no lesion of the pancreas has been found.

In Cecil's series they are in the minority, in others they are in the majority, while in others again the numbers are about equal. I do not think it is difficult to account for these cases, for in an absence or diminution of secretin the pancreas would be without its normal stimulant, co-ferment would not be produced, and glycosuria would result. It may be asked is the secretion of co-ferment dependent, like the external ferments of the pancreas, on a hormone from the intestine; the successful treatment of some cases of diabetes with secretin would strongly tend to prove that it is, for in no other way than the stimulation causing the pancreatic cells to produce a larger amount of co-ferment could this substance produce improvement.

Further, in some cases of diabetes dead from coma, prosecretin was found absent, while in other cases dead from other causes it was present. Long-continued absence of secretin may account for the small size of the pancreas, which is otherwise normal—in some cases of diabetes the small size being due to atrophy of the cells of the parenchyma and a diminution of the cell-islets in size and number owing to disuse.

Hypoplasia of the pancreas has also been said to be congenital in some cases, and may be a reason why children of diabetics sometimes develop the disease.

I am not aware that any observations have been made on the intestinal mucous membrane in diabetes; I know enteritis was present in one case that I examined in which there was no marked lesion of the pancreas except that it was smaller, darker, and firmer than normal, and

there was some interlobular fibrosis. This patient had fatty stools with no obstruction of the duct of Wirsung *post-mortem*. Stomatitis and gastritis are common in the disease, and so enteritis may be also, but, of course, the inflammation may be secondary not primary.

It has long been suspected by some that many cases of the disease were due to infection by micro-organisms, the occurrence of the disease in husband and wife, or in several members of the same family, lending support to this view. It seems to be more common in some places than others; for instance, it was quite common in Sutton Bridge, where I practised, while my medical neighbours saw comparatively few cases. The drinking water in Sutton Bridge was particularly liable to sewage contamination.

Wright mentions a case of diabetes whose symptoms varied with the opsonic index to a coliform organism isolated from the patient's stools. As already mentioned, I always find that the negative phase after an inoculation is reflected in the urine. McWaters has observed great improvement in several cases suffering from furunculosis which he treated with vaccines made with staphylococci isolated from the boils.

Three of my cases were peculiarly liable to sore throat, and always had increased excretion of urine and sugar during the attacks.

I always look for a source of infection, and find one of the commonest is severe pyorrhœa alveolaris. This disease offers easy opportunities for blood infection, and the constant swallowing of virulent organisms is undoubtedly a common cause of gastritis and enteritis.

I think some of these facts are very suggestive that the enteritis and pancreatitis are due to micro-organisms—in some cases at any rate.

There is one other possible cause of the non-production of secretin, and that is that there may not be sufficient acid in the gastric content when it passes into the duodenum to convert the prosecretin into secretin.

Diagnosis of the exact cause of glycosuria in a given case must always present difficulties.

If it is due to an overdose of carbohydrates it will be only transitory, and the diagnosis can be confirmed by giving the patient 150 grammes of dextrose. If no sugar appears in his urine his glycolytic apparatus is probably normal.

The form which is hypothetically due to a temporary diminution of the glycogenic functions of the liver would also be only temporary, and would disappear with a reduction in the amount of carbohydrate ingested. I do not see, however, how it is possible at present to distinguish such a form from one due to a diminution in the co-ferment production by the pancreas, the condition of the patient corresponding to that of a partially pancreatectomised dog. I think there is some statistical evidence that some of these cases develop typical diabetes later on. These cases ought to have their urine tested at fixed intervals.

Cases of glycosuria associated with brain lesions ought to present little difficulty owing to collateral symptoms.

While the small number which may be due to neurasthenia present a picture like the glycogenic ones—viz., a temporary diminution of carbohydrates producing a restoration of glycolytic functions.

There remain the patients in whom a strict non-carbohydrate diet produces a freedom from glycosuria, but in which any attempt to give them sugar again produces the glycosuria, and those who excrete sugar on the strictest diet.

These cases I believe are always due to functional or

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organic disease of the pancreas, or perhaps to both—that is, there is diminution of the production of secretin and a lesion of the pancreas as well.

A symptom that is sometimes present, and which suggests a lesion of the pancreas, is pain and tenderness on pressure over the region of the gland.

Fatty stools suggest obstruction of the duct of Wirsung, and so are of localising significance.

Cambridge's reaction may also help in the diagnosis.

The improvement of the patient under secretin may suggest that the lesion is chiefly intestinal.

While if the lesion is solely pancreatic the patient does not improve under secretin, but does under the co-ferment extract.

Diagnosis will be difficult until we can test accurately the amount of co-ferments circulating in the blood.

Treatment.—I need not refer further to the treatment of those cases of glycosuria which clear up with a temporary restriction of carbohydrates, or of those connected with a gross nervous lesion. While the treatment of those cases occurring as a terminal event in exophthalmic goitre would be the same as that of a typical case of diabetes plus the exhibition of thyroid-globulin.

The above-mentioned considerations of ætiology give two lines of treatment which are complementary to each other—the first specific, the second symptomatic.

