The patient's progress since then has been uninterruptedly satisfactory. A glucose loading dose showed normal absorption with the highest blood-level after one hour. A lactose-tolerance test, on the contrary, produced only a negligible rise in blood-sugar, while the response to a glucose-galactose mixture was normal. The result of a second lactose absorption test was identical with that of the first.

At no time, not even after a lactose loading dose, was a reducing substance found in the urine; nor was lactose found in the fæces. Random blood-sugar estimations throughout the day showed persistently low levels, around 50 mg. per 100 ml., even when lactose (10 g.) was added to the milk feeds. Lactose absorption tests on the two older siblings evoked a normal response with a rise of 50–60 mg. above the fasting blood-sugar values.

Conclusion

The first of these two cases was one of severe lactose intolerance which was nearly fatal, and would have undoubtedly been so had lactose-containing foods not been rigorously excluded from the diet, which had to be as strict as that enforced in galactosæmia. The pathogenic effect of the milk-sugar was not unlike that attributed to gluten in cœliac disease, but the pathogenic mechanism is unknown.

The second infant was unable to absorb lactose, and, as a result of the caloric deficit, malnutrition developed. The milk-sugar itself did not seem to exert any toxic effect and did not interfere with the absorption of other nutrient components of the diet. The loose frothy stools were most probably due to bacterial fermentation of the unabsorbed disaccharide in the gut. No lactosuria occurred. Replacement of the added lactose by cane-sugar terminated the diarrhœa; and a satisfactory gain in weight ensued on a standard formula of National dried milk.

Summary

In a case of severe lactose intolerance in infancy the clinical manifestations were diarrhœa, vomiting, lactosuria, glucosuria, and intestinal malabsorption. Symptoms were dispelled by completely eliminating lactose from the diet.

This disorder differs from alactasia (of which a case is described) in which malnutrition due to lack of absorption of lactose can be remedied by administration of sucrose.

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". . . the greatest advances of medicine during the last century have been in the realm of infectious disease. These successes were based upon the fundamental discoveries which were made by Pasteur, Koch and others of the relation of microorganisms to disease processes. Many chronic diseases, of which arterial disease is one, have not as yet been shown to have any comparable unifying thread to connect them. They are at the stage of examination by the collection of data from whatever source they can be gleaned. If in the future a clear picture of what happens during the development of arterial disease is obtained, I hope that the person who records the last observations will not be credited with making a ' breakthrough '. We hear too much of ' breakthroughs ' in these days, for in my opinion such language tends to obscure the fact that all of us depend on the work of our predecessors. This to my mind is nowhere more clearly demonstrable than in the steps that lead to the elucidation of the complicated changes of pathological processes."—Sir HOWARD FLOREY in his presidential address to the Royal Society on Nov. 30, 1962.

MANGANESE-INDUCED HYPOGLYCÆMIA

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THE use of substances unrelated to insulin which nevertheless lower the blood-sugar has been reported from time to time. But, with the striking exception of the oral hypoglycæmic drugs, these substances have had only limited success in controlled trials, and they have not been used in the treatment of diabetes mellitus because of their toxicity or unreliability.

Recently we treated a young diabetic who responded to infusions of alfalfa (lucerne, *Medicago sativa*) with precipitous falls in blood-sugar (Rubenstein et al. 1962).

Case-report

The patient, aged 18, was admitted to hospital in March, 1961, in hypoglycæmic coma. He had been a diabetic for seven years, and there was no family history of diabetes. His course had been punctuated by numerous admissions to hospital in hyperglycæmic and hypoglycæmic coma.

The striking feature was his large size and tremendous muscular development (height 6 ft. 2 in.; weight 214 lb.) which were taken to be the result of his voracious appetite. There were no obvious complications of diabetes. The thyroid gland, adrenal medulla and cortex, and pituitary gland were functionally normal. The hæmoglobin, white cell-count, erythrocyte-sedimentation rate, and the levels of urea, electrolytes, uric acid, calcium, and phosphorus in the blood were normal. Liver-function tests showed no abnormality. Radiographs of the skull, abdomen, and chest were normal, and a barium-meal examination did not reveal peptic ulceration. An augmented histamine test showed free acid in normal amounts.

