commonly confused by patients and doctors with "the normal ageing process." However, Starr (1955) has commented: "Old people are not normally hypothyroid; middle-aged people should not be allowed to become hypothyroid." In approximately 90% of the cases in our series, the general practitioners referring the case did not suspect hypothyroidism. Most were sent as examples of heart failure, cerebral thrombosis, anaemia, or bronchitis, with a few labelled simply as "senile."

In our experience hypothyroid patients are almost always attractive people, and before the onset of their illness many of them were well known and liked in their circle for their mental and physical energy. When such people become "old" (hypothyroid) they are usually well supported by their relatives and friends, and this fact reduces their chance of recognition. There can be little doubt that many unrecognized cases of hypothyroidism are recorded as dying of uncomplicated cerebro-cardiovascular accidents. We have been unable to find a series in the literature which is comparable to ours in age distribution. This factor alone precludes a statistical comparison of incidence between our series and any of the published series. Our figures show a very high incidence of hypothyroidism (1.7% of new cases seen) in a relatively large sample of elderly people (3,417) referred to hospital in a period of two and a half years. It is of interest to note that we encountered more cases of hypothyroidism than hyperthyroidism; the ratio was 2.9:1.

Starr (1954) has suggested that the early stages of hypothyroidism are asymptomatic and has advocated estimation of serum P.B.I. as a routine screening test for all middle-aged and elderly patients. We attempted in every case to assess the duration of symptoms, but accuracy was not possible in this respect. The majority of cases indicated a duration of three to five years; as most of them had come to live with their symptoms the actual duration was probably much longer. It is interesting to speculate on the age at which our cases first became hypothyroid and whether adequate treatment with L-thyroxine from this point would have reduced or even prevented the arteriosclerotic complications which affected so many. We now have some experience of treating elderly hypothyroid patients who also exhibit evidence of myocardial insufficiency. A paper dealing with this subject is in preparation. In our opinion treatment of middle-aged or elderly hypothyroid patients should be undertaken with great care. If it is not possible for these patients to be seen frequently by a medical attendant and to rest physically during the initial few weeks of treatment, then treatment is best carried out in hospital. The decision to treat with thyroxine a middle-aged or elderly person showing signs of congestive failure or complaining of angina of effort should be taken only after the most careful assessment of cardiac and thyroid function.

Summary

Out of a total of 3,417 new patients referred to a geriatric unit during a period of two and a half years, there were 58 cases of hypothyroidism and 17 cases of hyperthyroidism. The incidence of hypothyroidism was 1.7% and of hyperthyroidism 0.5% of new cases seen. Details of diagnostic criteria and age distribution are given. It is suggested that hypothyroidism is a disease commonly confused with ageing.

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DIABETES MELLITUS AND PRIMARY CARCINOMA OF THE PANCREAS

BY

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Primary carcinoma of the pancreas has often been reported in association with diabetes mellitus (Urmy, Jones, and Wood, 1931; Pygott and Osborn, 1937; Llamas and Molina, 1955). Marble (1934), in an extensive study of diabetes, regarded the relationship as purely fortuitous, a view supported by Joslin, Root, White, Marble, and Bailey (1946) and Lawrence (1955). Bell (1957), in a review of necropsy records, showed that cancer generally occurred less often in diabetics, with the exception of cancer of the pancreas, where the incidence was twice as great as in non-diabetics. We have recently observed a case of sarcoma of the pancreas in a patient who first attended the diabetic clinic 15 months previously. This led us to review the case records of all patients with proved neoplasm of the pancreas and of all patients suffering from diabetes seen in this hospital during the years 1955–9. We have found that certain types of diabetes are closely associated with this condition.

Results

Of 65 patients suffering from primary neoplasm of the pancreas in the period under review, 10 (15.4%) also had diabetes mellitus. Table I shows that the diagnosis was confirmed at operation in 53 cases (81%), a positive biopsy being obtained in 35 (53.8%). Necropsy was performed in 19 cases (29.2%). The mean age was 64.2 years (range 40–81 years) and the ratio males/females was 2.1/1.

