Discussion

The present case of x-ray dermatitis with ulceration showed that the patient had in the course of years received very large doses of x rays on the right foot. The chances of exposure to radiation were as follows: (1) The patient operated the shoe-fitting fluoroscope 15 to 20 times daily. While doing this she was standing on the floor to the left of the fluoroscope, where the feet were exposed only a little. However, if, during the transillumination, she supported her right foot on the platform in front of the foot opening it was exposed to intense irradiation. (2) New shoes bought were always fitted by transillumination. (3) If children were afraid of the transillumination the patient would now and then put her foot into the apparatus to show that "it did not hurt" (this did not happen every day, however). (3) If there were no customers the shop assistants would occasionally try new shoe models under transillumination.

The site and development of the x-ray dermatitis of the right foot show it to have been due mainly to the first-mentioned chance of exposure.

Preliminary investigation by Stewart *et al.*⁹ have shown that x-ray examination of the abdomen of a pregnant woman may provoke leukaemia or cancer of the foetus. On repeated and possibly prolonged transilluminations in these shoe-fitting fluoroscopes pregnant customers will have received considerable doses of x rays against the abdomen.

The increasing use made of ionizing rays within industries and in medicine will expose a steadily rising number of people to an irradiation of the gonads greatly exceeding that which these receive from the natural background radiation (radiation from radioactive substances in soil and organism, as well as cosmic radiation). Any form of ionizing radiation is mutagenic. There is no lower limit to the dose of rays provoking mutations, and the number of these will ostensibly rise proportionally to the dose received by the gonads.¹¹

To counteract the increasing risk of radiogenic damage thus involved, preliminary investigations have been made to assess to what extent different sources of radiation raise the radiation dose to the gonads. Various writers⁶⁻¹⁰ agree that medical use of ionizing rays is the main factor in this rise.

In the Frederiksberg Hospital⁸ 19,000 x-ray examinations are carried out each year, of which 7,578 are grouped round the pelvis. Apart from salpingographies and x-ray examinations in pregnancy and sterility (216 patients), the age incidence shows a maximum for age group 50 to 70 years. In the Roskilde County and City Hospital¹ 7,586 patients were in 1955 submitted to a total of 12,800 x-ray examinations. Only 860 patients under 46 years of age had examinations made involving the gonads. By a good technique the dose can generally be kept as low as 1 or 2 r per examination. Hammer-Jacobsen⁴ has calculated the radiation dose received by the gonads in the Danish population from diagnostic radiology to be 122,313 r a year, corresponding to 29% of the dose received from the natural background radiation.

Roughly 60,000 transilluminations were carried out annually with the two fluoroscopes. The transillumination time was 30 to 45 seconds. During this period a non-screened beam of rays passed from the front part of the foot platform to the direction of the customer's abdomen. In adults the beam intensity was of the order of 1 r a minute, while in children it might be much higher. It is seen that a single defective shoe-fitting fluoroscope will raise the total radiation dose to the gonads much more than even very large radiological units. In assessing the genetic hazards only irradiation of fertile individuals is to be considered. This fact adds still further to the difference, because shoe-fitting fluoroscopes are used chiefly for child customers, whereas x-ray examinations comprise mainly elderly individuals.

The genetic hazards of increased gonad radiation being uncertain, it is necessary to compare the value of the use of each source of radiation with the possibility of increased

risk. Owing to the great danger involved by the use of shoe-fitting fluoroscopes there is reason to examine whether correct measuring and trying on do not fulfil the requirements of exact fitting of shoes, so that these fluoroscopes might be prohibited.

Summary

A case is reported of x-ray dermatitis with ulceration caused by a shoe-fitting fluoroscope.

The physicist's examination of the apparatus revealed that during transillumination of the feet a non-screened beam of x rays passed from the front part of the foot platform in the direction of the customer's abdomen. The rise of the radiation dose to the gonads caused by such a defective fluoroscope is much greater than that from even large radiological units.

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ORAL TREATMENT OF DIABETES WITH TOLBUTAMIDE

BY

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Bänder *et al.* (1956) reported the successful therapeutic use of tolbutamide (D.860, "rastinon") in selected diabetic patients. The following clinical study was designed to ascertain the effect of the drug in Indian patients, and covers the period from August, 1956, to June, 1957.

