steatorrhoea, and other tests for absorption were normal. Her anaemia responded fully to folic acid, relapsed when she discontinued the tablets, and responded when she again took folic acid.

The impression gained from examination of the records of the 67 patients with oesophageal cancer was that they were all very sick people and that the pressing need for relief of oesophageal obstruction may have obscured less obvious symptoms. Furthermore, signs of underlying malabsorption states might easily have been attributed to starvation secondary to oesophageal obstruction. In particular, haemoglobin values may have been relatively high owing to dehydration and anaemia therefore missed.

Even when the possibility of malabsorption is considered in these cases, conventional investigation is difficult. It is impossible to perform peroral jejunal biopsy, and failure of patients to ingest a standard diet confuses interpretation of absorption studies.

Discussion

More is known about the aetiology of oesophageal cancer than about cancer elsewhere in the gut. Evidence incriminating alcohol is found in the Mortality Tables for 1921, 1931, and 1951 (Registrar-General, 1927, 1938, 1958). Our four cases are of interest in this respect, as none of them had any history of alcoholism. The evidence against tobacco is less convincing (Clemmesen, 1965), but in this context also our patients were relatively abstemious.

In achalasia the incidence of squamous carcinoma is high, but there is little evidence that peptic oesophagitis commonly complicating duodenal ulcer or hiatus hernia is a cause. The growths sometimes associated with hiatus hernia are normally adenocarcinomas and usually have a gastric origin.

The evidence for nutritional deficiency as a factor in oesophageal cancer is strong but non-specific. The curiously high incidence in parts of Africa (Hutt and Burkitt, 1965), part of the Chinese province of Honan, and the island of Curaçao is unexplained (Almy *et al.*, 1964). The high incidence in the Bantu reserve is apparently not related to general malnutrition, but it is obviously difficult to exclude some specific deficiency which affects the oesophageal mucosa.

In the five-year survey of the London Hospital cases of squamous carcinoma of the lower two-thirds of the oesophagus referred to above 12% of the patients had long-standing dyspepsia. If the single case of achalasia in which oesophageal stasis alone may be important is excluded it would seem that nutritional deficiency could have been significant in one-tenth of the series.

Iron deficiency has long been associated with postcricoid lesions, but the specificity of the relation has been questioned by Elwood *et al.* (1964). Iron deficiency could be presumed in our cases of steatorrhoea and was clearly present in Case 4, but, in contrast to the Patterson-Kelly syndrome, gross physical signs of iron deficiency were lacking, the anaemia was macrocytic or normocytic, and the growths were situated in the mid-oesophagus in all cases. In the circumstances we feel justified in concluding that, though iron deficiency may have been a factor in the genesis of carcinoma in these cases, some other nutritional deficiency may be more important.

Summary

Four cases of carcinoma of the thoracic oesophagus occurring in patients with malabsorption syndrome are reported. These cases differ from the Patterson-Kelly syndrome in several respects, and it is suggested that nutritional deficiencies other than iron may be of aetiological importance.

Over 10% of patients in a series of 67 cases of squamous carcinoma of the thoracic oesophagus had long histories of dyspepsia and possible nutritional deficiency.

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Preliminary Communications

Relation between Antibody and Insulin Dose

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Though antibodies to insulin constitute a recognized form of insulin resistance (Lerman, 1944; Skom and Talmage, 1958; Oakley *et al.*, 1959), all authors agree that insulin antibodies play no significant part in determining insulin dosage in the non-resistant diabetic patient (Moinat, 1958; Berson and Yalow, 1959a; Palumbo *et al.*, 1964a, 1964b). Recent observations from this laboratory (Devlin and Brien, 1965) on the preferential binding of beef, pork, dalanated (de-alaninated) pork, and human insulin by diabetic sera suggested that the role of antibodies in determining insulin dosage was probably more significant than has been hitherto accepted. The present work is an attempt to answer the question of whether antibodies

to insulin are a determining factor in insulin dosage in the non-resistant diabetic patient.