By specific I mean the removal of the cause of the inflammation, which may be present in the intestine or pancreas.

In every case an exhaustive examination for a source of infection should be made. As before mentioned, pyorrhœa is very commonly present, and should be cleared up with a vaccine. If furunculosis is present it should be cleared up in a similar way, also carbuncle. I have seen

most marked improvement in a case with severe pruritus vulvæ after inoculations with a staphylococcus vaccine, the organism being isolated from the lesion. So, too, any chronic tonsillitis or nasopharyngeal catarrh should be cleared up. I believe the swallowing of mucopurulent matter from the nasopharynx is a common cause for chronic gastro-enteritis. Lastly, if no other source of infection can be found, a bacteriological examination of the fæces ought to be made, and the patient's opsonic index tested against the organisms isolated, and if this indicates the infectivity of any of them a vaccine should be prepared.

Several observers have obtained good results with this line of treatment, and I have also obtained improvement in several cases. At any rate, nothing but good can result to the patient from ridding him of micro-organisms which are infecting him, although they may not be the source of the specific disease from which he is suffering. I have found it very difficult to clear up pyorrhœa in a case with well-marked acidosis, owing probably to the fact that antibodies do not act well in an acid medium.

There is another class of diabetics which also require removal of the cause, and they are those with fatty stools. The majority of these cases have, I think, obstruction of the pancreatic duct either by a gall-stone in the ampulla of, or pancreatic calculi in, the duct itself. Cammidge and Robson have published cases in which the former had made the diagnosis of obstruction by means of his reaction and a careful examination of the stools, and in which the glycosuria disappeared after suitable operative interference. I believe there are certain cases with fatty stools which have no obstruction of the duct, the fatty stools being due to complete absence of secretin or to its diminution to such an extent that very little of the pan-

creatic external ferments are formed. I think such cases are exceptional, however.

Turning now to the other line of treatment. It is an attempt to replace the absent or supplement the diminished co-ferments.

I begin by giving the patient secretin.

Clinical evidence and experimental evidence seem to be at variance as to the efficacy of giving this substance by the mouth. Starling positively declares that this substance is not absorbed when given in this way. A few cases of complete disappearance of sugar and of complete recovery from diabetes have been recorded which could be accounted for in no other way than that they were due to the exhibition of secretin. I myself have had no case of this kind, but I have undoubtedly seen improvement occur, and many observers have had cases in which they have seen improvement with secretin.

If the patient does not improve markedly with the secretin I give a pancreatic extract.

The first extract I used was an extract containing all the pancreatic products. With this I obtained a very marked improvement. The patient was a child of twelve, in a very bad condition when I saw her first—emaciated and cyanosed, and passing at least fifteen pints of urine in the twenty-four hours, containing about 10 per cent. of sugar. At the end of a year she was passing two and a half to three pints of urine, containing 3.5 per cent. of sugar. After treatment commenced she soon lost her thirst and abnormal hunger, and began to feel well, and played about like an ordinary child. She had several relapses during the year with some return of symptoms, and these were always preceded by a sore throat, and accompanied by pain and tenderness over the pancreatic region. After the year, treatment was stopped

owing to expense, and much against my will. She remained in the condition stated with no symptoms of the disease except the sugar in her urine. She then suddenly relapsed, and died without treatment, in spite of my emphasising to her parents the probability of relapse. From start to finish no alteration was made in her diet.

Being convinced that such marked improvement in such a severe case in a child must be due to the treatment adopted, I was anxious to find out what substance in the whole extract produced the improvement. I, therefore, had a pancreatic extract made, from which all the coagulable proteins and external ferments were removed, and this extract is the one I now use.

It is made up as follows :—The proteins are precipitated from the press-juice of pigs' pancreas by keeping it at 80° C. for three hours. The coagulated proteins are filtered off, and the filtrate is mixed with 20 per cent. of glycerine. The extract, which is made by Messrs. Fairchild Brothers and Foster, to whom I am much indebted, is to be obtained commercially under the name of "hormonadin."

The dose for an adult is 3i, and the number of doses in the twenty-four hours must be worked out for each case, for I find that there is an optimum dose just as Cohnheim found that there was an optimum amount of pancreatic extract in his experiments—too much of this producing diminished glycolysis as well as too little.

Now, as to the results obtained. I have not yet had a sufficient number of cases to enable me to dogmatise, but I have seen a sufficient number, which were going to the bad on the ordinary lines of treatment, improve and resume their ordinary mode of life, and this on an ordinary full diet, to encourage me in the idea that I am working on the right lines.

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The patients soon begin to lose their abnormal thirst and hunger, and the wretched feeling of weakness and illness. In some cases the amount of sugar and of urine decrease rapidly, but I have never succeeded yet in entirely getting rid of the sugar, although the patient has declared himself feeling well and strong and able for his full quantum of arduous work. I do not know if the extract would cause the sugar to disappear in a mild case, because, so far, I have not had such a case to treat.

I believe in one case, not treated by myself, diacetic acid has disappeared under the treatment.