He was treated with soluble insulin and long-acting insulin intramuscularly in large doses (100–200 units daily), but he responded poorly. Even when there was glycosuria of more than 2% acetone was rarely present on six-hourly urine testing. Random blood-glucose measurements done during this time fluctuated wildly between normal and grossly hyperglycæmic levels, but ketonæmia and acidosis were not observed. The glucose-oxidase test (Salomon and Johnson 1959) confirmed that the blood-sugar was, in fact, glucose.

During this period of poor control the patient often mentioned that over the past year he had been taking an extract of lucerne (an old folk-medicine used occasionally by some diabetics in South Africa) and that this had controlled his diabetes adequately. With an interest born of despair, we allowed him to prepare in the ward an extract by boiling the green leaves of alfalfa in water, and to drink the infusion. By this time his blood-sugar level had reached 648 mg. per 100 ml. *Two hours later, he had clinical signs of hypoglycæmia and his blood-sugar was* 68 *mg. per* 100 *ml.* The test was repeated thereafter on twelve occasions, the alfalfa extract being administered when his blood-sugar varied between 190 mg. and 580 mg. per 100 ml. The infusion was also given at different intervals after food and at varying times of the day. On each occasion there was the same predictable hypoglycæmic response (fig. 1).

Response to Manganese

The nature of the active principle in the alfalfa leaves was puzzling, for its constituents did not contain any known hypo-

glycæmic agent or unusual substance that might be suspected of having such an action. It was noticed, however, that it did contain 45·5 mg. per kg. of manganese, which is a significant quantity (Spector 1956). Accordingly, manganese chloride in small amounts (5–10 mg.) in aqueous solution was administered orally, and the effect resembled the fall in blood-glucose after taking alfalfa (fig. 2). This unexpected finding was then confirmed fourteen times, each test showing that the blood-sugar, irrespective of its original height, fell to lower levels. The maximum effect occurred at two to four hours, and on three occasions unconsciousness was produced with recorded blood-glucose levels of between 10 and 20 mg. per 100 ml.

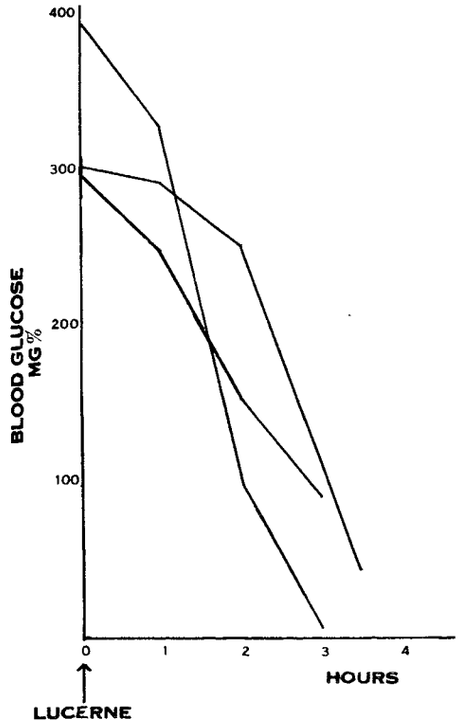

Fig. 1—Blood-sugar levels (mg. per 100 ml.) after administration of lucerne extract. Three representative curves.

The correcting influence of alfalfa and manganese chloride (8 mg.) upon the diabetic glucose-tolerance curve is shown in fig. 3. Subsequently, 20 μg. of manganese chloride was given intravenously over one hour, and this caused a drop in the blood-sugar from 726 to 216 mg. per 100 ml.

In order to ascertain whether the patient's response to manganese was specific, zinc, magnesium, cobalt, iron, and sodium salts were given by mouth but these had no significant effect on his blood-sugar; L-leucine had no effect, and the patient's response to oral tobutamide was slight. Glucagon, given subcutaneously when the blood-sugar was 330 mg. per 100 ml., resulted in a rise of 60 mg. per 100 ml. with no subsequent hypoglycæmia. The alkaloid vincamine given intravenously failed to influence his blood-sugar level (Kaldor and Szabo 1960).

The available members of the patient's family (mother, father, 4 brothers, and 2 sisters) all had normal glucose-tolerance curves, and did not respond to alfalfa. A number of experiments were then carried out to assess manganese metabolism in the patient. Since stable manganese could, for technical reasons, not be measured, isotopic manganese (specific activity 2·3 μC per μg.) was used. Radioactive $^{54}MnCl_2$ (10 μC) was incubated with the patient's plasma for thirty minutes, and was administered intravenously. The uptake by the liver, spleen, and sacrum was determined by surface counting, and the subsequent decrease in counts over the next seven days was determined. The rate of fall of counts over the liver and spleen of the patient was slightly more rapid than in controls, but the differences were not significant. In a second experiment, the daily excretion of labelled manganese in stools after an intravenous dose was measured, but no obvious difference between the patient and control groups was demonstrated. The patient's urinary excretion of ^{54}Mn, however, was higher than that of controls, even though the actual amount of manganese excreted in the urine was small (fig. 4).