MATERIALS AND METHODS

Forty-two beef-insulin-treated diabetic patients were studied. Sex, age at onset of diabetes, and insulin dosage are given in Table I. The beef preferential binding capacity of the sera with reference to pork, dalanated pork, and human insulin was determined by the method previously described (Devlin and Brien, 1965), with the results shown in Fig. 1. This consists in determining the relative effectiveness of beef, pork, and human insulins to displace beef insulin, 1/125 from the sera tested. The relation between the predicted clinical effectiveness of pork insulin (relative to beef) obtained from the preferential binding-capacity studies and the actual effectiveness of pork insulin in 15 patients who were transferred from beef to pork insulin are shown in Fig. 2. Eight of

the patients were studied as inpatients, and in four of these the transfer from beef to pork insulin was carried out without previous knowledge by the clinician of the serological findings. Adequate control of diabetes was assessed in the usual manner by clinical well-being, urinary-glucose output, and repeated blood-glucose estimations. The mean beef, pork, and human requirements calculated from the mean preferential binding capacities are given in Table II. Human insulin assaying 23.5 μ /mg. was kindly donated by Dr. F. O. Mirsky, Pittsburgh, Pennsylvania. Pork insulin and dalanated pork insulin were kindly donated by Dr. J. D. Galloway, Lilly Research Laboratories, Indianapolis, Indiana.

RESULTS

As can be seen from Fig. 2, the laboratory findings of preferential binding of beef versus pork insulin agrees closely with the ascertained clinical requirements of pork insulin in beef-insulin-treated diabetic patients. The mean preferential binding of sera for beef insulin with reference to pork and dalanated pork insulin is similar, 1.6, 1.7 (Fig. 1), while the mean preference for beef versus human insulin is much higher, 2.55 (Fig. 1). The mean beef-insulin requirements of the diabetics under 40 was 92.5 units and of the maturity-onset

FIG. 1.—Preferential beef-insulin-binding factors of the sera tested with reference to pork, dalanated pork, and human insulins.

diabetics 43.0 units (Table II). With the exception of five patients, approximately 10% of those studied, all were stabilized on less than 100 units of insulin daily, and were not thought to be insulin-resistant.

DISCUSSION

This study is made possible by the species purity of British insulin, which is manufactured entirely from the ox pancreas. All diabetics studied were initially stabilized on beef insulin. The fact that the majority preferentially bind beef insulin is acceptable from previous studies on the antigenicity of heterologous and homologous insulins in experimental animals (Lockwood and Prout, 1965) and in isolated human subjects (Berson and Yalow, 1959b; Feldman *et al.*, 1963). The close correlation between the laboratory and clinical studies reported here (Fig. 2) confirms the pilot study reported previously (Devlin and Brien, 1965).

The difference in preferential binding capacity between the pork insulins and human insulins was highly significant ($P < 0.01$). In view of the fact that dalanated pork and human insulins are very similar, this shows the importance of the three-dimensional structure of the antigen (Berson and Yalow, 1963).

As the daily insulin requirements of the patients studied were less than 200 units in all except two, and less than 100 units in all except five, the observations relating to beef/pork insulin requirements apply to non-resistant diabetic patients. Insulin antibodies, therefore, do play a significant determining part in the insulin requirements of such patients. It has been shown by Palumbo *et al.* (1964a, 1964b) that the insulin

FIG. 2.—Correlation between predicted effectiveness (from beef/pork preferential binding ratio) and clinical effectiveness (ratio of beef to pork insulin dosage in units) in 15 beef-insulin-treated patients. The regression line is: $Y = 1.89 + 0.89(x - 1.9)$, $r = 0.992$.

TABLE I.—Sex Distribution, Age at Onset of Diabetes, and Insulin Requirements of Patients Studied

Sex		Age at Onset		Insulin Dose (Units)			
Male	Female	Under 40	Over 40	50	50-100	100-200	> 200
19	23	27	15	17	20	3	2

TABLE II.—Calculated Mean Pork and Human Insulin Requirements of Patients Studied

	Under 40 Years	Over 40 Years
Mean beef-insulin requirements (units) ..	92.5	43.0
Calculated pork-insulin requirements ..	57.8	26.8
human-insulin requirements ..	38.5	17.9

requirements of diabetic patients alter with changes in physiological stress without simultaneous alteration in insulin antibody levels. This does not of course prove that insulin antibodies do not influence the insulin requirements from patient to patient. The studies reported here, showing that the majority of beef-insulin-treated diabetic patients can be maintained on a smaller dose of pork insulin, which can be predetermined by preferential insulin antibody-binding studies, indicate that antibodies to insulin account for a fixed aliquot of the daily insulin requirement.

The immediate clinical problem raised by this study is the necessity to exercise caution in changing diabetic patients from a pure beef-insulin preparation to a pure pork-insulin preparation. The theoretical possibility of deliberately inducing bovine-insulin antibodies and subsequently altering to porcine insulin in view of the failure of porcine insulin to produce a primary antibody response under these circumstances (Devlin and Stephenson, 1966) must be considered.