The cases that have done least well in my hands have been cases with a large amount of acidosis, which could not be materially reduced by alkaline citrates and carbonates given in large doses. The extract seems to improve these cases to a certain extent; at any rate they seem to maintain their weight and not be so liable to coma. In fact I have had one case recover from coma by giving the extract intramuscularly, and giving large quantities of water and citrates by the mouth, and another case which, owing to inadvertence, had not been having the extract and began to develop the symptoms of the onset of coma, rapidly lost them under similar treatment.

I believe the treatment can be improved, for the giving of a dose of co-ferment three or four times a day is a poor substitute for the continuous secretion of the normal ferment. I, therefore, think the oftener a small quantity of the co-ferment is given the better the results ought to be. The makers, at my request, are, therefore, trying to obtain the substance in a dry form, so that the patient can carry it about in his pocket in the form of a tablet or pill, and take one every half hour or so.

I find that many patients do best if they take both secretin and co-ferment, and so I am having a tablet con-

taining both made. In cases with fatty stools the whole extract should be used.

In conclusion, I do not think it possible in the majority of cases to cure diabetes, because when the patient comes under treatment the cells producing the essential substances are so far damaged that they cannot be restored, but I do think it possible to prevent, at any rate in many cases, the disease getting worse, and by means of giving the affected substance to enable the patient to live an ordinary life on an ordinary diet.

It seems the cases which can recover completely are those acute cases in young people whose glycolytic mechanism can be restored if tided over the acute phase, just as acute nephritis can be completely recovered from.

DR. MOORHEAD said the treatment of diabetes mentioned by Dr. Crofton was built up by hypothesis based upon hypothesis. He asked what proof existed that Dr. Crofton's extract contained a co-ferment in this fluid. The only proof that he could find that this fluid contained any active principle was the statement published in a paper by Dr. Crofton last year, that this fluid enables the body to burn up its carbohydrates better, but that was an obvious *petitio principii* which no scientific man can accept. As regards secretin, he mentioned Dr. Starling's statement that this substance cannot be absorbed from the intestine, and he (the speaker) said that his experience was that this drug was valueless in pancreatic diabetes. Dr. Crofton had stated that he had seen cases of improvement follow which could not be attributed to anything else, but you will find variations in the amount of sugar and the absence of diacetic acid in diabetics without any treatment at all. He had given the drug a fair trial, and did not believe it to be of any use. As regards the combined action of pancreatic extract and muscle on carbohydrates, Cohnheim's experiments were still the subject of controversy. If they were not confirmed a great deal of Dr.

Crofton's paper falls to the ground. Cohnheim's theory is first assumed to be true, and secondly it is assumed that quite likely the pancreas produces an immune body which takes part in metabolism. Another assumption is that there is a liability to bacterial infection—a liability which he quite admits—but when he comes to the explanation that it is due to the absence of an immune body he finds merely unproved assumption based upon unproved assumption. As regards lesions in the pancreas it depended on whether one was looking for them or not. One person says that the islands of Langerhans are positively destroyed, while another says that the islands have nothing to do with diabetes. Dr. Crofton laid special stress on the fact that his patients improved on the extracts, and that with giving a full diet. He (the speaker) could not see where was the improvement considering the so-called improved patients passed more water with a greater percentage of sugar. A mere statement by a patient that he felt better was worthless, and until Dr. Crofton could adduce definite proof of improvement in his cases he (the speaker) thought that the less said about his method of treatment the better.

PROFESSOR COLLINGWOOD said as regards Cohnheim's experiments it is possible that they were due to bacterial invasion. There is a further action of secretin which has been neglected. If pancreatic ferments are mixed with secretin these ferments are activated by the fact that secretin has come in contact with them.

DR. KIRKPATRICK said he had tried secretin in several cases, and he could not say there was any satisfactory result. He mentioned the case of one patient who continued to lose weight under secretin, but increased in weight by 5 lbs. with Dr. Crofton's extract, and no longer complained of thirst or hunger. His experience of the drug in other cases justified his continuing its use.

SIR JOHN MOORE referred to the uses of codein and liquid extract of cascara sagrada. The former he regarded as more useful than any ferment in the treatment of diabetes mellitus.

DR. CROFTON said his extract differed in no way from Cohnheim's. He made his extract from pure pancreas. He did not see how this could affect the co-ferment. He referred

to the improvement which his patients have had when taking this extract, and he laid emphasis on the fact that he did not pretend to cure, but to render his patients' lives more comfortable. As regards Cohnheim's theory that the malady was due to micro-organisms, this could be put out of court at once, for it was proved that microbic action was entirely absent. As to the metabolism of fat, it is no hypothesis, but an established fact. It is certain that if you inject into the body foreign protein you will get these co-ferments. There was no great anatomical change in the pancreas. In some there was an interlobular fibrosis, atrophy of its secreting epithelium, and the cell islands seemed to be diminished. It looks like a pancreas which was undergoing atrophy. As regards mental influences he did not think the improvement could be put down to that, as the patients were very sceptical about the drugs they were getting. As regards the treatment by codein, he thought it very useful. It may act by blocking the messages sent to the brain asking for more sugar, or, by combining with dextrose, it in some way renders it easier for oxidation than it was before.