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.

It is suggested, therefore, that in view of the above advantages hyaluronidase be given routinely in deep insulin therapy, even though the benefits do not appear to be as significant as was initially thought.

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Medical Memorandum

Inheritance of Human Cancer: Five Cases in One Family

Several extensive surveys have been published with regard to the inheritance of cancer. Some important records of pedigrees, showing apparent transmission from mother to daughter, were published nearly a century ago. The most remarkable were those recorded by Broca (1866), in which four generations of females had cancer of the breast. It is a point of general agreement amongst recent authors that mammary cancer is familiarly transmitted—Penrose *et al.* (1948a, 1948b) and Smithers (1948) following Wassink (1935) and Jacobsen (1946). But here uniformity ends, and a divergence of opinion appears on the issue whether cancer of other sites is increased in frequency amongst relations of patients with carcinoma of the breast. By Busck's (1948) computations on Jacobsen's (1946) results it has been demonstrated that close relatives of patients with mammary cancer show a significantly increased number of cancer cases.

In the family reported below there seems to be strong evidence that cancer of the breast is familial and does predispose to malignant tumours of other sites.

In this family of 10 children three sisters developed carcinoma of the breast proved by hospital records (Cases 1, 2, and 3). Patient No. 2 had two children—a girl (Case 4) who had fibrosarcoma of the right mandible, and a boy (Case 5) who died from hepatoblastoma of the liver. There was no history of cancer in any near relation of the father or mother, and no blood relationship between the parents.

CASE REPORTS

Case 1.—This patient was a married woman. There is one daughter, aged 16, alive and well and unmarried. The patient underwent right radical mastectomy on February 7, 1946. Pathological report: (1) solid and trabecular polygonal celled carcinoma of breast; (2) carcinoma infiltration of skin and nipple (Paget's disease and subadjacent breast tissue); (3) carcinomatous infiltration of ducts and lymphatics in surrounding tissue; and (4) secondary carcinoma in four axillary lymphatic glands. Operation was followed by radiotherapy. The patient was readmitted with extensive multiple secondary deposits (spine, pelvis, femora), and died on April 23, 1947, aged 29.

Case 2.—This patient, a sister of Case 1 and the mother of Cases 4 and 5, married at the age of 23. There was no blood relationship between her and her husband. Her first child (female) was born on March 28, 1943, and her second child (male) on June 19, 1948. The mother still remained fit, and breast-fed her second child for nine months. In 1949 she developed a lump in her left breast and attended hospital. She was operated upon in November, 1949, for carcinoma of breast. The appearances at operation were typically those of a scirrhous carcinoma. Operation was followed by radiotherapy. She died on October 3, 1950.

Case 3.—The 34-year-old married sister of Cases 1 and 2 had one child, a girl aged 9. Hospital notes reveal that she had an anaplastic carcinoma of one breast removed on August 24, 1955, and an adenocarcinoma of the other breast removed on September 15, 1955. At the time of writing she was having radiotherapy.

Case 4.—The elder child of Case 2, born March 28, 1943, had had chicken-pox, measles, and tonsillitis. Her tonsils and adenoids were removed in 1952. She remained very well and was examined in July, 1955, when she was fit. On September 5, while on holiday, she developed a swelling on the right side of her face. She returned home and was treated by her own doctor. The swelling did not respond to treatment and she was admitted to hospital. Investigations showed that the lump was a spindle-cell tumour with the morphology of a fibrosarcoma of the right mandible. A course of x-ray therapy caused little diminution in the size of the tumour. When last examined (February 27, 1956) she had lost weight and had a large hard mass over her right cheek extending below the jaw, over the parotid to the ears, and causing limitation in opening of mouth.

Case 5.—The younger child of Case 2, born June 19, 1948, had had whooping-cough, measles, mumps, and chicken-pox. When examined at school on March 30, 1954, he was found to be suffering from recurrent tonsillitis and earache. There was nothing else abnormal, and he had been referred to an E.N.T. surgeon for his opinion. In July, while on holiday, he developed severe abdominal pain and was admitted to hospital, where a large mass was discovered in his abdomen. In August a very large hepatoblastoma, very malignant in type, was removed from the right lobe of his liver. He received deep x-ray therapy and recovered sufficiently well to attend school for a short period. He developed ascites in February, 1955, and died on March 26.

COMMENT

This is a family of which three daughters developed the same type of carcinoma of breast at a very early age (29, 28, and 30 years respectively). In the second generation two children of the second daughter developed cancer at an extremely early age (6 and 12 years respectively). The hereditary basis in this particular family is indicated by the appearance of the same cancer in three daughters and by the early onset of cancer in the first and second generation.

Note: Since writing this memorandum Case 4 has died.

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