in whom the mean distance, measured by the same observer, was 1.4 in. (3.5 cm.), with a range of 1.1 to 1.8 in. (2.7 to 4.6 cm.).

Examination of the family of Case 2 revealed a number of interesting abnormalities. Only one (E.C.) had arachnodactyly, but five out of the six siblings were strikingly tall and thin, and the patella was high in four. Whittaker and Sheehan (1954) have recorded instances of aortic lesions without arachnodactyly in the families of patients with Marfan's syndrome, and although the father had no skeletal abnormality it is tempting to consider his aortic incompetence as possibly of congenital origin. Unexplained exophthalmos, illustrated by F.C., has been described in patients with arachnodactyly (Baer *et al.*, 1943), and abnormalities of the lobes of the lungs, which were present in the sister, O.C., are not uncommon (Rados, 1942). Another sister suffered from epilepsy, a finding also reported by Marfan in one of the siblings of his original case (Marfan, 1896).

The aetiology of Marfan's syndrome, like so many other congenital anomalies, remains obscure. Weve (1931) explained the skeletal and visceral abnormalities on the basis of a congenital mesodermal dystrophy, but it has been repeatedly stressed that, if this theory were true, urogenital abnormalities should also occur (Rados, 1942). In fact, genital abnormalities have been reported from time to time. The two cases reported by Olcott (1940) and by Fischl and Ruthberg (1951) illustrate that congenital lesions of the urinary tract may also be found with arachnodactyly. These findings lend some support to Weve's hypothesis, but it is interesting to speculate how a dystrophy affecting one of the germinal layers may at the same time result in excessive growth of the extremities.

Summary

A brief survey of the abnormalities which may be found in patients with Marfan's syndrome is given. The apparent rarity of the association of arachnodactyly with genito-urinary abnormalities is stressed. Two patients who had arachnodactyly and congenital lesions of the urinary tract are described. The first had bilateral polycystic kidneys, and the second had chronic pyelonephritis resulting from a congenital stricture of the lower end of the right ureter. These findings lend some support to the hypothesis that the visceral abnormalities associated with Marfan's syndrome may be due to a congenital mesodermal dystrophy.

The first patient also had dystrophia myotonica. The coincidence of arachnodactyly with this disorder has not previously been described.

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A SIMPLE METHOD OF BLOOD-SUGAR ESTIMATION

BY

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Many methods of blood-sugar estimation are available at present—for example, Hagedorn and Jensen, Maclean, Folin, Harman, and Somogyi. In recent years, moreover, the "true glucose" methods have become more and more popular, Nelson's modification of the Somogyi technique, giving close approximation to the true glucose level, being widely used in hospital practice. While there can be no doubt that these methods, particularly the latter, give accurate and consistent results, all of them require laboratory facilities to a greater or less extent and are best carried out by a person experienced in the particular technique involved. Very often, however, when faced with a problem involving the need for a blood-sugar estimation, it is adequate for the clinician to know that the blood sugar lies within a certain range. The method described below requires a minimum of technical equipment and training, and can be readily performed in the consulting-room or the patient's home, the results being available within ten minutes.

Method

The outfit for this simple method is manufactured by Ames Company (London) Ltd., who supplied it for the purpose of this investigation. The test is in essence a quantitative copper reduction method, the test solution being compared with a standard colour range chart, and the blood-sugar range being read directly from this chart. The total equipment is two standard test-tubes (7.2 by 1.4 cm.—"clintest" pattern) graduated in millilitres, a metal test-tube rack, two pipettes, filter papers, and two small bottles of reagents conveniently presented as tablets (A and B). No external heating is required. The whole apparatus can be packed in a box some 3 by 3 by 1 in. (7.5 by 7.5 by 2.5 cm.), and is therefore very readily portable.

The test-tubes are set up in the rack, 2 ml. of water is put into one tube, then one tablet A is added and allowed to dissolve completely. Then 1 ml. of venous blood is placed in this solution and thoroughly mixed with a glass rod, this procedure deproteinizing the blood. A filter cone is then placed in the second test-tube and the solution from the first test-tube poured into the cone. A clear filtrate is obtained and 1 ml. is collected. (These measurements are very easily made, as the tubes are graduated in millilitres.) To this solution one tablet B is added; vigorous boiling occurs, during which time the tube should not be touched. After the boiling ceases the test-tube is shaken briskly three or four times, there is a wait for 30 seconds, and the colour is then compared with the standard scale provided. This colour scale shows three definite stages—blue, olive green, and tan—corresponding to blood-sugar levels of 100, 150, and 200 mg. per 100 ml., but with a little experience intermediate levels of 125 and 175 mg. can be judged reasonably accurately. This range—that is, 100 to 200 mg. per 100 ml.—is the standard range claimed by the manufacturers. An attempt has been made to extend this range to increase the usefulness of the method. The effective range of the scale can be readily extended to a level of 400 mg. per 100 ml. by simple dilution of the filtrate, 0.5 ml. of filtrate being collected, making up to 1 ml. with water, the actual testing being carried out as above, and the result obtained being multiplied by two. Further dilutions to an upper level of 800 mg. per 100 ml. can be readily made if desired.

