eating or other physiological exercise, should raise a suspicion of gall-stones or tabetic crises. Epigastric pain, absent at times of rest but immediately induced by certain efforts, is almost undoubtedly due to cardio-vascular disease. Of special times of occurrence it is also noteworthy that angina, in concert with other "spasmodic complaints," as observed by Heberden, has a predilection for the early hours of the morning after the first sleep. The hunger pains of duodenal ulcer often wake their victims between the hours of midnight and 2 a.m., and gall-stone pains at a somewhat later hour.

Among *aggravating factors* (taking again the better known types of pain) exertion, cold, annoyance, and particularly exertion after food, may all be provocative of anginal seizures. Jolting is apt to evoke pain in biliary, renal, and vesical calculus, and also in sufferers from chronic colon spasm, a disorder which is highly responsive also to the influence of cold, fatigue, worry, tobacco, and purgatives. Gentle thumping of the loin will more readily evoke the pain of calculous renal disease than simple deep palpation. Of *relieving factors* rest of body and mind and warmth are common to the majority of painful visceral disorders. Amyl nitrite has an almost specific effect in anginal pain, but not so in the status anginosus of coronary occlusion. Alkalis and belladonna (both probably by facilitating pyloric relaxation) have a well-known efficacy in gastric pain. Abdominal pressure, ill tolerated in inflammatory abdominal disease, may alleviate the pain of intestinal colic.

Now I would not for a moment have it supposed that an interrogatory such as I have outlined can be employed by every busy physician in every case of visceral pain with which he is confronted; but I would suggest that some such method is not only appropriate but essential if we are to prosecute a careful inquiry into any single type of pain; and further, that it may be of decided value in practice in elucidating what I have described as "difficult pains," and more particularly in those unhappily plentiful cases of chronic abdominal disease in which physical signs are scanty or altogether lacking. I can think of nothing better calculated to stay the epidemic of injudicious abdominal operations than an extension of interest in pain as a diagnostic symptom.

If I were asked to enunciate a few important principles for the everyday clinical study of pain my choice would fall upon the following:

First, in obscure cases and important decisions to try, whenever possible, to see the patient when his pain is present, for then and then only will his own observations be accurate and reliable, and not dependent upon memory, and physical signs, absent at other times, may be in evidence. We all know how few and far between (especially in consulting and hospital practice) are these opportunities of seeing our patients in pain. This circumstance alone is evidence of the rarity of continuous pain (excepting in advanced inflammatory and malignant disease), and supports the contention that visceral pains come and go in a physiological sequence and in obedience to physical laws.

Secondly, to pay particular attention to the patient's gesture, and, if he makes none spontaneously, to ask for a manual demonstration with the clothes removed. "A pain in the stomach" may mean a pain anywhere between the manubrium sterni and the symphysis pubis, and our endeavour must ever be in the direction of greater precision. I have several times seen the mistake made of supposing a pain to be gastric because it was related to food. Colonic pains may also be influenced for better or worse by food, but they are situated in the lower abdomen, whereas gastric pains are always epigastric.

Thirdly, to remember the close association which exists between visceral pain and the functional activity of the viscus in question. I once had a case referred to me by a cardiologist on a suspicion of stomach trouble with a request for a gastric analysis. The patient was an elderly man complaining of high epigastric pain after food. Before examining him I ascertained that the same pain was also evoked by walking, and that the case was undoubtedly one of angina pectoris.

It remains for me to cite from my personal store a few case histories which serve to show the value of a full

analysis of pain, and how such an analysis may lead to a more correct opinion or may modify judgement or treatment in important ways. I have been careful to include mistakes of my own as well as those of others. How often these mistakes give us insight into matters previously debatable or obscure.

[Case histories illustrating the following conditions were here recounted, the detailed descriptions being omitted owing to lack of space.]

(1) A case in which examination of the patient during an attack of pain altered a diagnosis, based on careful investigations, from duodenal ulcer to gall-stones.

