Case 2.—A patient aged 34 was suffering from severe pain in the right side of the thorax, which radiated into the right hypochondrium. *X*-ray examination revealed no pulmonary lesion, but the right dome of the diaphragm was raised and moved imperceptibly with respiration. A diagnosis of subdiaphragmatic disease, most probably amoebic hepatitis, was made, and examination of the stools revealed the presence of *E. histolytica*. After five days' treatment with 400 mg. of furazolidone per 24 hours the chest pain disappeared and the diaphragm was moving almost normally. After a further five days' treatment the patient was very much improved, and no amoebae could be found on repeated examination of the stools. The curative value of furazolidone in this case is certainly not established, and investigations are still in progress.

Discussion

Of a total of 58 patients suffering from diarrhoea due to various causes, 54 were restored to normal within a week of being treated. There is no doubt that some patients may have been cured without chemotherapy, particularly those in whom no growth of pathogenic bacteria could be obtained from the stool before beginning treatment. In my experience the rate of cure for all the patients was most satisfactory and compared favourably with the results previously obtained with antibiotics and sulphonamides.

Twelve patients suffering from salmonella infection responded most promptly to treatment, and within a day or two there was great relief from the muscular aches, fever, diarrhoea, and tenesmus with which this infection is associated. Some of these patients had previously been treated with other measures to which they had not responded. Nine patients with shigella infections were passing characteristic dysenteric stools with mucus and blood when treatment was begun, and a gratifying response was noted within 8 to 10 hours of beginning therapy. Clinically, the patients soon felt very much better, and within 24 hours the stools began to lose their liquid character and developed a more normal colour and consistency. On the average, within three days most patients were subsequently very much better, and once the stools had been reduced to a normal number each day the patients were much improved, but still very weak. It must be stressed that treatment does not cease with the relief of symptoms. Patients require subsequent management with adequate diet and fluids before they are able to return to full employment. This is a common finding with most acute illnesses in my practice, and is certainly due to the normal physical condition of the patients even when no dysenteric infection complicates their living conditions.

It is interesting that seven patients suffering from *G. lamblia* infection responded most satisfactorily to furazolidone after other measures had failed. The four patients suffering from *E. histolytica* infection responded satisfactorily to the treatment, but it is, however, most common to find that in cases of amoebiasis a superimposed infection with a dysentery-producing organism is present. It is clear that furazolidone will readily control the superimposed infections in amoeba-infested patients. Case 2, with the presumed diagnosis of amoebic hepatitis, responded extremely well to furazolidone, as did the other three patients with amoebic colitis. It is far too early to comment on the possibilities of furazolidone in the control of amoebiasis itself, and investigations are being continued. I have no information to offer on sigmoidoscopic examination of the intestinal wall of these four patients, and it is essential that a detailed investigation into this disease should be made.

The side-effects of treatment with furazolidone are said to be nausea and vomiting. It is very difficult to know how serious these may be, because most of my patients presented initially with nausea and vomiting as symptoms of the infection. Only one patient was unable to take the tablets, but none of the others complained of any untoward effects which could be attributed to the drug in question. The results in a group of patients where the pathology is not always simple have encouraged me to continue with this work, and I hope to report later in more detail on certain aspects of what is one of our major problems—amoebiasis.

Summary

58 patients suffering from diarrhoea due to a variety of causes were treated with a new preparation, furazolidone.

The results have shown that furazolidone is a convenient and valuable addition to the drugs available for the treatment of these conditions.

The possibility of the value of furazolidone for the treatment of amoebiasis is being pursued.

I thank Messrs. Smith Kline and French Laboratories Ltd. for the supply of furoxone, and am grateful to Mr. P. Lizioli, of Pharmed Private Ltd., Bombay, for his assistance and co-operation.