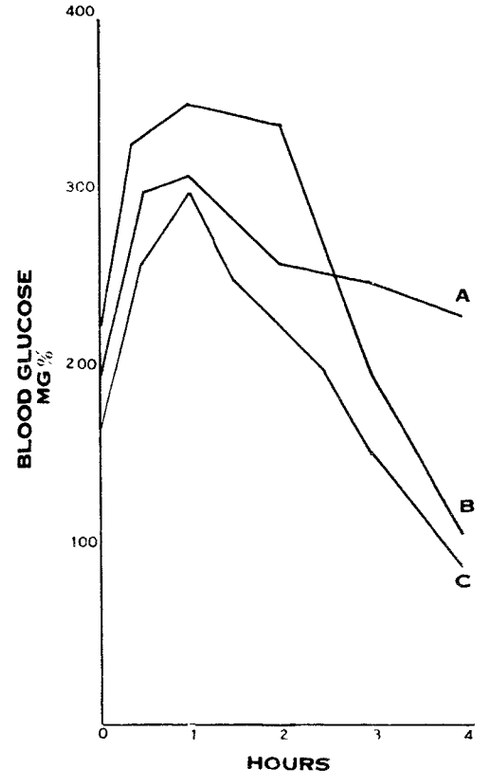

Fig. 3—Glucose-tolerance curves: A after 100 g. glucose orally. B after 100 g. glucose and lucerne. C after 100 g. glucose and 5 mg. manganese (as manganese chloride). Lucerne and manganese were given with glucose.

The disappearance of ^{131}I-insulin from the plasma was then measured under two different circumstances. In the first experiment, 5 μC of ^{131}I-insulin (specific activity, 65·05 μC per μg.) was injected intravenously when the blood-glucose level was 420 mg. per 100 ml. blood-samples were taken at intervals of fifteen minutes, and the radioactivity was measured. The number of counts in the urine was also determined. In the second experiment, 10 mg. of manganese chloride was given orally, and this produced a fall in the blood-sugar. While this decrease was taking place, ^{131}I-insulin was injected intravenously, and the disappearance curve of radioactivity in the plasma was again followed. Each curve had an initial fast component and a subsequent slow component. The $T^{1/2}$ of the fast component was twenty minutes with oral manganese and ten minutes without oral manganese, whereas the $T^{1/2}$ of the slow components was one hundred and

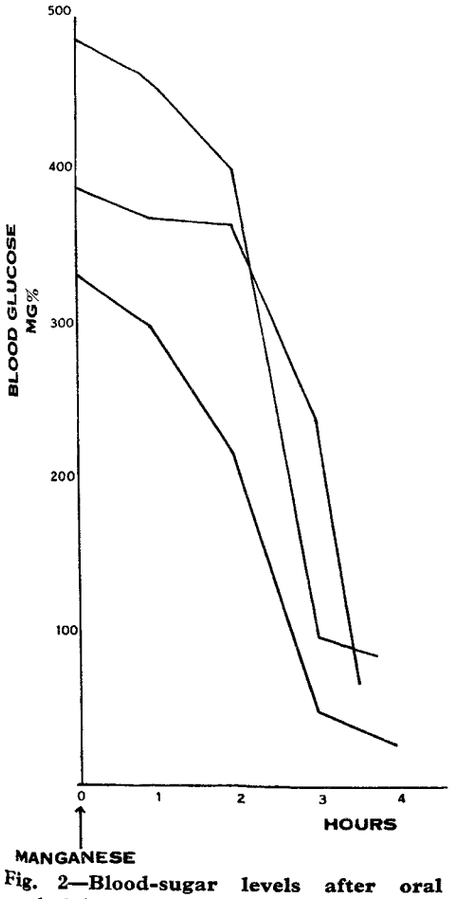

Fig. 2—Blood-sugar levels after oral administration of 5 mg. manganese (as manganese chloride). Three representative curves.