(2) A case in which the severity of the pain led to a diagnosis of gall-stones and a fruitless operation; in which a radiologist later found a lesser curvature ulcer; but in which the clinical analysis led to a diagnosis (proved at a second operation) of "chronic posterior duodenal ulcer adherent to the pancreas."

(3) A case of chronic colon spasm previously diagnosed as (a) gastric ulcer, (b) renal colic, and leading to laparotomy.

(4) A case of chronic right-sided colon spasm for which appendicectomy was performed.

(5) A case of aortic disease with abdominal angina subjected to investigations of the alimentary tract.

(6) A case in which opinions as diverse as coronary arterial thrombosis and gall-stones were entertained by different observers.]

CONCLUSION.

It is a criticism sometimes levelled at the clinician that his work is regrettably unscientific. In general the criticism may seem justified, and we know well enough that we cannot make of medicine an exact sort of science. But in particular it is indisputable that a careful clinical examination or inquiry is just as much a scientific procedure as any other measure of research. According to Huxley's definition, "Science is nothing but trained and organized common sense"—a definition which we should be very ready to accept, and which applies particularly well to clinical work.

We hear much talk at the present day of research in general practice. I marvel at the temerity of anyone who can suggest that the busy practitioner should add another burden to his arduous life; but if there is one way of research not involving too great a consumption of time, and open alike to the general practitioner or to any other branch of the profession, it is that of keeping very full clinical notes on selected cases with a view to the solution of a selected problem in symptomatology. No symptoms better lend themselves to such a process of inquiry than some of the common pains of daily practice. A series of cases of headache, backache, or abdominal pain, as fully investigated as circumstances will permit, and carefully followed through the years, will certainly provide individual rewards for their investigator, and may ultimately furnish the material for a reasoned contribution to morbid physiology. System and patience are necessary, together with an inquiring mind. The only essential apparatus for the research is a good card index.

GANGRENE FOLLOWING THE USE OF ERGOTIZED RYE BREAD.

BY

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EARLY in 1923 we reported at the Liverpool Medical Institution a case of gangrene in symmetrical toes, a condition which followed upon a diet of ergotized rye bread.¹ In view of the recent article in this *Journal* describing symptoms, resembling those of ergotism, among foreign Jews in the Manchester area,² a synopsis of the essential features of epidemic ergotism and of this case of gangrene will now have greater interest.

Although the ergot fungus (*Claviceps purpurea*) occurs most commonly in rye, it occasionally infects wheat, oats, and barley, and, failing its usual host, it can exist on the following grasses: Poa, Phleum, Anthroxanthum, Agrostis,

Elymus, and others. The conditions favourable to propagation are a poorly cultivated or damp, clayey soil, and a wet season, together with the presence, at the borders of the field, of grasses which can harbour the fungus. The chief active principles of ergot have been proved by Barger, Dale, and others to be the alkaloids ergotoxine and ergotamine, and the amine bases tyramine and histamine.³ Ergotoxine, which stimulates the peripheral motor sympathetic mechanism, causes the arterial constriction which, when prolonged, results in gangrene; excessive doses of ergotoxine paralyse the myoneural junctions of the motor sympathetic endings; tyramine, like adrenaline, stimulates both motor and inhibitory sympathetic receptors; and histamine, which is a direct stimulant to involuntary muscle, causes, as is well known, a large fall in blood pressure.

Ergotism may be of two types—the convulsive and the gangrenous. The former predominated in epidemics in Germany, Russia, and Eastern Europe; the latter in France and Switzerland.

The onset of the convulsive type is characterized by malaise, dizziness and headache, nausea or vomiting, colic with chronic diarrhoea, and cold extremities—symptoms of small diagnostic value. The more characteristic symptom of formication begins in the fingers and toes, and may spread to the body. Severe cases exhibit gastro-enteritis with muscular twitchings or painful clonic and, later, tonic contractions of different muscles, while, finally, contractions, chiefly of the flexor muscles of the limbs, may result.