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TUBEROUS SCLEROSIS ASSOCIATED WITH SPONTANEOUS HYPOGLYCAEMIA

BY

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Tuberous sclerosis is a rare familial disease of protean manifestations, involving primarily the skin and the nervous system. The characteristic sclerotic patches, to which the disease owes its name, were first described by Bourneville in 1880, and the classical triad of epilepsy, mental retardation, and adenoma sebaceum which characterizes the disorder has been recognized since 1908 (Vogt, 1908). Until then no certain diagnosis had been made in life.

While tuberous sclerosis is often referred to as one of the neuro-cutaneous syndromes, other tissues are often involved. Since the term tuberous sclerosis refers primarily to the changes in the brain, a broader term—"tuberous sclerosis complex" (Moolten, 1942)—is employed to denote the coexistence of tumour-like formations in other organs, notably the skin, heart, kidneys, retina, thyroid, breast, duodenum (Russell

Brain, 1955), large bowel (Budenz, 1950), adrenals (Murphy *et al.*, 1958), bones (Berland, 1953), and lungs (Dawson, 1954).

Though some textbooks (Allen, 1951; Harrison *et al.*, 1958) mention the pancreas among the manifold internal organs involved in this disease, we have found in the literature no reported cases of tuberous sclerosis where the pancreas was affected; the absence of such reports was also stressed by Pagenstecher in his review of the literature on the subject published in 1955.

The following report concerns a case of tuberous sclerosis associated with a secreting adenoma of the pancreas.

Case Report

The patient, an unmarried woman 24 years old, was the second of three children. There was no kinship between her parents; she was born after an uneventful pregnancy and a normal delivery.

At the age of 3 years she had convulsions, not typical for epileptic seizures. Since then the family noticed some degree of mental retardation. Nevertheless the child was enrolled in a regular public school, and not until the age of 9 was she transferred to a school for retarded children, which she left at the age of 12 because she was unable to keep pace with the class. Since early childhood she has loved music, and though she has been unable to learn to read a musical score she plays the piano well, and was pronounced by her teachers to have a sense of absolute pitch.

When she was aged 18, epileptiform seizures appeared, most often in the early morning, between 4 and 6 o'clock. The seizures began with agitation, groaning, and jumping on the bed; then stiffness of the extremities developed and the patient's face grew livid, almost black. A few times involuntary micturition occurred; sometimes she bit her tongue, and once foam appeared on her lips. The most intense seizures occurred during her menses.

At about the same time her father noticed that she sweetened her tea excessively, taking up to six teaspoonfuls of sugar to a cup. She started to sleep very late and would oversleep for hours if not wakened. Eventually the father found that he could wake her by forcing some sweet liquid into her mouth.

The patient was admitted on September 30, 1956, to the Psychiatric Hospital, Talbieh, in Jerusalem, for investigations. On admission she looked her age, behaved strangely, was very agitated, and was anxious to return home. Small reddish-brown spots were noted on her cheeks and chin. All over the body signs of folliculitis were seen. Routine laboratory studies showed no pathological findings, and the neurological examination was normal. A skin biopsy from the face showed a large amount of sebaceous glands. Fasting blood-sugar values were 40–60 mg./100 ml.; the glucose-tolerance curve was as follows: 0 min., 40; 30 min., 104; 60 min., 125; 120 min., 124; 150 min., 90; 180 min., 50 mg./100 ml.

The patient was transferred to Medical Department A of the Hadassah Hospital, Jerusalem, with the diagnosis of tuberous sclerosis, grand mal, and suspected hypoglycaemic crises. The possibility of an insulinoma was raised and a laparotomy suggested, but she had to be discharged a few days after admission because of the Sinai campaign.

During the next two years the frequency of the seizures increased until they became almost daily occurrences; the patient's mental state deteriorated and she put on weight. She was admitted to the Beilinson Hospital on August 26, 1958.

Physical examination showed an obese female with a dull facial expression. Her speech was slow and infantile, and she had no ability for simple arithmetic. Nor did she show any comprehension of her surroundings. Greasy reddish-brown papules, 1–5 mm. in diameter, were scattered in a butterfly pattern over the bridge of the nose and nasolabial folds. Over the breasts and back there were numerous café-au-lait spots.

