A CONTRIBUTION TO THE STUDY OF LONG-CONTINUED FEVERS.¹

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THROUGH the kindness of Dr. F. H. Humphris, of Honolulu, there was referred to me in July, 1906, a lady of forty-seven years with the following interesting history: There had been no tuberculosis or malignant disease in the family. She had been twice married—the first time at sixteen—and had one child living and well. As a girl, she was said to have had malaria. In 1893 she had been infected with syphilis, which was treated three months at Arkansas Hot Springs, and again for some weeks in 1900. For ten years there had been a cough each winter lasting three or four months, annoying rather than serious, and only occasionally keeping her in bed. During these years there had been four or five attacks of so-called “la grippe,” attended with fever for a few days, cough, and aching. In 1895 a curettage was done for some slight uterine derangement, but there had never been serious pelvic symptoms. In 1898 an acute attack of abdominal pain was referred to the appendix, and Dr. Murphy, of Chicago, operated later in the year and removed an appendix showing slight pathological changes.

During 1902 and the first half of 1903 she was very well and travelled extensively. In the latter part of 1903 and the first months of 1904 she had three attacks of sudden, severe abdominal pain. The pain was general throughout the abdomen, colicky, lasted a few hours, and was thought due to eating fruit and drinking mineral water. In Paris, during the summer of 1904, she was tired, nervous, and had little appetite, but felt well during the autumn in St. Louis. A little later, in Chicago, there was fever for a few days, with headache and aching in the muscles, and she felt badly for a month. The usual bronchitis kept her rather miserable during the winter of 1904 and 1905 in Paris, and an attack called “la grippe” confined her to the house for a few days in March. In the summer months, in New York, she felt tired, had very little appetite, and was said to have liver trouble. She was much better a little later in Canada and the Northwest, and felt perfectly well when she sailed for Honolulu in September, 1905. The patient had always been a great traveller. She spent 1902 in France, Italy, and Austria. In 1903 she was in Japan, Honolulu, Mexico, France, and Spain; in 1904 in Italy, the Riviera, Greece, Turkey, the Mediterranean and Egypt.

¹ Read at a meeting of the Association of American Physicians, Washington, D. C., May 7, 8, and 9, 1907.

The present illness began on the steamer two days before reaching Honolulu, in September, 1905. There was intense muscular soreness, considerable pain in the joints, and fever lasting a week. She was then perfectly well for two weeks until pain and fever recurred on the trip to Australia. This attack lasted a week, and was followed by an apparent complete recovery. After two weeks, however, she had recurrence of the familiar prostration and fever and was under the care of Dr. Hooper, of Melbourne, for a time. A blood examination, made October 24, 1905, by Dr. F. W. Wilkinson, showed red corpuscles, 4,600,000; white corpuscles, 8000; hemoglobin, 90 per cent.; no malarial parasites; a distinct increase of large mononuclear leukocytes.

After this attack she felt well, and was able to travel considerably about Australia. From October to February there were three similar periods of pyrexia, but she was not confined to bed. In February there was a severe attack in Rotorua lasting a week, during which joint and muscle pains were intense. Since that time there has been absolutely no pain, and recurrent pyrexia has been the sole feature (see the accompanying chart).

The course of the disease to August 28, 1906, when the patient died, is given in the subjoined table.

No. of attack.	Pyrexia.	Apyretic interval. (Approximate.)
1	7 days	14-days
2	7 "	14 "
3	10 "	not known
4	7 "	" "
5	7 "	" "
6	7 "	" "
7	7 "	10 days
8	7 "	10 "
9	3 "	14 "
10	7 "	14 "
11	22 "	14 "
12	22 "	9 "
13	75 "	

During the first attacks aching in the muscles and joints was intense, and suggested dengue. In the intervals health was perfect,

and the patient travelled, ate well, and nothing suggested a return of the trouble until fever recurred. The temperature rose rapidly, but not abruptly, and fell by lysis; during the intervals, when measured, it was slightly subnormal. With the recurrence of temperature, there was increased constipation, some bloating, malaise, and, in the later periods, great prostration, occasional chills, and great discomfort from sweating. Under Dr. Humphris' observation, the pulse was of good quality, from 74 to 90; quinine did not affect the temperature, and made the nervous symptoms worse; pyramidon, in 5-grain doses, was found to give much relief, with a quick drop in temperature and profuse sweating. Until July there was no evidence of cachexia, and the absence of symptoms and signs was in striking contrast to the monotonous daily temperature.

When seen July 20, the patient had a peculiar earthy color, not unlike that seen in liver abscess. There was fever of a marked remittent, intermittent type. Shaking chills occurred every three or four days. At the height of temperature, there was great restlessness, sometimes mild delirium, but no pain. Pyramidon was occasionally required to control temperature; 5 grains would be quickly followed by a drop of 3° to 5° and a drenching sweat. Even without pyramidon, profuse sweating was frequent.