The gangrenous type may exhibit similar initial symptoms; then follows, after intervals varying from a few days to several weeks, great pain with an erysipelas-like reddening of the skin and swelling in some peripheral part. This gives place to pallor and anaesthesia, cyanosis, darkening of the part, and the appearance of gangrenous blisters with separation of the epidermis; a sharp demarcation line generally results.⁴

From a study of the epidemics it appears that some individuals are more sensitive to ergot than others; thus instances are noted where some members of families eating the same ergotized bread remained unaffected or mildly affected while others were severely poisoned.⁵ The time of appearance of gangrene is also uncertain; it is stated to have occurred four days after the consumption of the ergot,⁶ or may be delayed for a month, or perhaps occur after consumption has ceased.⁷ Some of these last cases appear doubtful, although Kobert recorded delayed poisoning in animals.⁸ Both Kobert and Grünfeld noted in Russia that epidemics occurred shortly after harvest time, and generally in years following a preceding bad harvest, which caused the people to eat the new season's rye shortly after it had been reaped. Grünfeld also showed that ergot kept in a dry room lost activity by one-half each two months succeeding the harvest.⁹ The proportions in rye which have caused epidemics vary from 1 per cent. in the Poltova, Kursk, and Tomsk epidemics¹⁰ to 7 per cent. in the Novgorod epidemic (1879) and more.¹¹ Ergot in doses of 0.2 gram daily for one month has been stated to cause gangrene two months later,¹² and 1 gram daily induced intestinal symptoms in a few days,¹³ while Lehmann regards 0.2 per cent. and upwards as likely to be injurious proportions in meal.¹⁴

The following is the clinical record of a man, aged 42, a Polish Jew, by trade a travelling salesman, who had lived in England for thirty-five years.

He was admitted to the Royal Infirmary, Liverpool, on November 9th, 1922, complaining of pain and discoloration of the second toe of his left foot. He stated that he noted first some numbness in the toe, which later became red and finally black. The process was slow and occupied some five weeks. His history revealed that the same toe on the opposite foot had been amputated twelve months previously for an exactly similar condition two or three months after the first appearance of a discoloration.

Condition on Admission.—The terminal phalanx was obviously gangrenous and quite dry, but showed no definite line of demarcation; the toe was very painful, especially at night. There was no arterio-sclerosis, diabetes, or renal disease, and, although it was impossible to feel pulsation in either the anterior or posterior tibial artery, the radial arteries were not unduly palpable or thickened. There was no apparent disease of the heart, and the systolic blood pressure—taken after operation—was 140 mm. of mercury. Either thrombo-angiitis obliterans or Raynaud's disease seemed the obvious diagnosis, but there had been no preliminary spasm of the arterioles. When asked what kind of bread he ate, he stated that

he always ate black or rye bread, known as "Kosher" bread. At the amputation of the second toe on November 17th there was an extraordinary lack of bleeding, but the wound healed well without further gangrene. The patient was seen on January 20th, 1923, and was well except that the circulation was still somewhat sluggish, although he had then given up rye bread for two months.

Pathological Report.—Dr. W. Howel Evans, lecturer in pathology, Liverpool University, reported as follows: The arteries of largest calibre, at the level of the first phalanx, show well-marked medial hypertrophy without calcification, and considerable regular, diffuse, intimal thickening and *ante-mortem* thrombosis; in one of them the clot is well organized and partly canalized. There is a very slight degree of fibrosis of the adventitia. In sections cut at the level of the second phalanx the more distal vessels show less marked changes, consisting chiefly of a moderate degree of intimal thickening, sometimes irregular and without thrombosis. In this region the muscle is largely necrotic, no definite changes are observed in the arterioles or the nerves, and there does not appear to be any gross alteration in the veins.