Laboratory studies showed a normal haemogram. Blood urea was 24 mg./100 ml., and blood cholesterol 205 mg./100 ml. The liver-function tests were normal, and so were the serum electrolytes and proteins. Analysis of urine showed a normal specific gravity, no proteinuria, and no cellular elements or casts. The urinary 11-ketosteroids were 7.2 mg./24 hours and 11-oxysteroids 1.2 mg./24 hours. Ophthalmoscopy showed normal eye grounds, and the electrocardiogram and encephalogram were normal.

Radiographic Studies (Dr. H. Salinger).—The chest radiograph showed clear lung fields. Antero-posterior and lateral views of the skull were normal; there were no signs of erosion of the sella. Pneumoencephalography did not reveal signs of a space-occupying lesion, nor were any abnormalities of the cerebral vessels seen. Examination of

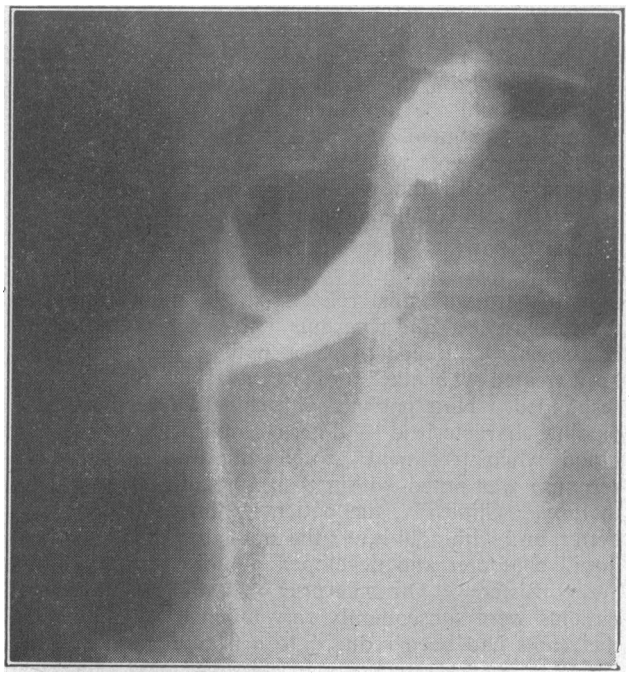

FIG. 1.—Retrograde pyeloscopy of right kidney; side view showing cysts in the renal parenchyma.

the gastro-intestinal tract did not show signs of a pancreatic tumour or of an increase of the mass of the pancreas. Intravenous pyelography showed both kidneys to be of normal size, but the upper and middle calices of the right kidney were elongated and crescent-like, most probably owing to pressure of cysts or expansively growing tumours; the outline of both adrenals appeared normal. This finding was corroborated on retrograde pyeloscopy of the right kidney; a side view (Fig. 1) showed that the cysts were situated ventrally, in the renal parenchyma.

Several biopsies of the skin lesions of the face showed a conspicuous increase of sebaceous glands only. Another biopsy of a facial nodule showed a small subcutaneous tumour (Fig. 2) with large, polyhedral, sharply demarcated clear cells (Fig. 3). This tumour was diagnosed (Dr. J. Casper) as sebaceous adenoma. In another nodular lesion of the face lymphangiectasia was seen.

Studies of the Carbohydrate Metabolism.—During the patient's stay in hospital we witnessed many seizures, which usually occurred around 4 a.m., while she was asleep. She became gradually agitated and started to toss in bed. Her pulse increased to 120/min., but the blood-pressure remained normal—110/70. Clonic movements of the extremities appeared, and passed rapidly into a state of utmost rigidity. A few teaspoonfuls of sweet tea terminated the seizures, and, without waking up, she passed