There were slight changes at both apices, but no evidence of an active process. The chief thing of interest in the thorax examination was the curved line of liver dullness, reaching to the fourth rib in the mammillary and anterior axillary lines, to the angle of the scapula and down to the eleventh spine at the vertebral column. Despite the enlargement of the liver upward, which showed beautifully on an x-ray plate, there was at no time any evidence of enlargement downward. The area of splenic dullness was frequently a little large, but the spleen was never palpated in almost daily examinations over a period of four weeks. The heart was markedly dilated, particularly the left ventricle, and there was a systolic murmur over the precordium, with greatest intensity over the base. The pulse was slow in comparison to the temperature, averaging 80 to 100.

The abdomen was considerably distended, not tender, and in the last days a small amount of free fluid could be demonstrated. Superficial glands could never be palpated, nor were there glands to be felt in the abdomen or by rectum. The follicles of the tonsils and base of the tongue were not enlarged—in fact the tongue suggested the smooth atrophy of Virchow, but was not positive. There was extreme myosis, which had been noted for some years. The pupillary outline was irregular, and reaction to light was practically absent. There were no fundus changes, and nothing else in the nervous system to suggest syphilis. Pelvic and rectal examination was negative. The urine at different times showed a trace of albumin, and a few hyalin casts. Diazo reaction was constantly present,

sometimes faint, and again well marked. In the last days urobilin was present in considerable amount, with a trace of bile. The stools were microscopically negative, and contained no occult blood.

Cultures in bouillon, made on two occasions, with blood from puncture of a vein gave no growths. Serum reactions with cultures of typhoid and paratyphoid bacilli, and *Micrococcus melitensis* were negative in dilutions of 1 to 50 and 1 to 20. Of principal interest in the blood counts (see the accompanying chart) was the moderate secondary anemia, with marked leukopenia and relative increase in the large mononuclear forms. Some of these cells were distinctly larger than the normal type.

Date.	Reds.	Whites.	Percentage.					Remarks.
			Poly-nuclear	Small mono-nuclear	Large mono-nuclear	Eosino-philic.	Hb.	
October 24, 1905	4,600,000	8000			In-crease.		90	No plasmodia. Made by Dr. John F. Wilkinson, Melbourne.
May 2, 1906	5,800,000	7200	75.0	21.0	1.0		...	No plasmodia. Made by Dr. Humphris, Honolulu, T. H.
May 21, 1906	5,600,000	5800	67.0	32.0		1.0	...	
July 21, 1906	4,416,000	3000	83.0	8.0	9.0		70	Temperature 102°. Slight variation in size of red cells.
July 21, 1906		5500	72.5	12.0	15.5		...	After chill. Temperature 104°.
July 28, 1906	4,032,000	2800	65.0	15.5	19.5		...	No plasmodia. Few degenerated reds.
August 4, 1906	3,100,000	5200	73.0	9.0	18.0		70	5 P.M., after chill. Temperature 103.6°.
August 11, 1906	3,272,000	2600	80.0	9.0	11.0		60	No nucleated reds.

With the peculiar recurrent pyrexia, the conditions considered in diagnosis were chiefly Malta fever, Hodgkin's disease or lymphosarcoma, syphilis of the liver, and gallstones in the common or hepatic ducts with catarrhal cholangitis. The aching of joints and muscles in the early periods, the undulant fever, the recent visit to many Mediterranean ports would suggest Malta fever, but the frequent repetition of attacks and the negative serum reaction decided against it. Serum reactions in this disease are not always unequivocal.²

Echinococcus of the liver was suggested by the shape of the right

² An army pathologist of wide experience sent a man to the hospital with the diagnosis of Malta fever from the agglutination test; but the recurrent fever later cleared up on drainage of an unrecognized empyema. In another case with positive serum reaction, gonorrheal infection was shown to be the cause of temperature and of joint symptoms.

lobe, but the radiogram gave no characteristic picture, and the absence of eosinophilia and leukocytosis spoke against it.

The absence of jaundice was much against a ball-valve calculus in the common duct. The occasional complaint of distress over the liver, with a feeling of distention in the abdomen, suggested the possibility of a calculus in the hepatic ducts, as in the cases of Frerich³ and Schmitz.⁴ The failure of a polynuclear leukocytosis just after a chill and rapid rise of temperature, was decidedly against an infective cholangitis. My experience has been that of Pick,⁵ that in cases of infective cholangitis (of pyelitis and nearly all cases of malignant endocarditis as well), there is a decided polynuclear leukocytosis just after a paroxysm of chill and fever. There may have been a normal count, or a leukopenia, with normal ratio, during the febrile or afebrile period before the paroxysm, and the sudden change in the blood picture is most striking.