Results

The method has been tried on blood specimens from 80 diabetic patients, simultaneous blood-sugar estimations using the Nelson method being carried out as a control. Five millilitres of venous blood was drawn into a fluoride tube and the specimen divided equally for testing by both methods. The results obtained are shown in Fig. 1. This

FIG. 1

Fig. 1.—Comparison of blood-sugar determinations by the Nelson method with the new test in 80 diabetic patients. Fig. 2.—Comparison of the Nelson method and the new test at intermediate levels in 31 patients.

gives the results of the test carried out without dilution of filtrate and without any attempt at intermediate readings on the test scale. It will be seen that within the range 100 to 200 mg. per 100 ml. the test gives a reasonably accurate estimate of the blood-sugar level, in the majority of cases within ± 25 mg. of the true level. It should be noted, however, that at both the lower and the upper range of the test considerable variations in the true levels may occur without any apparent variation in the test colour. While a more accurate estimate of levels over 200 mg. per 100 ml. may be made by simple dilution, it is important to recognize that levels below 100 mg. per 100 ml. cannot be assessed, and hypoglycaemic levels may be present without any definite indication from the test results.

After the initial test, inquiry was made whether a more precise estimate of the blood sugar could be arrived at by use of the method. By judging the colour given by the test as approximately intermediate between the colours on the standard scale, a reading of 125 or 175 mg. per 100 ml. might be possible. This was tried in 31 cases and the results were compared with those obtained by Nelson's method. The findings are summarized in Fig. 2. It will be seen that in the majority of cases intermediate levels can be judged with a fair degree of accuracy and that most of the results can be determined to within ± 25 mg. of the true level. Fig. 2 also illustrates the inability of the test to distinguish between levels below 100 mg. per 100 ml.; here true levels of 100 and 35 mg. per 100 ml. appear identical.

Fig. 3 shows the results in 49 patients. The initial tests showed the rapid development of an orange colour sug-

FIG. 3.—Comparison of the Nelson method and the new test at levels between 200 mg. and 400 mg. per 100 ml. in 49 patients.

gesting blood-sugar levels above 200 mg. per 100 ml. in these patients. Dilution of the filtrate 1 to 2 was performed and the test repeated. Here the majority of the results can be estimated to within ± 50 mg. of the true level; indeed, the greater number of the results are within ± 25 mg. of the true level. In three cases when preliminary testing

had shown a blood-sugar level above 400 mg. per 100 ml. further dilution of 1 to 4 of the filtrate was carried out. The results were:

Case	Nelson method	Test
1	650	600-700 mg. per 100 ml.
2	838	700-800 " " "
3	565	500-600 " " "

When dilutions of this order are carried out the degree of precision is less, but the results do give a useful guide to the blood-sugar level.

Comments

The method described gives blood-sugar estimations of reasonable accuracy in the range 100 to 400 mg. per 100 ml. The most accurate results are obtained when the blood-sugar level is between 100 and 200 mg. per 100 ml., and the accuracy diminishes with dilution of the filtrate. The procedure is easy to carry out, and requires no elaborate equipment. It could, if necessary, be performed in the patient's home or in the consulting-room. It is a rapid test and on average can be completely carried out in 10 minutes.

A real difficulty in the technique is in deciding the colour of the tested solution when comparing it with the standard scale. When it compares exactly with the standard range then the result is obvious, but intermediate colours are frequent and may cause considerable difficulty. With experience intermediate values can be estimated with reasonable accuracy, although absolute precision is not possible.

Certain features in the method merit comment. First, occasional difficulty was encountered during the period of filtration and a cloudy filtrate was at times noted, presumably associated with defective filtration. Testing this solution gave inaccurate results, and it is therefore important to note that the filtrate is clear before completing the test. Secondly, the importance of the time interval before reading should be noted. The colour change must be read at exactly 30 seconds after shaking. If this interval is prolonged, further colour changes may occur, with resultant discrepancy in the readings. On the other hand, shortening of the interval gives readings much below the true level.

The test appears to be a simple, rapid, and reasonably accurate method of blood-sugar estimation. While it does not give a high degree of precision in many cases, it may well be of value where an approximation is adequate—for example, in a busy diabetic clinic. Two patients illustrate this: both were pregnant diabetic women showing a heavy glycosuria. The test (confirmed by Nelson's method), however, showed their blood sugar levels to be within satisfactory levels, indicating lowering of the renal threshold. The method may also be used in the management of diabetic ketosis in emergency, when full laboratory facilities are not available. The values obtained, although approximate, give adequate information for the assessment of the response to treatment and the adjustment of insulin dosage. It is important to note, however, that the test is of no help in distinguishing between normal and low blood-sugar levels, and hypoglycaemic levels may be reached without any indication from the test. This would appear to be the major disadvantage of the method.

Summary

A simple method of blood-sugar estimation has been tried in a series of 80 diabetic patients, the results obtained being compared with blood-sugar estimations by the Nelson method.