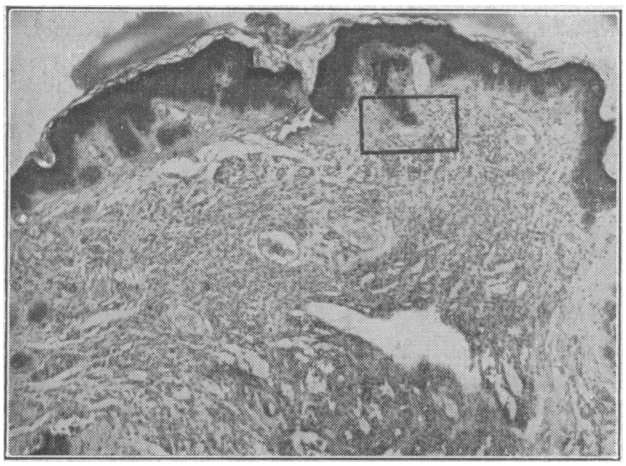

FIG. 2.—Small sebaceous adenoma. (Haematoxylin–eosin. Approx. ×20.)

into a quiet, deep sleep. Repeated blood samples during the seizures showed sugar values of 37–46 mg./100 ml. Fasting of 24 hours invariably released a seizure.

During one of the seizures arterial blood was drawn for estimation of insulin activity of the plasma. The determination (Dr. J. Groen, the Medical School, Jerusalem) was carried out by comparing the effect of the patient's serum, diluted with buffer solution, on the glucose uptake of the isolated rat diaphragm (Groen *et al.*, 1952), with the effect of insulin solutions of known strength on the glucose uptake of the other half of the diaphragm. Her serum had a significantly higher insulin content than 10 milliunits per ml., possibly somewhere between 20 and 50 milliunits per ml. The upper limit for normal ever found was 3 milliunits per ml. (variation of normal 0.1–3.0 milliunits/ml. (Groen *et al.*, 1958)).

Clinical Course.—A laparotomy was performed by Dr. P. Nathan on October 30, 1958, and a round cherry-red tumour, about 3 cm. in diameter, was removed from the body of the pancreas. Palpation of the kidneys disclosed many cysts of various sizes on both sides.

The insulin content of the tumour was determined (Dr. J. Groen), but for technical reasons this was done only after six weeks of refrigeration. The insulin content was found to be 1.6 u./g. of tissue by the ordinary mouse assay method, and 1.0 u./g. by the rat-diaphragm technique. These values are not above those of the insulin content of normal pancreatic tissue (Wrenshall *et al.*, 1952); possibly the insulin content of the tumour may have decreased during the refrigeration period.

Histological examination (Dr. Y. Boss) showed the tumour to be a well-encapsulated islet-cell adenoma of the pancreas, 1.8 × 3 cm. in size, with the typical structure of an incretory organ tumour (Fig. 4), partly with a distinct tubular pattern. No mitoses and no atypical cells were found. Aldehyde fuchsin (Gomori) and chrome alum hematoxylin phloxine (Gomori) stain (Lillie, 1954) showed a relatively small number of cells with fine violet and blue granules respectively, indicating beta cells.

Since the operation (a follow-up of four months) the patient has had no seizures, and supported uneventfully a 36-hour fast, which would have been unthinkable before the operation. The blood-sugar value at the end of the fast was 98 mg./100 ml.

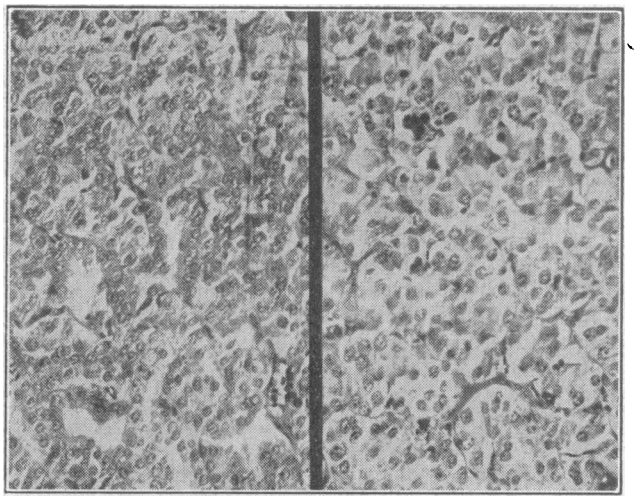

FIG. 4.—Islet-cell adenoma of pancreas: (*a*) typical structure of an incretory organ tumour; (*b*) tubular pattern. (Haematoxylin–eosin. Approx. ×80.)