A specimen of the rye bread usually eaten by this patient was examined microscopically and revealed mycelial tissue, which, in chloral hydrate solution, exhibited the oil globules characteristic of ergot. An extract was prepared with 60 per cent. alcohol acidified with citric acid; it was purified with absolute alcohol, and the residue, after evaporation, was dissolved in water. This extract, in doses representing 88 and 46 grams of bread, injected intramuscularly into a white Leghorn cock, produced after an hour distinct cyanosis and blackening of the back part of the comb and marked pallor of the anterior borders of the wattles.

With the assistance of Dr. W. Hanna, deputy medical officer of health, Liverpool, we found that samples of the flour also contained ergot tissue, and that, in the rye at the mill, ergot was obviously present. One sample picked over showed 0.1 per cent. by weight adulteration with pure ergot, and, in addition, many of the rye grains were blackened and microscopically revealed mycelium. In our opinion 0.1 per cent. represents the minimum of adulteration, and, from the relative frequency of mycelium in the first loaf, we surmise that the adulteration before our inquiries were broadcast was probably greater. We were informed that the rye flour was partly diluted with wheat flour by the baker, but he was vague about the exact proportion of the admixture; microscopical examination indicated that it was approximately one-half. As a precautionary and prophylactic measure the medical officer of health gave instructions for the dilution with wheat flour to be increased.¹⁵

It was ascertained that the rye had been grown in a comparatively restricted area of Lancashire; the farmer was quite well aware that his rye was infected, and, since 1922 was a wet year, it was presumably more heavily infected than usual. This patient, however, had suffered from gangrene a year previously, and it may be that in this area the relative infection shows merely seasonal variations.

Samples of the pure ergot taken from the rye were extracted, and when the extract was added to the isolated virgin guinea-pig uterus suspended in Tyrode's fluid it produced powerful contractions of the uterus in doses representing 0.02 gram of ergot.

An important warning must here be emphasized—namely, that this pharmacological test is fallacious and misleading if it is performed with the rye bread or an extract prepared from it, because certain cereals and starches contain a principle which induces powerful uterine contractions, but instead of causing, like ergotoxine, a rise in blood pressure, it induces a very marked fall—actions resembling those of histamine. This was noted by Macdonald and Grier¹⁶ in testing the rye in Manchester. Our investigations showed that this uterus-contracting principle was present in wheat, oatmeal, maize, rice, and potato in variable amounts, and in their starches, but it was not present in specimens of chemically pure Lintner's starch. By various methods, such as that of Kutscher,¹⁷ attempts were made to isolate the pure principle. It was found that concentrated extracts produced a decided red colour with Pauly's diazobenzene reaction, which is given by both tyrosine and histidine, and also with Totani's reagent,¹⁸ which is believed to be characteristic of histidine, but it has not been possible to prepare either a crystalline picrolonate or picrate, and, by determining the melting point of the salt, to identify finally the principle with histamine. The pharmacological actions and colour tests make it probable

that it is histamine or a nearly related substance, and that our inability to obtain other than an amorphous picrate may be due to some impurity.

The chief difficulty is to distinguish this case from Buerger's thrombo-angiitis obliterans, which affects usually the lower limb of a male between the ages of 30 and 40, and may recur in the other limb later. As Buerger¹⁹ and Parkes Weber²⁰ have shown, this disease is common among Jews, but it is not confined to this race.²¹ Evidence has been adduced to suggest an organismal²² and also a nicotine²⁰ etiology.

We delayed full publication of our knowledge because we were not satisfied that our isolated case could be ascribed solely to ergot poisoning, and we should similarly hesitate to accept as proofs of ergotism evidence of numbness and coldness in the extremities of Jewish tailors, whose working attitude involves popliteal compression and whose workrooms may be cool. Since careful inquiries by Dr. W. Hanna, the deputy medical officer of health, in 1923, and again recently, failed to reveal other cases exhibiting symptoms of ergotism amongst foreign Jews in the Liverpool area, the presence of 0.1 per cent. of ergot in rye has not been proved dangerous, and we must regard our case either as a sporadic one of idiosyncrasy to gangrenous ergotism, or as a case of slight thrombo-angiitis obliterans contributed to by a diet containing ergot, for the following reasons: (1) the man ate exclusively rye bread containing at least 0.1 per cent. active ergot; (2) his attacks occurred in succeeding Novembers, about two months after the fresh ergotized rye was milled; (3) the absence of general arterio-sclerosis and diabetes;