Despite the characteristic alternating pyrexia, the absence of palpable glands and spleen, and of enlarged mediastinal glands, was much against Hodgkin's disease or lymphosarcoma limited to the liver; although the cases of Naunyn⁶ and Rolleston⁷ had lately been brought to my mind in reviewing a case of intermittent hepatic fever.⁸

Naunyn mentions the case of a woman of forty with intermittent fever for some months and paroxysms of chill, fever, and sweating recurring about 4 P.M. daily. There was considerable liver enlargement and an irregular tumor of the left kidney. The patient demanded operation on account of the unsupportable chills and sweating. The left kidney was removed, and contained a sarcomatous mass the size of an apple. The liver appeared normal. The chills and fever ceased, and the patient improved until, after four weeks, the fever recurred. Death occurred from exhaustion, and at autopsy metastases were found in retroperitoneal and mediastinal glands, and a large central mass in the liver.

The history of syphilis, the pupillary changes, the signs of some liver affection, demanded specific therapy. Mercury was given by inunctions and hypodermically, and iodide was administered up to 6 grams daily in combination with ascending doses of Fowler's solution. There was no improvement at the end of three weeks; the

³ *Leberkrankheiten*, Band II, 495.

⁴ *Berl. klin. Woch.*, 1891, 915.

⁵ *Zur Diagnostik der Infekte der Gallenwege*, Mittheil. aus den Grenz., d. Med. u. Chir., viii, 174; *Ueber Intermittirendes Gallenfieber*, *Deut. Arch. f. klin. Med.*, lxi, 1.

⁶ *Cholelithiasis*, S. 69.

⁷ *Diseases of the Liver*, p. 388; *Ibid.* p. 152.

⁸ Rolleston in writing of lymphosarcoma of the liver records that: "Exceptionally the organ is very considerably enlarged, and if the superficial lymphatic glands available for clinical examination are but little affected, the clinical aspect of the case, especially when there is a hectic temperature, may suggest hepatic abscess, as in a case under my care." Again, "Some years ago a man was under my care with a pedunculated mass in the left groin of many years' standing, which turned out to be lymphadenoma; he developed a hectic temperature and considerable enlargement of the liver. The condition was not unlike hepatic abscess, and the question of operation was raised during life."

patient was weaker, slight icterus developed, and moderate ascites could be demonstrated. Operation was demanded by the patient for relief of the intolerable discomfort caused by the temperature and sweating, and an exploratory laparotomy was done by Dr. Beverly MacMonagle in the hope of finding an abscess, or, as in Israel's case, a gumma that could be reached surgically. On opening the abdomen a moderate amount of blood-stained fluid escaped. The liver edge was a little above the costal margin, was irregular, rounded, and the liver was studded with whitish, irregular nodules the size of a pea or a small marble. A piece of the liver was removed and sent to Dr. William Opbül for examination. The wound was closed, and the patient sent to bed in fair condition, but death occurred next day from exhaustion.

The following is Dr. Opbül's report: "Sections show multiple tumor nodules, which, in the periphery, consist almost entirely of very large round or oval cells. Many of these cells show mitotic figures. The central parts of the nodules are made up of somewhat smaller cells, with some connective-tissue fibers between them. No caseation. In the periphery the tumor infiltrates the liver tissue following the course of the lymphatics along the capillaries. No definite alveolar arrangement can be made out in any place. The tumor has the appearance of a sarcoma."

At the autopsy the lungs were found emphysematous, with puckered scars and shrinking at both apices. The heart was flabby, much dilated, the endocardium normal, the ascending aorta dotted with atheromatous patches. Near the hilum of the right kidney, which was in normal position, was a large retroperitoneal gland the size of a golf ball. This was the only gland enlarged anywhere in the body, except a few pigmented glands the size of small beans, such as one usually sees about the roots of the lungs. The follicles of the gastro-intestinal tract were not enlarged. Chiefly remarkable was the enlargement of the dome of the liver, as had been determined clinically; the diaphragm was pushed up to the third rib. The failure of the liver to enlarge downward was explained by the puckering of the rounded edges by several deep scars and the presence of several firm adhesions to the anterior abdominal wall—plainly the result of an old luetic process. Great numbers of whitish nodules studded the right lobe of the liver; there were only five or six in the left lobe. The spleen was not enlarged, 12 by 7 cm.; on section there were three whitish, irregular nodules the size of lima beans similar to the growths in the liver. Microscopically the tumors of the lymph gland, liver, and spleen showed a similar structure to the nodule removed at operation. There was no caseation. Giant cells and eosinophiles were not present. No tubercle bacilli were found in the smears from the gland tumor. The growth would be best classed, therefore, as a lymphosarcoma.