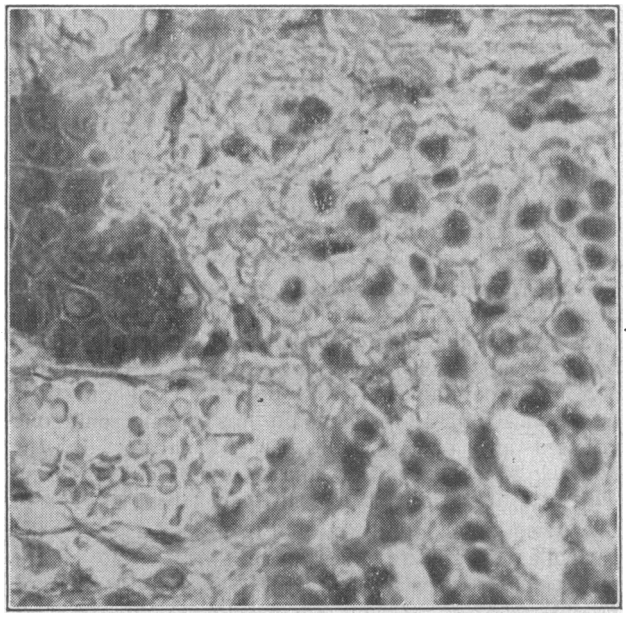

FIG. 3.—High-power view of Fig. 2. The tumour cells of the sebaceous adenoma: large, polyhedral, sharply demarcated clear cells. (Haematoxylin–eosin. Approx. ×190.)

Discussion

The clinical diagnosis of tuberous sclerosis is possible if two or more of the following features can be demonstrated: mental retardation, epilepsy, adenoma sebaceum, phakoma of the retina, multiple mixed tumours of the kidneys, and a familial history of the disease (Moolten, 1942).

The case described showed the following features: mental retardation, grand mal, adenoma sebaceum, and multiple cysts of the kidneys. Therefore it seems to us that the diagnosis of tuberous sclerosis is unquestionable. Tumour-like changes of lymph vessels and blood vessels are known to be associated with tuberous sclerosis (Allen, 1951).

The grand-mal seizures were not of cerebral origin, but proved to be precipitated by spontaneous hypoglycaemia. The elevated serum insulin activity strongly suggested that the hypoglycaemia was due to an insulin-producing tumour of the pancreas (Groen *et al.*, 1952; Vallance-Owen *et al.*, 1955; Willebrands and Groen, 1956). After the excision of the tumour the seizures did not recur during a follow-up period of four months.

The incidence of tuberous sclerosis with mental defect is about one in 300,000 in the general population

(Dawson, 1954), and secreting islet cell tumours of the pancreas are not a common phenomenon. Therefore it would seem that the coexistence of both diseases would not be a mere coincidence. Though this case is, to our knowledge, the first of this kind reported, the possibility may be raised that in a certain number of cases of tuberous sclerosis the "epilepsy" may be caused by an insulin-secreting pancreatic tumour. An appropriate clinical investigation, followed by surgery, may relieve the patients of one of the aggravating symptoms of the disease.