The symptoms thought to be due to carcinoma are arranged in order of frequency in Table II. The insidious nature of the disease may be judged by the mean duration of symptoms—5.8 weeks (range 1 day—

TABLE I.—*Sex Distribution of Patients with Carcinoma of Pancreas, Mean Ages, and Method of Confirming Diagnosis. The Number of Diabetic Cases is Also Shown.*

Year	No.	Male	Female	Mean Age	Diabetes	Operation	Biopsy	Necropsy
1955	9	8	1	61	1	8	6	3
1956	15	11	4	63	2	11	5	4
1957	17	8	9	66.5	3	12	9	6
1958	13	8	5	67.6	2	12	8	3
1959	11	9	2	61.2	2	10	7	3
Total	65	44	21	64.2	10	53	35	19

TABLE II.—*Frequency of Presenting Symptoms in Carcinoma of Pancreas*

Total No. of patients	65
Weight loss	52 (80%)
Jaundice	40 (61.5%)
Abdominal pain	36 (55.3%)
Back pain	16 (24.6%)
Diarrhoea	13 (20%)
Venous thrombosis	5 (7.7%)

15 months)—before admission to hospital, and the fact that only two cases were regarded as suitable for radical surgery designed to cure. The grave prognosis is emphasized by the evidence that 22 patients (33.8%) died in hospital on their first admission. Of the 65 patients with neoplasm of the pancreas, 10 also had diabetes mellitus, and all 10 were investigated in the metabolic unit. The diagnosis of diabetes was confirmed by the glucose-tolerance test. There is no record of the urine having been examined in four cases, two of the patients dying within 24 hours of admission to hospital.

Case Histories of Diabetic Patients

Case 1.—A man aged 69 attended the diabetic clinic and was found to have diabetes. One month after starting treatment he began to have abdominal pain. After another month he was admitted to hospital with obstructive jaundice. At laparotomy an inoperable carcinoma of the head of the pancreas was found, the diagnosis being confirmed by biopsy.

Case 2.—A woman aged 78 was admitted to hospital with weight, loss, thirst, and polyuria of about two months' duration and jaundice for one week. Diabetes mellitus was found, and later a laparotomy disclosed an inoperable carcinoma of the head of the pancreas.

Case 3.—A woman aged 72 was admitted with abdominal pain, the provisional diagnosis being subacute intestinal obstruction. The pain had been present for two weeks, but she admitted to having suffered from thirst and polyuria for five weeks. Diabetes mellitus was present, and subsequently a carcinoma of the body of the pancreas was seen at laparotomy.

Case 4.—A woman aged 75 was admitted, having had severe back pain, anorexia, and nausea for six weeks. Glycosuria was noted and the diagnosis of diabetes was later proved. Laparotomy showed an inoperable carcinoma of the body of the pancreas.

Case 5.—A man aged 62 had complained of polydipsia and polyuria for three months, and severe back pain for two months. He was admitted to hospital deeply jaundiced. A diagnosis of diabetes mellitus was established and treatment started, but he died after three days in hospital. Necropsy showed carcinoma of the pancreas with portal-vein thrombosis.

Case 6.—A woman aged 63 gave a history of thirst and polyuria for five weeks. Diabetes mellitus was confirmed, but three days after admission to hospital she became jaundiced. A tumour of the head of the pancreas was found at operation. She died one week later, and a necropsy was performed.

Case 7.—A man aged 63 was admitted for investigation of jaundice and diarrhoea which had been present for five weeks. Glycosuria was found and the presence of diabetes

mellitus established. At laparotomy a carcinoma of the head of the pancreas with metastases was seen. He died two weeks after operation, and a necropsy was performed.

Case 8.—A man aged 68 was admitted with jaundice of two weeks' duration. Diabetes mellitus was found in association with a carcinoma of the head of the pancreas.

Case 9.—A man aged 63 was admitted with a history of back pain, weight loss, thirst, and polyuria of several weeks' duration. Diabetes mellitus was found. A barium-meal examination showed distortion, widening, and irregularity of the duodenum consistent with a diagnosis of carcinoma of the pancreas. Operative intervention was refused, and he died three months later.