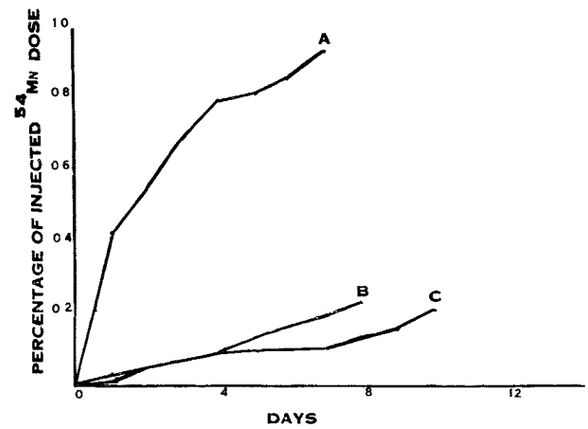

Fig. 4—Cumulative urinary excretion as percentage of original injected dose of labelled manganese. A patient. B and C control subjects.

twenty minutes and eighty-five minutes. The stability of the ^{131}I attachment to insulin was not measured.

Subsequent Progress

With 10 mg. of manganese chloride orally three times a day, fairly satisfactory diabetic control was obtained and it was possible to discharge the patient on this regimen. After two months, however, it became obvious, even though the blood-sugar levels could be lowered by manganese, that the large fluctuations of blood-glucose to which he was prone could not be prevented. He was unreliable, and did not take his prescribed medicine with regularity. Hypoglycæmic episodes after taking manganese persisted, and during these attacks the patient was violent and dangerous. Moreover, apart from the predictable drop in blood-glucose after giving manganese and lucerne, occasional hypoglycæmic episodes did happen. Whether these were related to the content of manganese in his food (particularly tea, which has an appreciable quantity of manganese) was difficult to decide with certainty. The attacks occurred periodically and mainly at night, and large quantities of intravenous glucose were needed for their relief.

Because of this and because the patient might have had an islet-cell tumour, he was submitted to laparotomy by Prof. D. J. du Plessis in August, 1961. There was no obvious macroscopic abnormality in the pancreas, bowel, adrenals, sympathetic chain, or liver. Because the lesion might have been microscopic in size partial pancreatectomy was performed in which the body and tail were removed. A liver biopsy specimen was also taken.

The resected pancreas was normal on macroscopic examination; no tumour was present. The histological findings were consistent with controlled diabetes mellitus. Sections of the liver specimen showed abundant glycogen, but no other significant abnormality was observed.

Even in the early postoperative phase, it became obvious that the diabetic picture had changed strikingly. The blood-sugar was now easily controlled by insulin in small amounts, and, on withholding insulin, the patient rapidly became ketotic.

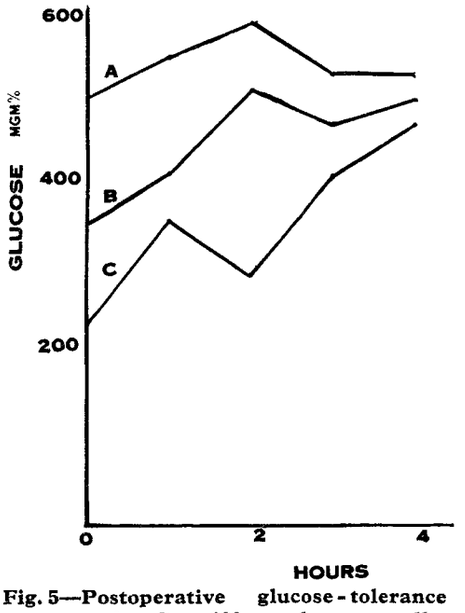

Fig. 5—Postoperative glucose-tolerance curves A after 100 g. glucose orally. B after 100 g. glucose and lucerne. C after 100 g. glucose and 5 mg. manganese (as manganese chloride). Lucerne and manganese were given orally with glucose.

From that time he required between 15 and 30 units of insulin daily for good control. His appetite decreased, and he lost 40 lb. in weight. Ten months after operation his weight was still at this level, despite the fact that the diabetes was well controlled, and that there was no steatorrhœa. Perhaps the most surprising finding is that oral manganese no longer has an effect on his blood-glucose levels, even with amounts ten times greater than those given before operation. His glucose-tolerance was tested with and without manganese six weeks and twelve weeks after the pancreatectomy (fig. 5). Intravenous manganese (900 μg.) given with insulin did not produce a greater fall in the blood-sugar than insulin alone. There has been no recurrence of the " spontaneous " hypoglycæmic attacks.