(4) if 0.2 gram of ergot daily be regarded as causing gangrene this man would have taken this amount in three-quarters to one pound of rye bread; (5) cases of thrombo-angiitis obliterans usually involve the larger vessels of the limbs, whereas our case was peripheral and circumscribed.

REFERENCES.

- ¹ Kelly and Dilling: *British Medical Journal*, 1923, i, 287; *Lancet*, 1923, i, 336, 460, 566, 620.
- ² Robertson and Ashby: *British Medical Journal*, 1928, i, 302.
- ³ Barger and Dale: *Journ. Chem. Soc.*, 1907, xci, 537; *Trans. Chem. Soc.*, 1910, xevii, 284; *Journ. Physiol.*, 1909, xxxix, 25; 1910, xli, 318.
- ⁴ For details and literature see Cushman, A. R.: "Mutterkorn" in *Hefter's Handbuch d. exper. Pharmacol.*, 1924, Bd. II, 1327.
- ⁵ Woollaston: *Phil. Trans.*, 1762, lli, Part 2, 523; Bonjean: *Lancet*, 1845, i, 701; *Compt. Rend.*, 1845, xix, 1367; Siemens: *Arch. f. Psych.*, 1881, xi, 116.
- ⁶ Franqué: *Med. Jahrb. f. Nassau*, 1856.
- ⁷ Maissonneuve: *Gaz. des Hôp.*, 1854, No. 18; Debove: *Soc. Méd. des Hôp.*, February 27th, 1880; Boissarie: *Ann. de Gynéc.*, 1880, xlii, 422.
- ⁸ Kobert: *Arch. f. exper. Path. u. Pharm.*, 1884, xviii, 335, 348-49.
- ⁹ Grünfeld: *Dissert.*, Dorpat, 1892, p. 42.
- ¹⁰ Kobert: *Lehrbuch der Intoxik.*, 1906, Bd. 2, p. 613. Griasnoff: *Lond. Med. Record*, 1883, xi, p. 78.
- ¹¹ Swiatlowsky: *Lond. Med. Record*, 1880, viii, 412.
- ¹² Debove: *Op. cit.*
- ¹³ Uberti: Quoted by Lehmann, p. 110.
- ¹⁴ Lehmann: *Arch. f. Hyg.*, 1893, xix, 113.
- ¹⁵ Report of Medical Officer of Health, Liverpool, 1922, p. 182.
- ¹⁶ Macdonald and Grier: *British Medical Journal*, 1928, i, 410.
- ¹⁷ Kutscher: *Zentralbl. f. Physiol.*, xxiv, 163; *Zeit. Natur. Genuss.*, 1905, x, 528; Barger and Dale: *Trans. Chem. Soc.*, 1910, xevii, 2594; *Idem: Journ. Physiol.*, 1910, xli, 499; Hanke and Koessler: *Journ. Biol. Chem.*, 1920, xliii, 543.
- ¹⁸ Totani: *Biochem. Journ.*, 1915, ix, 387.
- ¹⁹ Buerger: *Amer. Journ. Med. Sci.*, 1908, cxxxvi, 567; *Circ. Disturb. of Extremities*, Lond., 1924, 317.
- ²⁰ Weber, F. Parkes: *Quart. Journ. Med.*, 1916, ix, 289; *Lancet*, 1925, ii, 25; cf., Sourasky, *British Medical Journal*, 1927, i, 444.
- ²¹ Telford and Stopford: *British Medical Journal*, 1924, ii, 1035; Wheeler: *Ibid.*, 1927, i, 225.
- ²² Rabinowitz: *Surgery, Gynecology and Obstetrics*, 1923, xxxvii, 353.