The possibility of involvement of the pancreas in some cases of tuberous sclerosis was raised by Pagenstecher (1955). He reported that an elder brother of a patient with tuberous sclerosis died suddenly at the age of 21 while serving in the Navy. The primary pathological diagnosis at necropsy was acute pancreatic necrosis, and the necropsy report read, in part: "The pancreas is normal in size. It is soft to the point of liquefaction, especially in the body. It is markedly hyperaemic, with hyperaemia not extending past the capsule. Some lobules are preserved. There is no evidence of calculi of the ducts." The author speculates on the possibility that a sudden change in a hypothetical (tubero-sclerotic) lesion, like rupture of a cyst or obstruction of a small duct, could have caused the acute necrosis, while the quick digestion of the tissues by the pancreatic enzymes destroyed all histological traces of the causative mechanism.

It should also be mentioned that van der Hoeve (1933) reported the occurrence of pancreatic cysts in von Recklinghausen's disease, which shows a close relationship to tuberous sclerosis (Lillie, 1954; Wechsler, 1958).

Summary

A case of tuberous sclerosis, marked by frequent epileptiform seizures, associated with spontaneous hypoglycaemia, is described. The patient was operated on and an islet-cell adenoma of the pancreas was removed. Elevated insulin activity in the serum was found. Since the operation the patient has been free from seizures. The possibility of a pancreatic tumour as an aetiological factor of the epileptiform seizures in some cases of tuberous sclerosis is discussed.

We are particularly indebted to Dr. J. Groen, of the Medical School in Jerusalem, for the determination of the insulin content of the serum and the tumour, and to Dr. H. Winnik, of the Psychiatric Hospital Talbieh in Jerusalem, for putting the case records at our disposal. We also wish to express sincere thanks to Mrs. Kaye Norton for producing the illustrations.

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PROCHLORPERAZINE AND IRRADIATION SICKNESS

BY

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A trial is described in which prochlorperazine is compared with pyridoxine and an inert tablet for the relief of side-effects due to therapeutic irradiation.

Prochlorperazine ("stemetil") is a brand of 1-[3-(3 chloro-10-phenothiazinyl)propyl] - 4 - methylpiperazine. This drug is one of the many new anti-emetic preparations now available. It resembles chlorpromazine in its range of pharmacological action, differing, however, in that it is several times more effective as an anti-emetic, but less active in reducing conditioned and instinctive reflex activity and in enhancing the activity of hypnotics and analgesics.

The most distressing side-effects associated with therapeutic irradiation are nausea and vomiting rather than any local reaction at the site of treatment. Anorexia and lassitude may accompany the symptoms of nausea and vomiting, or may occur alone.

Until recently the drug most commonly used in the control of these side-effects was pyridoxine (vitamin B_6), and some authorities have claimed relief of symptoms in a large percentage of cases (Shorvon, 1949; Ellis and Stoll, 1952; Stoll, 1957).

With the advent of a number of anti-emetic drugs having a primarily central action on the "vomiting centre," the suppression of the side-effects of irradiation has become easier.

Stoll (1957) compared a number of these drugs with pyridoxine and discussed their mode of action in the treatment of irradiation sickness. Prochlorperazine was not included in this trial. The use of prochlorperazine has been investigated in the control of vomiting due to a number of unrelated causes (Gray, 1957), and has been compared with chlorpromazine and other drugs in the suppression of artificially induced vomiting in experimental animals (Ducrot and Koetschet, 1956; Boyd, 1957). Ducrot and Koetschet (1956) found that prochlorperazine was four times more effective than chlorpromazine and superior to any of the other drugs used.

As pyridoxine was found to be relatively ineffective in reducing irradiation sickness, a trial series of patients were given 10 mg. of prochlorperazine orally thrice daily before meals prior to the first exposure to irradiation, and were maintained on this dosage throughout their treatment. Of 12 patients on this regime, only one vomited and one developed slight nausea. It was decided to compare the efficacy of prochlorperazine with that of pyridoxine and an inert tablet.

Method.—For uniformity, two tablets of the particular drug were given three times a day before meals. This gave a total daily dose of 30 mg. of prochlorperazine, 60 mg. of pyridoxine, or six inert tablets. The tablets were made up in anonymity, being labelled: A, B, and C; the only person knowing which was which being the pharmacist. Patients were selected