Retrospectively, it would seem that the attacks of abdominal pain

in 1904 marked the beginning of the disease, probably in the retro-peritoneal gland, and that the fever, general pains, and indefinite symptoms in the hepatic region of the last year signalled the invasion of the liver. It is difficult to assign a definite role in etiology to syphilis, nor can the limitation of the malignant process to one lymph gland be in any way explained. Syphilis may perhaps have rendered the liver less resistant to invasion of the growth. Treatment would probably have availed little at any stage of the disease. Large doses of arsenic and specific treatment were given during the last month of life without effect. X-ray treatment and Coley's serum might have been tried in the apyretic intervals. X-ray treatment was out of the question while the patient was under my care, owing to the pyrexia and cachexia; it is, even in afebrile cases, at times distinctly detrimental.⁹

Recurrent fever in tuberculous lymphomas, in Hodgkin's disease, in lymphosarcoma or sarcoma of other varieties has been chronicled in numerous papers: Dr. Musser reviewed the literature, and added two personal cases in a communication to this Association in 1901. Graves mentioned occurrence of the peculiar temperature in some cases of lymphomas before Murchison's¹⁰ paper in 1870. Gowers¹¹ introduced the name alternating pyrexia in his article on Hodgkin's disease in Reynold's *Practice*; Southey (1875) and Sainsbury were among the early English authors recording cases; Pel¹² in 1885, and Ebstein¹³, in 1887, called general attention to the peculiar fever type, and Ebstein thought he was describing a new clinical entity, which he termed "das chronische Rückfallsfieber." It soon became recognized, however, that recurrent fever is a symptom and not a disease. The papers of Graves, Murchison, Southey, Gowers, Sainsbury, Pel, and Ebstein dealt with Hodgkin's disease. In Klein's¹⁴ case, reported as cirrhosis of the liver and pseudoleukemia with recurrent fever, the history suggests strongly that fever was of the intermittent hepatic variety. Two of Kast's¹⁵ cases would be classed clinically as Hodgkin's. In a boy of seven, with enlarged glands, spleen, and liver, there were nine periods of pyrexia, and toward the last a leukocytosis (the kind not described)

⁹ In an old man with generalized Hodgkin's disease, who had previously had periods of pyrexia, a few x-ray exposures were followed by remittent fever, which persisted till death some three weeks later. A man aged forty years had recurrence of lymphosarcoma in the spleen and liver six months after a primary tumor in the glands of the right axilla was removed. Four attempts were made at x-ray treatment. Each time, after three or four short exposures over the liver and spleen, there would be a chill followed by rapid rise of temperature to 103° or 104°, prostration, loss of appetite, and persistence of fever for four or five days.

¹⁰ Trans. Path. Soc. Lond., 1870, xxi, 372.

¹¹ Reynolds' System of Medicine, 1879.

¹² Zur Symptomatologie der sogenannten Pseudoleukämie. Berl. klin. Woch., 1885, 3; Pseudoleukämie oder chronisches Rückfallsfieber. Berl. klin. Woch., 1887, 644.

¹³ Das chronische Rückfallsfieber. Berl. klin. Woch., 1887, 565.

¹⁴ Ein Fall von Pseudoleukämie nebst Lebercirrhose mit recurrierendem Fieberverlauf. Berl. klin. Woch., 1890, 712.

¹⁵ Ueber Rückfallsfieber bei multipler Sarkombildung.

of 100,000, and later, 270,000. Grawitz mentioned a case with enlarged glands becoming softer during the attacks of fever, negative blood cultures, and no bacteria in the glands at autopsy. Janz¹⁶ extirpated the spleen in a case reported as pseudoleukemia; streptococci were found in many glands and tubercle bacilli in one supraclavicular gland. Fischer,¹⁷ reporting 12 cases of Hodgkin's disease, in which cultures from the blood and glands were negative, mentioned one instance with periodic fever in which organisms were found in the blood during the pyrexia, but not in the intervals. Laache¹⁸ saw Hodgkin's disease with alternating pyrexia, and noted decrease in size of the glands during the fever and increase in the apyretic intervals. He mentions that Fiedler reported recovery in a case of Hodgkin's with recurrent fever. The communications of Van der Scheer,¹⁹ Barbrock,²⁰ Kissel,²¹ Westphal, Verdelli,²² Freudweiler,²³ likewise deal with Hodgkin's disease or "pseudoleukemia," as do recent articles by Hirschfelder²⁴ and Clarke, Stoll,²⁵ Ruffin,²⁶ and Tschistowitsch.²⁷

Shortly after Ebstein's paper it was shown that "chronisches Rückfallsfieber" might occur as a striking symptom of malignant disease. Renvers²⁸ reported lymphosarcoma of the retroperitoneal glands, liver, and spleen, marked clinically by recurrent pyrexia in seven periods of seven days each. In Voelcker's²⁹ case, with typical undulant fever, there was a sarcoma of the lumbar spine and retroperitoneal glands. Hanser³⁰ reported ten cycles of fever with an epigastric tumor regarded as sarcoma. In Hewelke's³¹ case of retroperitoneal lymphosarcoma, staphylococci were found four times in blood cultures taken during both febrile and afebrile stages. Multiple myelomas were found as the cause of fever recurring at

¹⁶ Zur Operation der leukemischen Mils. Beitr. z. klin. Chir., 1899, xxiii, 287.