SUMMARY

The majority of a beef-insulin-treated diabetic population preferentially bind beef, pork, and human insulins in the order beef>pork>human. The theoretical implications of this observation are briefly discussed.

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JAMES G. DEVLIN,* M.D., M.Sc., M.R.C.P.I.,
Consultant, Endocrine Immunology, St. Vincent's
Hospital, Dublin.

T. BRIEN,† M.Sc.,

N. STEPHENSON, B.Sc.,
Research Assistants, Department of Medicine and
Therapeutics, University College, Dublin.

* Wellcome Trust Research Fellow.

† Present address: Institute of Nuclear Medicine, the Middlesex Hospital, London W.1.

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Medical Memoranda

Case of Cobalt Poisoning

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The main therapeutic use of cobalt in large doses has been in the treatment of refractory anaemias, particularly associated with renal failure. While it is sometimes effective in raising the haemoglobin level, there have been several reports of toxicity (Gardner, 1953; Kriss *et al.*, 1955). The following case is reported because of the unusually widespread nature of the toxic effects of cobalt.

CASE REPORT

A 35-year-old spinster first began to feel unwell in January 1965, complaining of nausea, vomiting, and breathlessness on exertion. In June she was investigated at another hospital, and found to have a haemoglobin level of 9.3 g./100 ml. and a blood urea of 196 mg./100 ml. A diagnosis of chronic nephritis was made. The only history relevant to the genitourinary system was that of cystitis at the age of 18. She was treated with a 20-g. protein diet and calcium lactate. For the anaemia she was given cobalt chloride 25 mg. q.d.s.

She was fairly well until November, when she started complaining of paraesthesiae in her limbs, numbness and occasional cramps in her legs, and unsteadiness on walking. At the same time she developed a slowly progressive swelling of the neck and an increasing difficulty in hearing. She also had frequency of micturition and nocturia, occasional dizzy spells, and bouts of nausea and vomiting, and by January 1966 she had lost 2 stone (12.7 kg.) in weight.

On admission to hospital in January 1966 the cobalt chloride was discontinued after six months' treatment, when she had had a total dose of approximately 18 g. Clinical examination showed a diffuse goitre without signs of hypothyroidism, bilateral nerve deafness, absent ankle jerks, tender calves, and a loss of vibration sense in the legs. The urine contained a little albumin, and a positive Clinitest showed the presence of glucose.

Investigations.—Haemoglobin 14.6 g./100 ml.; blood urea 90 mg./100 ml.; serum calcium 8.3 mg./100 ml.; serum proteins—total 6.9 g./100 ml., albumin 2.9 g./100 ml.; serum cholesterol 242 mg./100 ml.

The glucose-tolerance test was normal, the fasting level being 76 mg./100 ml., with a maximum rise of 160 mg./100 ml. after half an hour. Radioactive iodine uptake carried out three weeks after stopping the cobalt was 77% in 24 hours. On repeating the uptake, 33% of radioactive iodine was discharged after giving 400 mg. of potassium perchlorate, indicating that there was a considerable amount of inorganic iodine in the gland. The urine was examined by chromatography and several amino-acids were identified, showing that these were increased generally. Audiometry demonstrated a general decrease of sound perception in all frequencies and caloric tests were also found to be abnormal. A diagnosis of chronic renal failure complicated by cobalt chloride poisoning was made.

During her stay in hospital the symptoms gradually improved, the goitre regressed in size, and she was walking better. Her dietary protein was increased to 40 g. daily and she was maintained on a high fluid intake.

The glycosuria persisted for a week after admission and then ceased. She was discharged from hospital in February, by which time her walking had greatly improved. In April the goitre had almost gone and she had no difficulty in hearing or walking. At that time the haemoglobin was 13.3 g./100 ml.; blood urea 90 mg./100 ml.; and chromatography of the urine showed no amino-acid, though the albuminuria persisted, and there was no discharge of radioactive iodine after administration of potassium perchlorate.

DISCUSSION

Cobalt chloride was first used therapeutically about 15 years ago as a haemopoietic in the anaemia of renal failure and other refractory anaemias. Though cobalt is often effective in raising the haemoglobin, its mode of action is not known, but it may act by causing direct anoxia of the bone-marrow cells by enzyme inhibition (Weissbecker, 1950).