Material

A total of 137 cases of established diabetes mellitus were treated (108 males, and 29 females). The age incidence was 27 to 76 years, excluding a child of 4 years with congenital diabetes. In 30 cases the disease was hereditary. The known duration of the disease ranged from 1 to 27 years. According to the standards set by the Metropolitan Life Insurance Company Statistical Bureau, quoted by Dunlop *et al.* (1953), 10 patients were asthenic, 64 were of ideal weight, and 63 were obese. Of the 105 patients who had symptoms of diabetes of varying severity, 46 had shown evidence of acetonuria some time or another, but only 17 of them were liable to ketosis within two to seven days of withdrawal of insulin therapy.

The cases were classified as "mild" (28 cases), "severe" (97 cases), and "very severe" (12 cases) on the basis of results of initial glucose-tolerance tests. In the mild cases the highest blood-sugar level was below 250 mg./100 ml., in severe cases it was 250 to 450 mg./100 ml., and in the very severe cases it was over 450 mg./100 ml. 82 cases had been taking insulin regularly.

Methods

Before starting oral antidiabetic therapy clinical examination was made of all patients, and their latest diabetic state was evaluated by means of a glucose-tolerance test after removing all dietetic restrictions and withdrawing

insulin treatment for seven days. During this period the urine was regularly examined for sugar and acetone for evidence of any metabolic breakdown that might have occurred on withdrawal of insulin. In six cases this tendency was very pronounced, and so the glucose-tolerance test was not done, the patients being assessed on the basis of results of blood-sugar levels estimated while fasting and two hours after a meal on withdrawing insulin for only one day. A routine haemogram recorded the pre-treatment haemopoietic state.

To evaluate the hypoglycaemic effect of tolbutamide the blood-sugar level was estimated once a fortnight while fasting and two hours after a meal and after instituting oral therapy. In those who developed hypoglycaemic symptoms more precipitately the blood-sugar estimations were carried out earlier, as indicated. When the results of the blood-sugar tests became more or less static a glucose-tolerance test was repeated during the course of oral treatment at the next follow-up examination to determine the influence of the drug on the actual metabolic pattern. A further follow-up was kept by periodic blood checks. Haemograms were repeated regularly once a month. Urine was examined for sugar, and if necessary for acetone, as often as desired. Liver-function tests were done at the end of six months' continuous treatment.

The patients were given a high-carbohydrate (250-300 g.) low-fat (20-50 g.) diet duly adjusted to individual needs. Tolbutamide was given in the following dosage: initially two tablets (0.5 g. each) twice daily for two days, subsequently the dose was reduced to one tablet twice daily. When adequate response to the drug was obtained maintenance dosage was worked out in each case. If, however, the response was inadequate the morning dose was increased from one tablet to two tablets. The tablets were taken approximately two hours before breakfast and dinner on an empty stomach. In patients subject to ketosis the previous insulin treatment was continued until the oral drug had had a hypoglycaemic effect. In all other cases insulin treatment was discontinued at once.

Most of the patients were already well versed in the routine management of their disease, and so ambulatory treatment was possible. This procedure did not involve any risk. Admission to hospital was not necessary in any of the cases.

Results

The result was considered very satisfactory in 94 cases (68%) and satisfactory in 32 (23%). There were 11 failures (9%). In the very satisfactory cases the patients were rendered aglycosuric, and their blood-sugar values were well within normal; in the satisfactory cases glycosuria was negligible and infrequent, and blood-sugar values showed corresponding improvement, but the glucose-tolerance test still revealed evidence of a mild metabolic deficit. In the failures the response was less marked. No additional advantage was obtained by increasing the dose of the drug if the response to the routine dosage scheme was inadequate or poor, except in the case of the child with congenital diabetes, who could be made completely aglycosuric with three tablets daily but not with two.

The glucose-tolerance tests done during the course of oral therapy at the time of maximum benefit from the drug showed the following patterns: blood-sugar levels that were merely subdued and, after treatment, a curve that was more or less parallel to the pre-treatment curve in 37 cases; a more or less normal curve in 75 cases; a fall, mostly in the fasting sugar level, in 8 cases; a fall, mostly in the latter part of the curve, in 10 cases; a more or less "flat" curve in 5 cases; and no appreciable change in 2 cases.