¹⁷ Ueber malignes Lymphom. Arch. f. klin. Chir., 1897, lv, 467.

¹⁸ Ebstein und Schwalbe's Handbuch, i, S. 844.

¹⁹ Een geval van pseudoleukemie med gedeeltelyk recurrend Koorstype. Nederl. Weekblatt, 1899.

²⁰ Ueber Pseudoleukemie mit intercurriendem Fieberverlauf. Virchow und Hirsch's Jahresberichte, 1890, ii, 331.

²¹ Maligne Neubildungen und chronisches Rückfallsfieber. Vratch., 1895, No. 35; Drei Faelle von Hodgkin'scher Krankheit bei Kindern Vratch, 1895, 651.

²² Archivio italiano di clinica medica, 1895.

²³ Statistische Untersuchungen über Fieberscheinungen bei Carcinom Innerer Organe. Deut. Arch. f. klin. Med., lxiiv, 544.

²⁴ A Case of Hodgkin's Disease with Chronic Recurrent Fever. Occidental Med. Jour., 1904, xviii, 11.

²⁵ A Case of Hodgkin's Disease with Slight Enlargement of Peripheral Glands. Med. Record, 1905, p. 773.

²⁶ Hodgkin's Disease. A Study of a Case with Relapsing Fever. AMER. JOUR. MED. SCI., 1906, p. 587.

²⁷ Ueber Pseudoleukemie mit periodischen Fieber. Deut. med. Woch., 1907, 502.

²⁸ Ueber Lymphosarkomatose mit recurriendem Fieberverlauf. Deut. med. Woch., 1888, 753.

²⁹ Ueber Sarkom mit recurriendem Fieberverlauf. Berl. klin. Woch., 1889, 796.

³⁰ Ein Fall von chronischem Rückfallsfieber. Berl. klin. Woch., 1889, 692.

³¹ Lymphomatosis retroperitonealis maligna cum febro recurrente Kronika lekarska, 1889, xii.

intervals of one to twelve days over a period of nine months in a case recorded by Hammer.²² Subohn²³ reported a questionable instance of recurrent fever with lymphosarcoma of the thymus, and Witthauer²⁴ noted periodic fever through five months in a round-cell sarcoma of the posterior mediastinum. Kast, beside the 2 cases mentioned above, described recurrent fever in a sarcoma of the hip and retroperitoneal glands occurring in a boy of sixteen. The papers of Puritz,²⁵ Bulubasch,²⁶ Kissel, Glaeser,²⁷ Hobenemser, deal also with the association of alternating pyrexia and sarcoma. Hampeln,²⁸ Anker,²⁹ Kobler,³⁰ Kast and Freundweiler write of its occurrence with carcinoma.

Delafield³¹, and a little later Askanazy³², first called general attention to the similarity of many cases of tuberculosis of the lymphatic system and Hodgkin's disease. Musser's³³ 2 cases of recurrent fever were tuberculous. In No. 8 of Sternberg's³⁴ series, this type of fever was noted, but the cases should be classed as Hodgkin's disease with terminal tuberculous infection. Schur³⁵ reported a combination of Hodgkin's disease and tuberculosis, with alternating pyrexia and a polynuclear leukocytosis of 30,000. Crowder described a case of generalized tuberculosis with irregular fever, a leukocytosis of 19,000, and the clinical picture of Hodgkin's disease; tubercle bacilli and staphylococci were found in the glands at autopsy. Strauss³⁶ saw a female patient with enlarged cervical glands and chronic recurrent fever. At one time there was such a marked lymphocytosis as to suggest lymphatic leukemia, but tuberculous glands were found at operation.

²² Primäre sarkomatöse Ostitis mit chronischem Rückfallsieber. Virchow Arch., 1894, 137, 280.

²³ Jahrbuch der Hamburger Staatskrankenanstalten Leipzig. 1892, 65.

²⁴ Intermittirendes Fieber als Symptom eines Mediastinaltumors. Münch. med. Woch., 1901, 224.

²⁵ Ueber Sarkom mit sogenanntem chronischem Rückfallsieber. Virch. Arch., Band 126, 1312.

²⁶ Sarkom der inneren Lymphdrüsen mit febris recurrens. Medicinische obroesme, 1894, Band 40-41, 601.

²⁷ Mit recurrirendem Fieber verlaufende multiple Sarkomatose. Med. allg. Centralzeitung, 1897, 601.

²⁸ Zur Symptomatologie occulter visceraler Carcinome. Zeit. f. klin. Med., viii, 221; Ueber intermittirendes Fieber im Verlauf des Magencarcinoms. Zeit. f. klin. Med., Band xiv, 566.

²⁹ Ueber das Vorkommen intermittirendes Fieber bei chronischen Krankheiten. Inaug. Diss. Strassburg, 1890.