Case 10.—A man aged 70 attended the diabetic clinic in October, 1957, with a complaint of weight loss, thirst, and polyuria for six weeks. Diabetes was diagnosed, and he was stabilized on 15 units of I.Z.S. In March, 1959, he was admitted to hospital complaining of increasing abdominal distension for one month. A large, smooth, firm, fixed swelling was present in the abdomen. Barium studies and pneumoperitoneum suggested a pancreatic cyst. There had been no deterioration in his diabetic state although he had clearly lost weight, accurate estimation being impossible owing to ascites and oedema. At operation in April, 1959, an extensive neoplasm replaced the pancreas, extending to the hilum of the spleen and infiltrating the duodenum. Histologically the tumour was a spindle-cell sarcoma (leiomyosarcoma) thought to be of relatively low-grade malignancy. No definitive procedure could be performed, and the patient died at his home two months later, 20 months after the discovery of diabetes.

In all these cases, except the last, symptoms of diabetes preceded by a few weeks those ascribable to neoplasm of the pancreas, or the diabetes was discovered incidentally on admission without any clear history of the typical symptoms. All patients were over 60 years of age and none fell into the category of obese diabetics. The diabetic state was assessed as mild to moderate, never severe, and a family history of diabetes was not present in any of these cases.

In Table III are recorded the number of new diabetics in age-groups seen in this region during the years 1955–9. 729 patients were found to be suffering from this condition in a population of approximately 400,000, an incidence of 0.03% new cases a year. The incidence of diabetes in this region has been calculated as 0.75% (A. Lyall, 1960, personal communication). Cancer of the pancreas is rare before the age of 40 years (Bell, 1957). In Table IV are shown the numbers of stable and unstable diabetes in age-groups from 40 to 70+ years,

TABLE III.—*Age Distribution of New Cases of Diabetes, 1955–9*

Year	<20	20–29	30–39	40–49	50–59	60–69	70+
1955	5	8	10	23	57	43	27
1956	5	9	11	26	39	48	21
1957	8	5	6	19	35	39	26
1958	2	5	3	11	35	40	35
1959	4	7	3	12	29	50	23
Total	24	34	33	91	195	220	132

TABLE IV.—*Incidence of Stable (S) and Unstable (U) Diabetes and Carcinoma of Pancreas (C) in Patients Over 40 Years*

Year	40–49			50–59			60–69			70+			Total		
	S	U	C	S	U	C	S	U	C	S	U	C	S	U	C
1955	15	8	—	54	3	—	41	2	1	27	—	—	137	13	1
1956	20	6	—	35	4	—	46	2	—	19	2	2	120	14	2
1957	16	3	—	35	—	—	34	5	3	24	2	—	109	10	3
1958	9	2	—	34	1	—	36	4	2	35	—	—	114	7	2
1959	10	2	—	27	2	—	48	2	1	21	2	1	106	8	1
Total	70	21	—	185	10	—	205	15	7	126	6	3	586	52	10

Carcinoma of the pancreas occurred only in unstable group.

together with cases of neoplasm of the pancreas. Stable diabetes is the accepted classification where the patient is overweight, and is relatively insulin-resistant, with no tendency to ketosis or ketonuria. On the other hand, unstable diabetics are usually underweight, with a tendency to ketosis and ketonuria, and are relatively insulin-sensitive. No case of pancreatic neoplasm occurred in a stable diabetic. Of 52 cases of unstable diabetes, 21 occurred in patients aged 60 and over and 10 (48%) of these had a primary neoplasm of the pancreas. We conclude that patients of this age-group found to be suffering from diabetes of the unstable type should be suspected of harbouring a pancreatic neoplasm until proved otherwise.

Discussion

The case records show that cancer of the pancreas is commonest in the sixth decade, the usual male/female ratio being 3/1 (Aird, 1957). The mean age in our patients (64 years) is higher than the 56 years reported by Berk (1941), and this may have an important influence on the association with diabetes which we have noted. The presenting symptoms, with the exception of those common to diabetes, conform to the accepted generality, the frequent occurrence of pain with jaundice being a noteworthy contradiction of older textbook references to painless jaundice in this condition. Back pain, emphasized by Silver and Lubliner (1948), was a prominent feature in 23%. Sproul (1938) noted the frequent occurrence of venous thrombosis in tumours affecting the body and tail of the pancreas. This occurred in five of our patients—carcinoma involving the body in two and affecting the tail in three, one of these being in a subject suffering from concomitant diabetes.