The renal threshold was lowered in 45 cases, raised in 16, and unaltered in 76 during the course of treatment with the oral antidiabetic drug. Of the 45 cases in which the renal threshold was lowered, 29 were chronic diabetics, and in them the lowering of the renal threshold was part and parcel of the general improvement. The rise in the renal threshold was, however, unaccountable. It was

very striking in one case, which turned out to be a failure. Before oral therapy this patient was slightly glycosuric, with a blood sugar of 218 mg./100 ml. During the course of oral therapy he became aglycosuric and started to complain of weakness. When the fortnightly blood check was done his postprandial blood sugar was 445 mg./100 ml., but there was no glycosuria; the results were confirmed by re-examination.

In 39 cases the highest blood-sugar levels after meals were below 120 mg./100 ml., and gross fluctuations in blood sugar from increases in diet (the equivalent of 200 to 500 calories) or from reasonable intake of free sugar did not occur. The fall in the blood sugar was attended with improvement in general health and increased capacity for physical exertion.

The time taken for a complete response to oral therapy in the 94 very satisfactory cases was two weeks in 58 cases, four weeks in 24, and six weeks in 12. Glycosuria was controlled earlier in about one-seventh to one third of the above periods.

Generally the more complete the response the lower was the maintenance dose. Thus in 39 cases in which the highest blood-sugar levels after meals were below 120 mg./100 ml. (see above) the maintenance dose was one tablet every two days. In 14 of these 39 cases it was subsequently possible to discontinue the drug for one to six weeks before a significant rise in the blood sugar, though still below the highest normal, took place again. So far there has been no definite evidence of drug tolerance in any case.

The drug was generally well tolerated and the incidence of adverse effects was very low. Transitory headache occurred in six cases during the first two days of treatment, when the dose of tolbutamide was 2 g. daily. Seven patients complained of muscular weakness, which was due to low blood sugar and which disappeared when the dose of the drug was reduced. Two elderly patients were extremely susceptible to the drug, and during the first week of treatment they became hypoglycaemic and developed temporary hemiparesis without previous warning. Two patients complained of tingling sensation in the finger-tips, toes, and lips whenever they took tolbutamide. Skin rashes occurred during the first week of treatment in two cases. In one of them the rash was mild and regressed spontaneously, but in the other case the rash was severe and the drug had to be discontinued.

Only minor blood changes were noted. There was no case of permanent platelet depression. In two cases there was an initial fall in the platelet count, but subsequently there was a rise to normal, and in another case the platelet counts showed a progressive increase before becoming stabilized. The changes in the total and differential counts were well within the recognized normal fluctuations. In three cases the leucocytic response was normal during an acute respiratory infection.

Liver-function tests done after six months' oral therapy did not show any abnormality, and there were no adverse effects from the drug in four cases of myocardial infarction during the acute or subsequent stages.

Discussion

The effects of long-term treatment with tolbutamide will not be known for some years. At present the immediate results in the above series indicate that the drug will decrease glycosuria and hyperglycaemia in about 90% of the so-called "adult-onset" diabetics. The success appears to depend on the availability of active insulin. When the metabolic deficit with the glucose-tolerance test was very severe and the patients were liable to prompt ketosis on withdrawal of insulin treatment, the results were significantly poor. Prolonged previous treatment, especially with larger doses of insulin, also adversely affected the results. Thus the result was very satisfactory in 80% of all cases which had been treated with insulin for less than one year, in 56% of cases treated with insulin for two to five years, and in only 6% of cases treated with insulin for more than

five years. It was also very satisfactory in 100% of cases which had received 10 to 20 units of insulin daily, in 75% of those who had 20 to 40 units daily, in 66% of those who had 40 to 60 units daily, in 31% of those who had 60 to 80 units insulin daily, and in none of those who had more than 80 units daily. The experimental work of Haist *et al.* (1940) and Lukens and Dohan (1942) suggests that in the latter cases the stores of endogenous insulin had probably been depleted as a result of prolonged insulin administration. Of the 20 cases on 60 to 100 units of insulin daily, 11 were comparatively insulin-resistant, and this seems to have played a major part in the poor response to oral therapy.