³⁰ Ueber typisches Fieber bei malignen Neubildungen des Unterleibs. Wien. klin. Woch., 1892, No. 23, 335; No. 24, 352.

³¹ A Case of Acute and Fatal Tuberculosis of the Lymphatic Glands. Med. Record, 1887.

³² Tuberculöse Lymphome unter dem Bilde febriler Pseudoleukemie verlaufend. Ziegler's Beit., 1888, iii, 413.

³³ Note on the Fever of Hodgkin's Disease. Amer. Med., 1902, ii, 13.

³⁴ Ueber eine eigenartige unter dem Bilde der Pseudoleukemie verlaufende Tuberculose des lymphatischen Apparats. Zeit. f. Heilkunde, xix, 21.

³⁵ Zur Symptomatologie der unter dem Bilde der Pseudoleukemie verlaufenden Lymphdrüsentuberculose. Wien. klin. Woch., 1902.

³⁶ Sarkomatose und lymphatische Leukemie. Char. Annaleo, xxiii, 343.

Although resting on different pathological bases, the clinical features of all these cases are strikingly similar. Febrile periods of from three to seven or ten days alternate with afebrile intervals of the same or slightly longer duration. As the disease progresses, the febrile periods usually lengthen, and continued fever of a remittent type may be present for weeks or months. The last attack in the case here reported was of seventy-six days' duration. The temperature usually rises and falls slowly, but there may be an abrupt rise with or without chill. Sweating is not uncommon. In the intervals between the first few febrile attacks the patients may feel and look perfectly well, but weakness, anemia, and cachexia gradually appear. Fever is frequently the first symptom. The onset may be sudden, as in one of Pel's cases. Pain in the abdomen, as an early symptom, was noted by Ebstein, Hanser, and Voelckers. It occurred in three distinct attacks in the case here described. In Hammer's case of multiple myelomas, pain in the chest was the first symptom. A patient of Musser had severe pain in the right inguinal region with each pyrexial attack.

Pel, Ebstein, Bulubasch, Klein, and Tschistowitsch described yellowish discoloration of the skin with patchy, brownish pigmentation. Terminal icterus was noted by Pel, Ebstein, Musser, and Klein. Enlargement of the peripheral glands was absent in not a few cases (Pel, Ebstein, Renvers, Barbrock, Voelckers, Hanser, Tschistowitsch). The retroperitoneal and bronchial glands are more frequently involved. Absence of splenic tumor is not recorded in any case, except the one here noted. Spleen, liver, and palpable glands nearly always increase in size during the periods of fever, and frequently become tender. Laache noted a swelling of the glands in the afebrile periods and decrease of size with pyrexia.

The urine showed no characteristic changes. Albumin was infrequent, urobilin and bile pigment were occasionally noted. Diazo reaction was noted by Renvers, Stoll, and in my case. Examination of the blood helps in the diagnosis chiefly by ruling out other causes of fever. Secondary anemia becomes marked as the disease progresses. Stoll recorded a count of 1,700,000 red cells and 30 per cent. hemoglobin. Leukopenia is more common than leukocytosis. Polynuclear leukocytosis would speak more for tuberculous lymphomas than for Hodgkin's disease or lymphosarcoma. Strauss, however, noted a marked lymphocytosis in a tuberculous case, and a leukocytosis of 270,000 was recorded by Kast in a boy of seven. Relative increase of the large mononuclear cells has been described in several instances. It must be remembered, in differentiating from septic affections, that positive blood cultures have occasionally been reported. Positive or suggestive evidence of syphilis was found by Pel, Klein, Renvers, Voelckers, Tschistowitsch and myself. In 27 instances in which sex was recorded, there were 16 males and 11 females. Recorded ages

varied from six to fifty-nine years. It is interesting to note that a number of patients had travelled extensively in the tropics. Recovery was noted in but 2 cases. Laache mentions a report by Fiedler, and Tschistowitsch observed prompt cure under iodide after many other drugs had been tried for months. Death has occurred in all other cases, usually from exhaustion.

Recurrent attacks of fever may occur over long periods of time in many other conditions, and differential diagnosis is by no means always easy. Repeated relapses in typhoid fever will not often give difficulty; blood cultures will help in the cases in which Widal reaction is absent or long delayed. Claisse⁴⁷ has lately written on typhoid fever with numerous relapses. In my opinion, great hesitation should attend the diagnosis of sporadic cases of Malta fever. Piroplasmiasis should be considered in all cases of continued fever from the tropics, and examinations made from splenic punctures if necessary.

Hampeln was the first strongly to emphasize the occurrence of fever in carcinoma. The papers of Kraussold and Max Freudweiler are more recent. Fever may be an early symptom; in a case of Hampeln there was fever for three months before a diagnosis was made. Continued fever is rare, and the remittent, intermittent, or hectic type the most common. Periodic attacks may be noted and 'ague-like' paroxysms of chills, fever, and sweating. In 475 cases of carcinoma collected by Freudweiler temperature over 38° C. was present in 24.6 per cent. The carcinoma may cause fever even without ulceration: in 14 out of 64 cases reported by Freudweiler there was no ulceration.

