were small indefinite, firm, pale-yellow areas. Microscopically, the testis showed normal senile atrophy while the yellow areas showed masses of cells arranged in the classical rosette pattern of an argentaffinoma. The affinity of these cells for silver was confirmed.

The patient was readmitted three months later for further investigations in an attempt to find the site of the primary growth in the hope that it would prove removable. He then considered he was quite well. (Only after the second operation did he realize in retrospect that he had had some constipation and colicky abdominal pain.) Complete x-ray examination of the chest and alimentary tract revealed no abnormality; nevertheless, a laparotomy was performed and the terminal 3 ft. (0.9 m.) of small intestine was seen to be studded with about 60 white plaques varying in size from 0.2 to 2 cm. in diameter, distributed at random beneath the serosa. The smaller ones produced little or no puckering of the serosa, while the larger ones caused gross puckering and marked stenosis of the intestine. There was a smooth mass 5 cm. in diameter replacing the lymph nodes in the mesentery, and several small secondary deposits were felt in the liver. Three feet (0.9 m.) of intestine and the mass in the mesentery were removed and a side-to-side anastomosis was performed in order to relieve the partial obstruction.

Photograph of part of the specimen bisected to show three tumours under the muscularis mucosa, one producing stenosis and a portion of the secondary mass in the mesentery.

Recovery was uneventful, and two years later, in 1946, the patient had put on weight and felt better than before the operation. Clinical, x-ray, and laboratory examinations then showed nothing abnormal. He died in 1947, three and a half years after the original operations, after a short terminal illness. The death certificate states that the cause of death was due to "myocardial degeneration due to secondary carcinoma," with "generalized oedema of the limbs" as a subsidiary cause. No further details are available.

The second specimen is illustrated in the accompanying photograph. There was little muscular hypertrophy at the proximal end of the specimen, yet there was marked stenosis at one point due to a growth some 2 cm. in diameter which had invaded the circular and longitudinal muscle and had produced constriction and hypertrophy of the muscle. The growths varied in size from this largest one to those causing only a slight mound 2 mm. across under the mucosa. On section they were all homogeneous, firm, and whitish yellow in colour. The mass in the mesentery was of similar texture and colour, and appeared to have absorbed much of the mesenteric tissue, causing shortening of the mesentery. Elsewhere the mesentery and glands were normal.

Histological examination of sections taken from many growths of different sizes shows that the neoplastic cells occurred first on the inner aspect of the muscularis mucosa, but that they soon spread through the muscularis while leaving the mucosa intact. The tumours appeared to extend

externally to the muscularis, slowly involving the circular muscle, while the mucosa throughout was not involved. The pattern of the neoplastic cells in the primaries and in the mesenteric mass was characteristic, with solid clumps or strands of small polyhedral cells lying in scanty stroma through which ran hypertrophied muscle bundles.

I have to thank Dr. A. H. T. Robb-Smith for permission to publish this case, and for much help in the preparation of the paper.

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ARGENTAFFIN TUMOUR OF THE ILEUM WITH PERFORATION

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The rarity of epithelial tumours of the small intestine is indicated by the work of Dockerty and Ashburn (1943), who systematically examined the histological details of 130 tumours encountered at the Mayo Clinic in the years 1906-43. Only 30 of these were accepted as argentaffin tumours. Similarly, Raiford (1933) recorded 29 argentaffin tumours of the alimentary tract among 62,000 pathological specimens at the Johns Hopkins Hospital, and, of those, 17 were of the appendix and only 9 in the small intestine. Ariel (1939) succeeded in finding 237 cases in the literature, and Dangremond (1942) added 46 cases to those quoted by Ariel.

The manner in which the tumour comes to light seems to be most commonly as an unexpected finding at necropsy. Of Dangremond's collected cases, 23 were discovered in this way and 15 were found during surgical intervention for acute or subacute obstruction, details of the remaining 8 being either irrelevant or lacking. Again, of Ariel's 11 cases six were discovered post mortem, and all the six reported by Willis (1950) were necropsy findings. Cooke (1931), in reporting 11 cases, describes the case of a man aged 60 who developed severe pain and general abdominal tenderness while under observation for recurrent epigastric pain. At laparotomy a tumour of the ileum 4.5 cm. in diameter was found which had perforated, a quantity of yellow fluid having leaked into the abdominal cavity, and the liver was studded with metastatic nodules. The patient died 14 days after the operation. This case is closely similar to the one now recorded. In reviews of the abundant literature Humphreys (1934) and Ariel (1939) do not mention perforation as a clinical feature of the disorder.