Discussion

The diabetic syndrome in this patient was unusual in that he had severe hyperglycæmia, insulin resistance, and no ketonæmia. Moreover, in contrast to the usual juvenile diabetic he was exceptionally muscular and tended to gain weight. Nevertheless, the fall in blood-sugar after the administration of the alfalfa or manganese before operation, and the disappearance of the response after operation were remarkable. The manganese was thought to act in one of two ways:

(1) It may act peripherally, and may accelerate cellular glucose uptake or utilisation either directly or by potentiating insulin action; or it may interfere with the action of glucagon in forming glucose from stored glycogen in the liver.

(2) Manganese may act on the pancreas by accelerating the release of stored insulin into the blood-stream, or by inhibiting the release of glucagon.

With regard to the peripheral action, magnesium, and to a lesser extent manganese, have been shown to increase the uptake of glucose by the isolated rat-diaphragm in the absence, but more so in the presence, of insulin (Bhattacharya 1961). Preliminary studies (carried out by Dr. G. S. Getz) on a specimen of rectus muscle obtained at laparotomy confirmed the increased uptake of glucose by the tissue when incubated in a medium containing insulin and manganese ions. Christensen (1961) found that manganese reverses uranyl-ion depression of glucose uptake by yeast cells, and he suggested that membrane-metal binding is part of the glucose-transport mechanism. Other workers have shown that physiological quantities of chromium and, to a lesser extent, of manganese strongly influence the glucose uptake of the rat-epididymal fat pad (Mertz and Schwarz 1961). Twelve other elements including iron, nickel, cobalt, and cadmium had no effect at all. The effect of chromium and manganese on the fat pad depended on the presence of small amounts of insulin, and resulted in a large increase in the incorporation of glucose into fat. In living rats, Schwarz and Mertz (1961) have shown that trivalent chromium ions are necessary to maintain normal carbohydrate tolerance.

The fact that ^{131}I-insulin disappeared from the plasma more slowly when manganese was causing a rapid fall in blood-glucose than when the blood-sugar levels were high seems to indicate that manganese had no effect on the utilisation of insulin or its uptake by the tissues. The failure after operation of simultaneously administered intravenous manganese and insulin to lower the blood-sugar more than insulin alone is also against a peripheral site of action of manganese. The quantity of circulating insulin and glucagon which has been greatly altered by the operation may possibly reduce the effect of manganese.

An excessive secretion of glucagon may have caused the intense hyperglycæmia in this case. Magnesium or manganese are known to be necessary in the activation of liver phosphorylase (Dixon and Webb 1958), but there is no evidence that manganese can block this reaction and precipitate hypoglycæmia by allowing the excess circulating insulin—secreted as a normal response to the hyperglycæmia—to exert its effect.

The loss of response to manganese after partial pancreatectomy favours the pancreas as the site of action of the metallic ion. It is known that insulin can chelate zinc and other metals (Craig 1962), and that the pancreas contains significant amounts of zinc (Fisher and Scott 1935). But Fisher and Scott (1934) showed that the quantity of extractable insulin bears no simple relation to the amount of zinc in the gland. Although the relationship of zinc to the physiological function of insulin and glucagon in the pancreas is still unknown, nevertheless, most workers think that a relationship exists (Vallee 1959).

After an intravenous injection, manganese becomes localised primarily in the pancreas, liver, and kidney (Maynard and Cotzias 1955) and, therefore, although there is no proof at present, manganese may be concerned in the release of insulin in a way similar to that postulated for zinc. In fact, Maske (1957) has suggested that insulin by its interaction with zinc is stored within the beta-cell granules, and that substances which form stronger complexes with zinc than they do with insulin, could bring insoluble zinc-insulin complexes into solution

by releasing the hormone from its zinc chelate. Various metabolites, such as citrate, oxalacetate, and glutathione have been shown to have this effect (Maske 1961) and manganese may possibly be necessary for the release mechanism of insulin. If manganese is reduced or unavailable, insulin release may be impaired.

The ^{131}I-insulin disappeared from the blood-stream more slowly after the administration of manganese. This could be interpreted as evidence in favour of an increased secretion of endogenous insulin under the influence of manganese, resulting in dilution of the radioactive insulin. On the other hand, there are two factors against manganese-induced insulin release. These are: (1) the complete lack of response to manganese postoperatively, even though the head of the pancreas is intact, and (2) the patient's insensitivity to insulin before operation would be inexplicable by this mechanism.