Heubner⁴⁸ mentions fever recurring in eight periods during the fall and winter in a child of four. At first there were only general symptoms during the febrile attacks, but later pus appeared in the urine, and the diagnosis of pyelitis was assured. The frequency of pyelitis both in children and adults needs constant emphasis. It must be remembered also that renal calculi may rarely give rise to recurrent paroxysms of chills, fever, and sweating without any urinary signs; the attacks are similar to those of intermittent hepatic fever. The attacks may occur, first, in tuberculous pyelitis; second, in calculous pyelitis; and, third, in rare instances of stone in the pelvis, without chronic suppurative pyelitis." (Osler.)⁴⁹

⁴⁷ *Fievre typhoïde prolongée avec rechutes multiples.* Bull. et. mem. Soc. med. des Hop. de Paris, 1906, xxiii, p. 571-574.

⁴⁸ *Ueber langdauernde Fieberzustände unklaren Ursprungs.* Deut. Arch. f. klin. Med., lxxv, 35.

⁴⁹ *On Fever of Hepatic Origin, Particularly the Intermittent Pyrexia Associated with Gallstones.* Johns Hopkins Hosp. Reports, vol. ii, p. 1.

Some years ago a woman aged forty-five years was under observation for recurrent fever of a years' duration. With periodic temperature, there would be occasional chills and

Romberg⁵⁰ mentions 2 cases with anemia, enlargement of the spleen and liver, and fever of months' duration—in 1 case of continued type; in the other with apyrexial intervals of weeks' duration. A mitral murmur was interpreted as of functional origin, and both cases went to autopsy with a diagnosis of Hodgkin's disease. The postmortem revealed malignant endocarditis. Fever and progressive weakness and anemia may be the only symptoms of infective endocarditis. There may be apyretic intervals of days and weeks at a time. The interpretation of heart murmurs in cases with high temperature and anemia is, as Bloch⁵¹ has pointed out, often peculiarly difficult. Infective endocarditis grafted upon an old valvular lesion may run an extremely chronic course, over a year (Dreschfeld), thirteen months (Osler), and fifteen months (Romberg). Cases under my observation with autopsy verification have lasted six, fifteen, and eighteen months. With absence of signs of heart involvement, diagnosis of the condition may be difficult or impossible. Cases of this kind have recently been reported by Cole⁵² and Bramwell.⁵³ In chronic cases, leukocytosis may not occur; repeated counts in a case lasting fifteen months showed a leukopenia of 3000 to 5000, with a relative lymphocytosis. Ewing⁵⁴ holds that "leukocytosis is present probably in all cases, but is often intermittent, and single observations may fail to discover it." There is frequently a decided increase in the polynuclear count after a chill, and abrupt rise of temperature. Blood cultures are of great help in diagnosis.

Frequent mention has been made of intermittent hepatic fever. Pain in the region of the liver and jaundice deepening after paroxysms of chill and fever usually make diagnosis reasonably certain. In a case seen some years ago there was no jaundice until eight months after fever was noted. The increase of leukocytes, after chill and fever, as described by Pick has been twice observed. Pain and jaundice may be absent, and the temperature curve the only characteristic feature. Frerichs has described long-continued intermittent fever with stone in the hepatic duct, and Schmitz reported 2 cases of recurrent attacks of intermittent

sweats, and complaint of dull aching in the right hypochondrium and lumbar regions. Leukocytes were normal in apyretic intervals, but after a chill and abrupt rise of temperature, there was several times noted a polynuclear leukocytosis of 28,000 to 36,000. There was a history of hematuria some years before, but the urine never contained albumin, blood or more than a few leukocytes. Operation revealed a large stone in the pelvis of the right kidney with a catarrhal pyelitis, no complete blocking of the ureter and no pyelonephritis. The fever with intermittent pyonephrosis (especially in tabetics) is, in my experience, frequently misinterpreted.

⁵⁰ *Krankheiten der Kreislauforgane*. Ebstein und Schwalbe, *Handbuch der Praktischen Medizin*, i, 685.

⁵¹ *Ueber Blutkrankheiten unter dem Bilde der akuten Endocarditis*. *Deut. med. Woch.*, 1903, 512.

⁵² *Johns Hopkins Hosp. Bull.*, xii, p. 252.

⁵³ *Clin. Studies*, Edin., 1905-1906, n.s. iv, p. 193-207.

⁵⁴ *Clinical Pathology of the Blood*, p. 360.

pyrexia without pain or jaundice, in which cessation of fever followed passage of gallstones.