Case History

The patient, a married Iranian woman aged 40, had been well until a year before her admission to hospital. At that time, during the fast of Ramazan, she had fasted for 24 hours and then drank a quantity of iced water. Immediately she was seized by violent abdominal pain, which

lasted several hours. Every two or three weeks after that she experienced the same pain for an hour or so, and on several occasions she vomited during the attack. The pain was always in the right side of the abdomen and the right flank.

Twenty-four hours before her admission to hospital she developed a violent pain over the lower half of the abdomen, accompanied by nausea. Her condition remained unchanged throughout this time. When examined the abdomen below the umbilicus was swollen and tender and no bowel sounds could be heard. No mass could be distinguished on abdominal palpation, but during vaginal examination a hard tender mass was felt above the right fornix.

Operation.—Laparotomy was undertaken through a lower right paramedian incision, and on opening the peritoneum thin pus welled up into the wound. The coils of small intestine were dilated and inflamed as in an ileus, and three tumours were found in the course of the ileum, lying respectively 4, 5, and 12 ft. (1.2, 1.5, and 3.7 m.) from the ileocaecal junction, which was abnormally situated on the left side of the abdomen. The lowest tumour, a mass the size

FIG. 1.—Photograph of the three tumours.

of an orange, had perforated posteriorly, this accident evidently being the cause of the peritonitis. All three tumours were resected and continuity of the gut was restored in each case by a side-to-side anastomosis. No interference with the enlarged mesenteric glands present was attempted. The operation site was dusted with sulphanilamide powder and the wound closed in layers without drainage. An intravenous infusion of glucose-saline was administered throughout the operation and for 12 hours afterwards. A course of 500,000 units of penicillin was given in the post-operative period.

The wound healed satisfactorily and the patient left hospital at

her own request on the twelfth day. She was the subject of a demonstration at the Abadan Medical Society two months later, and at that time appeared well.

Gross Pathology (Fig. 1).—The uppermost tumour involved about 2 in. (5 cm.) of gut, and appeared simply as a stricture with a diffuse thickening of the wall of the gut on either side of it. The stricture admitted the tip of the little finger, and the gut above it was dilated. The second tumour was also stenosing, but was visible on the peritoneal surface as an irregular collection of yellowish-white plaques. The lowest and largest tumour had a stenosing zone at both its upper and lower ends, between which a sac-like cavity coincided with the irregular yellowish-white mass seen externally. The perforation in the tumour was no more than 1/10 in. (2.5 mm.) in diameter.

Histology.—Sections of all three masses showed small anaplastic cells, supported by a delicate reticulum of fibrous tissue. The more usual arrangement of well-defined islets embedded in an abundant stroma was nowhere to be found. Sections stained by Levaditi's method showed an abundance of brownish-black granules in the tumour cells (Figs. 2 and 3).

FIG. 2.—Low-power view of intestinal mucosa showing obliteration of normal mucosal epithelium.

FIG. 3.—High-power view of the tumour cells.

Discussion

Argenteaffin tumours of the small intestine are about as frequent as adenocarcinomas (Willis, 1948). They are believed to originate from the Kulitschitzky cells of the crypts of Lieberkühn, which have similar staining reactions. Other theories are that they are true carcinomas of the intestinal epithelium, that they are possibly related to basal-cell carcinomas of the skin, that they arise from embryonic rests, and that they originate from the sympathetic nervous system. They are slow in growth, as evidenced by the case reported by Cope (1930), in which many large masses of growth were present and a short-circuit operation was done to relieve almost complete obstruction, the patient returning in eight years in excellent health but with the abdominal masses present and apparently unaltered. This case developed the remarkable feature of a testicular metastasis. Further evidence of the slow progress is provided by the high proportion of the published cases which have been discovered at necropsy, no history of abdominal disturbance being obtained, or very often a history of abdominal pain or altered bowel function insufficient to merit laparotomy.

As a rule the tumours are small, and the one in this case was unusually large, as was that reported by Cooke, which perforated. The histological picture in both was a mass of undifferentiated cells, and not of well-defined cell islets. The larger tumour is possibly more apt to undergo a central necrosis.

Summary

A case of perforation of the small intestine resulting from one of three argentaffin tumours of the ileum is described. Treatment was by excision of all three, restoration of the continuity of the gut, and closure of the abdomen without drainage after liberal application of sulphanilamide powder to the operation sites. The patient recovered uneventfully.