An alternative action of manganese on the pancreas in this case may be the inhibition of excess glucagon release by alpha cells. This mode of action of manganese would best explain the insulin insensitivity before operation and the postoperative improvement. The result would resemble that following an inhibition of the peripheral action of glucagon.

Manganese is present in the body in trace quantities (approximately 20 mg. in adults) and it is extremely difficult to measure its level accurately in the plasma without highly complex techniques such as neutron activation (Smith 1962). Accordingly, isotopic manganese was used as a tracer in an attempt to study the handling of stable manganese in this patient. The results indicated that the only abnormality may be an excessive loss of manganese in the urine, but tracer studies without the measurement of stable manganese-levels are obviously difficult to interpret. The plasma clearance, organ uptake, and fæcal excretion were comparable to that observed in controls, but these crude investigations may not enable detection of abnormalities in the valency of the active manganese or of its intracellular distribution.

The quantity of manganese which was needed to produce the hypoglycæmia was so small that it seemed probable that its action was physiological rather than toxic. It followed, therefore, that the patient was absolutely or relatively deficient in manganese. As there was no dietary deficiency, and as the daily requirement of manganese is very small, an absolute deficiency seemed unlikely, although this possibility could not be entirely excluded, because of the observation of an increased loss of manganese in the patient's urine. However, it seems much more likely that his manganese was in some way unavailable to him. The absence of abnormal findings in the pancreas indicated that the disorder was probably subcellular although it is still possible that the volume or total number of islets in the pancreas was abnormal.

Whether manganese has an effect on normal people or on other diabetics is unknown, but preliminary studies on several normal controls, on obese and juvenile—onset diabetics, and on a diabetic with chronic calcific pancreatitis did not show a significant drop in blood-sugar levels after manganese was given either in the same dose or in very much larger doses than our patient had. Nevertheless, isolated published reports of changes in carbohydrate tolerance after the administration of chelating agents suggest that metallic ions do have an important place in intermediary metabolism in man. Thus, Meltzer et al. (1961a) observed that certain diabetic patients needed less insulin after the administration of disodium ethylenediamine tetra-acetate. They found significantly increased zincuria (Meltzer et al. 1961b), but they did not measure manganese excretion. The effect was noted in patients receiving insulin only, and no effect was obtained on normal persons or on diabetic patients not receiving insulin. On the other hand, Seven (1960) reported glycosuria in 2 persons treated with chelating agents; hence the matter is by no means settled.

Summary

An exceptionally muscular young diabetic, aged 18, required about 100 units of soluble insulin daily to achieve rather unsatisfactory control of his glycosuria. He was conspicuously free from ketosis but very prone to attacks of hypoglycæmia during which his behaviour was aggressive and dangerous.

After the patient claimed that an infusion of lucerne (alfalfa) controlled his diabetes better than insulin, an infusion was found to lower his blood-sugar, sometimes with hypoglycæmic symptoms, including coma. Because of the high content of manganese in lucerne, 5 to 10 mg. of manganese chloride was given by mouth, and was found to produce similar effects on the blood-sugar on all occasions. Oral manganese controlled the diabetes no less satisfactorily than soluble insulin.

The mode of action of manganese was investigated in this patient and in controls, using radioactive manganese.

We are indebted to Prof. B. J. P. Becker, Prof. H. B. Stein, Dr. G. S. Getz, and Dr. B. A. Bradlow of the department of pathology and microbiology, University of the Witwatersrand, and to Dr. J. Metz and Mr. D. Hart of the radioisotope unit of the South African Institute for Medical Research for their assistance and advice. We are grateful to the photographic unit, department of medicine, for the illustrations.

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SOME COMMON CAUSES OF EYE INJURY IN THE YOUNG

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AN injured eye may affect a child's whole life. The eye may be so badly damaged that it requires removal, perhaps leaving a discharging socket; or the eye may be left with no useful vision and become shrunken or otherwise disfigured. Because of a temporary loss of sight (as with hæmorrhage or lens damage) the vision may be suppressed, and the eye become amblyopic and divergent; or less severe after-effects may cause lack of binocular vision or a reduction in visual acuity.

Some eye injuries in young people could be prevented. This paper deals with eye injuries in patients under 16 years who required admission for at least forty-eight hours