Many interesting papers of late have dealt with fever in visceral syphilis. Janeway³⁵ presented a communication on "Fever in Tertiary Syphilis" to this society in 1898. Riedel³⁶ cites remarkable cases in his article "Ueber die fieberhaft verlaufende Lues der Gallenblase, Gallengänge, sowie der Leber," and quotes "den alten Satz, dass man bei unklaren fieberhaften Krankheiten immer zuerst an Tuberculose, so dann an Lues, endlich an Aktinomykose denken soll." F. Kemperer³⁷ reports several cases of syphilis of the liver with fever; in 1 case there was alternation of pyrexia with afebrile intervals over a period of a year. Recent literature on the subject is given in the articles of Klemperer and Raubitschek.³⁸

In the past year Gilman Thompson called attention to the similarity between some cases of exophthalmic goitre and infective endocarditis. Two years ago an army captain was under my observation for some months. The chief complaint was of weakness, irritability, with occasional attacks of diarrhoea, chills, fever, and sweating. There was cachexia, a mitral systolic murmur, a pulse of 120 to 140, and irregular temperature recurring at intervals of days or weeks. The case was regarded as one of malignant endocarditis, until tremor, the general nervous picture, and Graefe and Stellweg signs decided for Parry's disease, even with absence of exophthalmos and goitre. A goitre developed later, and an operation by Dr. Halsted led to great improvement.

It is not uncommon to see children or young adults with long-continued or, more rarely, recurrent pyrexia, dependent upon tuberculosis of mediastinal, mesenteric, or retroperitoneal glands. A boy of eight was seen a year ago who had had moderate fever almost daily for six months. There was a history of pertussis one year before and examination showed enlarged bronchial glands. A young woman, seen four years since, had, as chief complaint, pain in the lumbar spine and in both loins. There was recurrent pyrexia of moderate degree over a period of eight months without satisfactory explanation. A radiogram showed the spine normal, but gave the shadows of several calcified retroperitoneal glands.

In a remarkable case, seen three years ago, a young woman of tuberculous family, had had recurrent pyrexia for over twelve years. Fever recurred two or three times in one year, and again not for two or three years. There were no symptoms during the attacks beyond prostration and temperature of 103°

³⁵ Fever in Tertiary Syphilis. Trans. Assoc. Amer. Phys., 1898.

³⁶ Ueber die fieberhaft verlaufende Lues der Gallenblase, Gallengänge, sowie der Leber. Mittheil. aus den Grenz., xi, 1.

³⁷ Ueber Fieber bei Syphilis der Leber. Deut. Zeit. f. k. Med., iv, 176.

³⁸ Zur Kenntniss der fieberhaften tertiär-syphilitischen Organ-Erkrankungen. Centralbl. f. d. Grenz., ix, p. 641.

to 105° for two or three weeks. During several attacks the cervical glands had enlarged and, when personally seen, there was evidence of bronchial gland enlargement. The liver and spleen were not palpable and the blood count was normal. Death occurred two years later from puerperal infection, but, unfortunately, no autopsy was obtained.

As seen above, alternating pyrexia may be a symptom of many very different conditions. Regularly repeated attacks over long periods of time are most suggestive of tuberculous lymphomas, Hodgkin's disease, lymphosarcoma or other varieties of sarcoma. In any recurrent pyrexia, the possibility of disease of deep glands should be remembered. Rarely, as in the case recorded by Rolleston, or in the one here described, the liver may be, clinically, the sole organ affected.

TRUE INTESTINAL DYSPEPSIA.¹

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By the expression "intestinal dyspepsia" we understand conditions in which the digestive function of the intestinal tract is disturbed: The idea of testing the functions of the intestines in a manner similar to those of the stomach prevailed among clinicians for a long while, but its execution was attended with great difficulties. To Adolf Schmidt² belongs the credit of having elaborated a method to that effect. This well-known clinician introduced the test diet, known under his name, for the purpose of examining the feces. By means of this method, Schmidt and Strasburger³ were enabled to discover a group of cases of intestinal dyspepsia, in which the starch digestion is particularly disturbed. They designated it fermentative dyspepsia.

Schmidt⁴ has recently described the occurrence of functional achylia of the pancreas; by this he understands cases in which there is a malassimilation of the food, and a temporary lack of nuclear digestion—assigned by him as characteristic of the pancreatic secretion.

In a former paper⁵ I have described similar cases, in which all nutritive substances were poorly digested. Yet I hardly believe it advisable to speak of achylia of the pancreas, because by achylia

¹ Read at a meeting of the American Gastro-enterological Association, at Atlantic City, N. J., June 3, 1907.

² The Test Diet in Intestinal Diseases. Translated by Charles D. Aaron, Philadelphia, 1906.

³ Deut. Arch. f. klin. Med., 1901, lxi, 570.

⁴ Functionelle Pankreasachylie, Deut. Arch. f. klin. Med., 1906, lxxxvii, 450.

⁵ Further Remarks on the Digestive Bead Test for Ascertaining the Functions of the Digestive Apparatus. Jour. Amer. Med. Assoc., February 2, 1907.