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EFFECTS OF HYPERTHERMIA AND ANTIBACTERIAL AGENTS ON TUBERCLE BACILLI

BY

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Since their first isolation, it has been recognized that the mammalian types of tubercle bacilli will multiply in artificial culture only within a narrow temperature range. The human type is more fastidious than the bovine in this respect, a property which has been correlated with the predilection of the human type for parasitizing those mammals which have relatively low body temperatures. Fever therapy, which has proved useful in general paralysis and in certain gonococcal diseases, has had limited trials in tuberculosis of man and experimental animals. For example, Kling and Rubin (1936) induced pyrexia in tuberculous guinea-pigs by means of periods of short-wave treatment lasting only ten minutes. Duncan and Mariette (1937) treated tuberculous guinea-pigs in a fever cabinet for periods of four to five hours once weekly for 10 weeks. They also treated patients with weekly periods of fever lasting one to three hours. No definite benefit was observed in these trials, but the short or infrequent periods of fever employed could hardly have been expected to have a direct effect on the tubercle bacilli. Some benefit may have been anticipated by the experimenters, however, from the effects of the fever on the defences of the host.

The present work initiates an investigation into the part which hyperthermia may usefully play as an adjuvant to the treatment of tuberculosis with streptomycin and chemotherapy, whose present limitations are becoming increasingly evident. The chief defects of streptomycin treatment are the restrictions imposed on dosage by toxicity, the frequent appearance of resistant strains during its course, and the failure of response of those lesions into which penetration of the antibiotic is difficult. In such lesions it seems that the appearance of resistant mutants is facilitated owing to the exposure of the bacilli to sublethal concentrations of streptomycin.

The experiments described below show that the sensitivity of tubercle bacilli to streptomycin may be considerably enhanced by cultivating the organisms at a temperature above the optimum. The temperature chosen was 40° C. (104° F.), which is one readily attained in fever therapy. The strains examined were all of the human type (judged by cultural characteristics). *Para-aminosalicylic acid* and a *thiosemicarbazone* (*p*-acetylaminobenzaldehyde thiosemicarbazone), which are the most promising of the newer synthetic drugs, were also investigated, while mercuric chloride provided the contrast of a simple disinfectant.

Experimental Methods

Sensitivity titrations at 40° C. ($\pm 0.2^\circ$ C.) were incubated in a large insulated water-bath (55 by 40 cm.) fitted with a "sunvic" unit. Owing to the temperature gradient between the centre and walls of the bath, the tubes of medium were not all at the same temperature, but by lagging the walls and avoiding the periphery of the bath the range was limited to 39.8°–40° C. A bath of the same type with a temperature range of 36.8°–37° C. was used for control titrations. Similar results were obtained, however, when controls were incubated in a 37° C. air incubator in which the temperature of the medium reached 36.5°–37° C.

The culture medium employed, derived from Dubos's work, had the following composition: KH_2PO_4 1 g., Na_2HPO_4 3.1 g., sodium citrate 1.5 g., MgSO_4 0.6 g., asparagin 2 g., "tween" 80 0.5 ml., glass-distilled water 1 litre. It was dispensed in 2.5-ml. amounts in $\frac{1}{4}$ -oz. (7-ml.) bijou screw-capped bottles and autoclaved at 10 lb. (0.7 kg. per cm.²) pressure for 15 minutes. Before inoculation, 0.1 ml. of a 9% solution of bovine albumin was added aseptically to each bottle. The thiosemicarbazone was autoclaved, but the *p*-aminosalicylic acid (sodium salt) and mercuric chloride were sterilized by heating 1% and 0.1% solutions, respectively, in a boiling water-bath for 15 minutes.

The strains of tubercle bacilli investigated had been recently isolated from cases of pulmonary tuberculosis. Before use they had undergone three weekly subcultures in Dubos's medium after their primary isolation on solid medium. The grown cultures were sometimes stored at 4° C. for short periods until required. One drop (approximately 0.03 ml.) of such a culture was used to inoculate each tube of a titration. The strains whose streptomycin sensitivity was studied were chosen from a group somewhat more resistant than the average, being inhibited (at 37° C.) by concentrations ranging from 0.25 to 4 units per ml.

Readings were made by comparing the turbidity of cultures with barium sulphate standards in bijou bottles. The amount of growth was recorded by a numeral representing the amount of barium chloride in mg. per 100 ml. giving a similar opacity in the presence of an excess of 1% sulphuric acid. Opacities less than 0.6 were recorded as "trace" and above 40 were not distinguished from 40. The intervals between standard tubes were 100%, but intermediate values were estimated when possible.

Results

Not all of the strains of tubercle bacilli tested gave sufficient growth at 40° C. to permit satisfactory titrations. Of 40 strains examined on this point, 10 developed opacities of less than 2.5 after seven days' incubation