NOTES ON THE INJECTION TREATMENT OF VARICOSE VEINS.

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THROMBO-PHLEBITIS and peri-phlebitis of a varix sometimes occurs during or very soon after a toxic fever, such as typhoid fever; and also after a direct blow on the varix; fibrosis and cure of the varix follow. The preceding phlebitis, however, has usually been treated with alarmed respect and lengthy rest in bed.

Recently I met with a traveller who, during a mild typhoid fever, developed phlebitis of the varicose veins in one leg. He rejected advice to remain in bed, and with a thick solid red tender vein from ankle to saphenous opening took a four weeks' journey home—and then permitted me to reproduce by injection-stages a very similar clinical condition in the varicose long saphenous vein of the other leg.

It has been noted that phlebitis of a normal vein is set up sometimes by its intravenous injection with arsenobenzol compounds, quinine salts, or chaulmoogra oil derivatives. In my experience this has been transient with the first two drugs; the oil derivatives more easily cause fibrosis and occlusion of the healthy vein.

In 1913 in West Africa, unable to find an arm vein in a fat alcoholic patient suffering from subtertian malaria with cerebral symptoms, I had recourse to a visible varix in his leg; 10 grains of quinine hydrochloride in 10 c.cm. of boiled rain water were injected into the varix, and the leg then lifted high. This produced thrombo- and peri-phlebitis. He survived to express satisfaction for the cure of the varix. Some time later I injected salvarsan into a varix in the leg of another patient, being foiled of an arm vein; cure of the varix resulted after thrombo-phlebitis and fibrosis. Such an experience led, with trepidation, to some "cures" of varicose veins with quinine injections until, after the war, Sicard's work brought encouragement to proceed less fearfully and sporadically.

During the last few years I have treated over 200 cases of varicose veins of the leg by injecting into the varices quinine hydrochloride, sodium salicylate, or sodium

chloride. In over 100 the quinine salt has been used. In my hands, of the three, it has been the least uncertain in effect.

Recently, with Dr. J. C. Gilroy, some observations were made on a perhaps callous, but consenting and rewarded, male patient in the Seamen's Hospital, Royal Albert Dock, who had many varicose veins in both legs. About two inches of uninjected varix were dissected out for control comparison; and also, at intervals of time, the same length of other varices, ten to fifteen minutes, twenty-four hours, and seven days after their intravenous injection with one or other of quinine hydrochloride 13 per cent., sodium salicylate 20 per cent., and sodium chloride 20 per cent.

Naked-eye and microscopic examination of the several injected varices revealed, ten to fifteen minutes after injection, no clot and no recognizable change in vein wall; twenty-four hours after injection, however, the lumen was filled with firmly adherent clot, the intima was swollen, with damaged cell nuclei, and there was round-cell infiltration of the tissue outside the vein. Seven days after injection the firmly adherent clot was undergoing organization.

The treatment has had its difficulties, tediums, and anxieties for patient and operator. I have found, as compared with many thousand injections into normal arm veins, that only the larger varices are easy to inject. In most cases the patient must stand to be injected. For the operator's convenience this standing must be on a level considerably higher than that of the floor—a severe trial for the nervous patient; all are nervous at first, and some always. Often the patient may sit high enough to suit the operator; very rarely can injection of a varix be performed with the patient lying down. A tourniquet above the varix helps not at all, one below it sometimes helps a very little.

The more advanced the varicose condition the less uncertain is the effect of the injected drug; but intensity of effect may vary in the same leg, with apparently the same size and condition of varix, and same dose of same drug. Sodii salicylate 20 to 30 per cent., sodii chloride 20 per cent., and quinine hydrochloride 13 per cent.—each sometimes has failed after more than one injection into a varix to produce the requisite obvious phlebitis. With each the thrombo-phlebitis and peri-phlebitis has sometimes extended quickly far beyond the usual one or two inches of vein above and below the point injected.