The most accurate results are obtained when the blood level lies between 100 and 200 mg. per 100 ml. In higher ranges the results are less precise, but often are adequate approximations.

The test is of no value in the diagnosis of hypoglycaemia.

Factors which may give rise to fallacies in the test are discussed, and possible practical applications are described.

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USE OF HYALURONIDASE IN INSULIN COMA THERAPY

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Hyaluronidase was first named by Chain and Duthie (1939, 1940), but it was as early as 1928 that Duran-Reynals isolated what he called a spreading factor from normal testis. Various sources of hyaluronidase have since been determined—ciliary body, cornea, skin, and spleen—and it is now recognized as a specific enzyme having the special property of depolymerizing hyaluronic acid—a mucopolysaccharide constituting the tissue cement or ground substance of the mesenchyme. The possible applications of such an enzyme, once extracted and standardized—namely, a substance which can, as it were, reversibly reduce the viscosity of the intercellular matrix—are numerous, and there is a great deal of evidence to indicate its useful application in the fields of surgery and midwifery.

It seemed feasible, therefore, that hyaluronidase could be of use in deep insulin therapy, perhaps increasing absorption rate and allowing for a smaller dosage of insulin, and indirectly minimizing the possibility of hypoglycaemic after-shock. Hyaluronidase has thus been used and reported on by various workers with conflicting results, but Gysin and Wilson (1954), investigating a series of 53 cases, found that the amount of insulin was reduced by some 40%, a smoother induction resulted, and late adverse reactions were reduced by about 73%. There is such great individual variation to the effects of injected insulin that such results should be regarded as very significant. One factor, for instance, is the undoubted possibility of injecting into fascial planes, causing variable absorption.

The object of this paper is to report on a series of 42 patients treated in the deep insulin unit over the period from January, 1956, to January, 1957, combining the use of hyaluronidase with insulin.

Method

Methods similar to those of Gysin and Wilson were used, the patients serving as their own controls. The dose of insulin was increased by daily increments until coma was produced, and then lowered until the patient was stabilized on a set dose. Once stabilized, treatment continued for approximately two weeks before hyaluronidase was introduced—the usual dose being 500 Benger units, and the quantity of insulin being reduced by a third. By comparison with overall figures for the previous year we were able to ascertain the incidence of other features, such

as smoothness of treatment and the presence of hypoglycaemic after-shocks. Also, there was always a group of patients, not on hyaluronidase at the time of the investigation, who could be likewise used for comparison.

The hyaluronidase was given with the insulin at the usual time of administration—that is, 7.30 a.m.—in the same syringe, there being no flocculation. The time of onset of coma, its depth, and the rapidity of recovery following interruption were carefully observed in all patients. Frostig's (1940) criteria of depth were used. A double check was made in the majority of cases stopping hyaluronidase after some 30 comas and restabilizing the patient, and again by reintroducing the hyaluronidase later in treatment.

Benger's "hyalase" was the preparation used for this investigation, 1,000 units being equivalent to 450 units (T.R.U.) of American products.

Results

With this treatment it was soon found that patients fell into one of three groups: (1) 26 (61.9%) responded as expected by going into coma on a much smaller dose of insulin (70% of original dose), induction was smoother, and recovery more rapid; (2) 10 (23.8%) who were for the most part on comparatively small doses (150 units or under) seemed to gain little benefit in dose reduction by the addition of hyaluronidase; (3) 6 (14.3%), even though on doses of 300 units or more, initially responded well to the hyaluronidase-insulin combination, but the coma-producing dose soon began to increase until the original level of insulin was reached or passed, even with hyaluronidase.

Over the year there was no significant reduction in the number of intravenous interruptions necessary or the incidence of hypoglycaemic after-shocks. Two important clinical features noted were: (1) the consistency of treatment—each individual patient going into coma to the same level daily without the tendency to daily fluctuation as normally occurs; and (2) a significant drop in the incidence of hangover effects—namely, headache, dizziness, malaise, and inertia.

The time of onset of coma for each individual remained unchanged and there were no toxic signs or signs of hypersensitivity to either the hyaluronidase or the insulin.

All other conditions remained unchanged in the deep insulin unit over the 12 months, there being the same medical and senior nursing staff in charge.

Summary

Hyaluronidase was found to be of most use in 61.9% of patients undergoing deep insulin therapy, these patients normally requiring high doses. Its main values lay in allowing a smaller dosage of insulin yet providing a smoother induction and a trouble-free coma. Two other advantages noted were the improvement in consistency of treatment and the elimination of hangover effects such as headache, dizziness, and inertia.

No explanation can as yet be given for the small group of patients who, in spite of hyaluronidase, became insulin-resistant. This feature had probably little to do with the introduction of hyaluronidase, and it seems reasonable to assume that these patients would have developed some degree of insulin resistance in any case.

In 23.8% the addition of hyaluronidase did not result in reduction of the dose necessary for coma, these patients being those on basically small doses initially. Smoothness of treatment and elimination of side-effects, as above, were enhanced, however.

There appeared to be no special influence upon the time of recovery or the incidence of hypoglycaemic after-shocks, though on the whole these latter were not so severe.