Excluding the effect of insulin deficiency, of whatever origin, and also the effect of insulin resistance, the results did not appear to have been influenced by the current age in the series, body weight, heredity, duration of the disease, and presence or absence of symptoms. There was, however, a tendency towards a quicker and more satisfactory response in some women. Thus, in five women who had fasting sugars of over 300 mg./100 ml. the response to oral therapy was complete within a week, and in two women with pulmonary tuberculosis and on a liberal diet it was possible to discontinue insulin treatment in favour of oral therapy with tolbutamide without prejudicing the response to antituberculosis treatment in any way. According to Wrenshall and Best (1956), with increasing years of survival after diagnosis of diabetes there is a slow decrease in the average amount of insulin extractable from the pancreas, especially in males. This may partly account for the fact that the women did comparatively better than the men.

There was a case for considering the use of the drug even in patients liable to ketosis on withdrawal of insulin therapy, as about one out of six such cases showed an unexpected very satisfactory response and in many others the required insulin and the fluctuations in the postprandial blood-sugar levels were significantly reduced. The drug was also effective in the case of congenital diabetes, and the child appeared to tolerate the drug well. Probably, however, in our present state of knowledge oral treatment is not advisable in children.

On account of the low toxicity of tolbutamide, it appears very probable that this drug will have a place in the long-term treatment of selected cases of "adult-onset" diabetes, especially where it may be possible to control the disease with low or intermittent maintenance dosage. It appears that if the drug is given on an empty stomach a smaller dose is required. The drug is also worth trying in cases of severe renal glycosuria, as benefit may accrue from a lowered blood sugar, a raised renal threshold, or both.

Although the mode of action of tolbutamide is still controversial the normal pattern of glucose tolerance obtained during the course of treatment suggests that in many cases the insulin mechanism reverted to the normal in some way or other.

Summary

136 cases of "adult-onset" diabetes mellitus were treated with tolbutamide. The results were very satisfactory in 94 cases (68%), satisfactory in 32 (23%), and there were 11 failures (9%). The result was also satisfactory in one case of congenital diabetes in a child of 4 years. No serious side-reactions were encountered. The factors influencing the action of the drug, and indications for its use, are discussed.

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D

AN ASSESSMENT OF BUTHALITONE SODIUM

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There has been a reawakening to the need to have available in anaesthesia an alternative agent to nitrous oxide for short-duration anaesthetics, particularly for out-patients. This can be seen in the recent work of the cyclopropane protagonists (Bourne, 1952) and in the revived interest in ultra-short-acting barbiturates other than thiopentone.

Our investigation and assessment relate to one such barbiturate for which striking claims were made. It was said that the patient need not stay in hospital, and is "strassenfähig" (capable of walking in the street) within half an hour of the administration (Weese and Koss, 1954). It was felt that if this claim were substantiated then anaesthesia for minor operations in casualty or out-patient department could be improved because the anaesthesia disturbed the physiology less.

Pharmacology

Buthalitone sodium is a thiobarbiturate first described in 1936 by Miller *et al.* Chemically it is the sodium salt of 5-allyl-5-(methylpropyl) thiobarbituric acid, with the structural formula:

("Thiamylal": replace ethyl with allyl)

It is a yellow powder which is readily soluble in water, giving, like the other sodium salts of the barbiturates, an extremely alkaline solution. The pH varies with the mode of preparation, ranging from 10.5 in the case of "transithal" to 10.0 in the case of "baytenal" and "ulbrevall." The solution is said to be unstable.

The therapeutic index for mice has been shown to be the same as that of thiopentone (K. F. Rivett, 1955, private communication). In dogs it has approximately half the potency of thiopentone (J. A. Anderson, 1955, private communication). Repeated massive administrations in rabbits showed no ill effects on the kidney or haemopoietic tissues (Weese and Koss, 1954). We have found no instance of venous thrombosis in man. Subcutaneous injections of a 5% solution in volunteers gave reactions in all ways indistinguishable from those of thiopentone: an initial burning pain, followed by a transient erythema and swelling, greater than that