Wilder (1940) suggested that cancer in the diabetic population was increasing, with carcinoma of the pancreas assuming greater proportions. Ellinger and Landsman (1944) have made similar observations, and Ingelfinger (1946) thought that this relationship between pancreatic carcinoma and diabetes was more than a casual one. Marble (1934) found a high incidence of pancreatic neoplasm in 10,000 diabetic patients and noted that the diabetes frequently preceded the carcinoma, often by a number of years. Bell (1957) found that the incidence of cancer is lower in diabetics than in non-diabetic subjects, with the exception of cancer of the pancreas and to a less extent cancer of the colon. Cancer of the large intestine is the commonest form of neoplasm in diabetic subjects, but the incidence of cancer of the pancreas in diabetics is more than twice that of the general population.

Bell (1957) calculated from several reports that the incidence of diabetes in 390 patients with cancer of the pancreas was 7.7%. Green, Baggenstoss, and Sprague (1958) found that 4.3% of 209 cases had previously been diagnosed as diabetic, the average duration of the disease being 9.7 years. In 15.3% of their cases the diagnosis of diabetes was made after the appearance of symptoms ascribed to carcinoma of the pancreas. In our cases, with the exception of the patient suffering from sarcoma, diabetes was discovered at the time of admission to hospital as a result of symptoms produced by the carcinoma, or the diabetic symptoms preceded this by a few weeks only. Thus there are two types of association: (a) cancer of the pancreas developing in patients who have suffered from diabetes for some years, and (b) cancer of the pancreas accompanied by

diabetes of recent onset. Most of our cases appear to belong to the second group. Diabetes of recent onset was found in 15.3% of cases of neoplasm of the pancreas, a figure identical to that of Green *et al.* (1958). The incidence of cancer of the pancreas in 729 new diabetic subjects seen in this region in the five-year period is 1.3%, and if only those patients over 40 years of age in the carcinoma of the pancreas age-group are included this rises to 1.8%. When patients over the age of 40 with diabetes are classified as stable and unstable it is clear that cancer of the pancreas affects the latter group to such a degree that it suggests cause and effect.

It is rare for primary carcinoma of the pancreas associated with diabetes to cause a significant reduction of the islet cell tissue (Aird, 1957). It is even more remarkable that secondary carcinoma of the pancreas (which is not uncommon) has seldom been found to be associated with diabetes. Willis (1952) reported a case where this occurred from a primary tumour of the ovary in a patient who suffered from diabetes for two years. Cutforth and Powell (1958) described a case where secondary deposits from a carcinoma of the bronchus had destroyed about 80% of the pancreas. The first symptoms of illness occurred five weeks before death, and were those of combined diabetes and respiratory disease.

Sarcoma of the pancreas is a rare condition (Hendry, 1952), though one diabetic subject with a leiomyosarcoma has been reported by Ross (1951). The case we record appears to be the second showing this association, and the relatively slow-growing tumour suggests a direct relationship though we have no histological evidence to support it. This cannot, however, be held to account for the relationship between the two conditions in the remaining cases, and the aetiology of the almost synchronous appearance of the two conditions in many cases remains obscure.

It is evident that careful consideration should be given to patients in the older age-groups presenting with diabetes of the unstable type, for the incidence of carcinoma of the pancreas in these patients is high. Schlesinger, Schwarz, and Wagenvoort (1960) have reached a similar conclusion in a recent study.

Summary

Carcinoma of the pancreas and diabetes mellitus are often associated. In patients who develop diabetes late in life, who are not obese, and who have no positive family history of this complaint, a full investigation should be performed to exclude pancreatic neoplasm.

A case of leiomyosarcoma of the pancreas associated with diabetes mellitus of recent onset is reported.

We are grateful to Dr. A. Lyall, consultant in charge of the diabetic clinic, for his encouragement to publish this report and for the data compiled in Tables III and IV. We are grateful to Mr. A. Fowler, consultant surgeon, for permission to publish details of Case 10.

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INHERITANCE OF HAEMOCHROMATOSIS

A REPORT ON A FAMILY WITH CONSANGUINITY

BY

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Idiopathic haemochromatosis results from an inborn error of metabolism in which excessive absorption of iron from the gut leads to massive deposition of iron throughout the body. Although the disease usually occurs sporadically, a familial incidence is now well recognized, and has been reported on a number of occasions (Sheldon, 1935; Lawrence, 1935, 1949; Nussbaumer *et al.*, 1953; Houston and Zilkha, 1955; Houston, 1957; McAlpine, 1959). The consanguinity of the parents has received attention in only one of these papers (Nussbaumer *et al.*). The familial incidence is of considerable importance, as it must be taken into account in any theories on the aetiology of this disease.

This paper reports a family in which a brother and sister have the disease and another sister, otherwise well, has a raised serum iron. Consanguinity is present, the patients' mother having married an uncle. The family pedigree is:

Case Report

A housewife aged 55 was seen in August, 1960, complaining of fatigue and intermittent diarrhoea for four months. Her husband said that she had become increasingly forgetful and lethargic over the previous 12 months, often forgetting her shopping and other household duties. Menstruation started when she was 13 and was scanty, seldom lasting more than two days (her sister gave a similar menstrual history). The menopause was at 48. Her past medical history was not helpful. She had lived a good deal of her life abroad as her husband was in the consular service, and during a two-year stay in the Far East had been taking oral iron for an unspecified illness.

Family History.—The pedigree shows a brother (III 1) who died in France in 1948 when he was 43 and who had been treated in a Parisian hospital for diabetes and hepatic cirrhosis during the war. His sisters said he had always been a "funny colour." Another brother (III 5) was a deaf mute and at the time of writing was still alive in France, but nothing further was known. A sister (III 4) died of an infection aged 7, and another sister (III 3) has been examined and found to have slight pigmentation of the forearms and a serum iron of 232 $\mu\text{g./100 ml.}$ The iron-binding capacity was fully saturated. Both the patient (III 2) and this sister are married, and each has a son. Neither of these boys has evidence of haemochromatosis. The patient's son (IV 1) had a serum iron of 60 $\mu\text{g./100 ml.}$ and her nephew (IV 2) had a serum iron of 158 $\mu\text{g./100 ml.}$ The iron-binding capacity was 330 $\mu\text{g./100 ml.}$, and the glucose-tolerance test normal. The patient's parents are both dead. The mother (II 1) died aged 80 of carcinomatosis after a carcinoma of the breast. No other abnormalities were noted during life; necropsy was not performed. The father (I 1) died aged 75 from coronary thrombosis and carcinoma of the bladder. Necropsy showed chronic venous congestion of the liver and histological changes of an early mild portal cirrhosis. He was not a diabetic.

Examination.—There was a slaty-grey pigmentation, especially on the face, neck, and forearms. Axillary and pubic hair was scanty, and numerous spider naevi were present over the arms and chest. The liver and spleen were both palpable two fingerbreadths below the costal margin, and felt very hard. No clinical abnormality was present in the other systems. The urine contained a trace of albumin and 2% sugar.

Investigations.—Blood count: Hb 85%; W.B.C. 4,200 (normal differential); E.S.R. 36 mm. (Wintrobe). Blood sugar 240 mg./100 ml. Serum iron 330 $\mu\text{g./100 ml.}$ I.B.C. fully saturated. Liver-function tests: total proteins 6.7 g./100 ml. (albumin 4.5 g., globulin 2.2 g.), electrophoretic strip showed some increase in α_2 -globulin. Flocculation tests normal. S.G.O.T. 75 units/ml. S.G.P.T. 58 units/ml. E.C.G.: sinus rhythm; rate 66/min.; P-R 0.2 second; inverted T waves in leads II, III, aVF, and VI-6; R-T segments depressed in II and III, and raised in V4-6. Liver biopsy: there was a well-established fibrosis of the interportal connective tissue and fibrous distortion of the lobes; both connective tissue and hepatic cells contained excessive deposits of coarse haemosiderin; haemofuscin not evident. Skin biopsy: pigmentation of basement membrane of sweat glands, but diagnostically inconclusive. Marrow puncture: normal cytology; granules of free iron pigment were scattered sparsely between the cells, and a few intracellular aggregations were present; the total amount was small. C.S.F.: normal manometrics and cells, etc.; glutamine level 22.7 mg./100 ml. Urine 17-ketosteroids 0.8 mg./day. Keplær coefficient 8.8. Urine 17-ketosteroids 8.3 mg./day after 20 units of A.C.T.H. for seven days. Fishbach and Rous tests both negative. X-ray examination of chest and skull showed nothing abnormal. Straight x-ray film of abdomen showed some splenic calcification, but the hepatic shadow was normal.