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ADDENDUM

Since this paper was submitted, immunological studies have shown that the serum of patients with Hashimoto's disease contains a precipitating auto-antibody which reacts specifically with human thyroglobulin. A preliminary communication of this work has appeared (Roitt *et al.*, 1956). The thyroglobulin precipitin test was positive in all the patients listed in Table I and in several from the post-operative group where only part of the thyroid had been removed; Case 3 and Case 4 still show the precipitin nine and twelve months after subtotal thyroidectomy, though results of serum protein tests are now normal. Case 5 has failed to show precipitins by the method used after 3 years of thyroid administration. Full results will be published elsewhere.

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VISCERAL LESIONS IN HERPES ZOSTER

BY

R. WYBURN-MASON, M.A., M.D.

The peripheral nerves and posterior and trigeminal sensory nerve roots contain not only various sizes of myelinated, but also unmyelinated "afferent" fibres. Distally the afferent unmyelinated fibres originate (or end) as free nerve endings not only in the epidermis or dermis, but also between the deeper tissues, including muscles, periosteum, joints, and fascia (Ranson and Davenport, 1931; Feindel, Weddell, and Sinclair, 1948). They also arise (or end) on the blood-vessel walls. Some of them are visceral in origin (Kuntz and Hamilton, 1938). All the evidence suggests that in the somatic tissues these fibres conduct impulses which give rise to diffuse, radiating, compelling burning pain (see Fulton, 1949).

In the posterior nerve roots all the afferent unmyelinated fibres of the peripheral nerves, whether they originate in the skin, deep somatic tissues, blood vessels, or viscera, are grouped together laterally. Division of the lateral part of these roots cuts the unmyelinated fibres, and now on stimulation of the peripheral nerve

distal to the section no autonomic reflex changes occur as they do in intact animals (Ranson and Davenport, 1931; Clark, Hughes, and Gasser, 1935).

Mode of Production of Lesions of Herpes Zoster

The skin lesions of herpes zoster lie in the area of sensory supply of the posterior and trigeminal nerve roots. They manifest themselves firstly as a reddening of the skin followed by oedema and blister formation—that is, the appearance of fluid between the epidermal layers. Typical inflammatory changes are found in the skin papillae, in the deeper parts of the corium, and in the hair follicles. Subcutaneous fat may also contain knots of inflammatory cells. Lewis (1927), in his classical researches, showed that irritation of sensory nerves and the posterior nerve roots results in vasodilatation and the release of a vasodilator substance (H-substance), probably histamine, in the skin. He further demonstrated that in cases of herpes zoster the same substance was released in the affected tissues and that "herpetic and herpetiform eruptions occur as sequels to lesions of the sensory nerve tracts; not only do they follow irritative lesions of the (root) ganglion, but they are produced also by lesions of those tracts distal to the ganglia themselves." It seems probable that the unmyelinated fibres of the posterior roots with free nerve endings in the skin and other tissues and on the blood vessels are those concerned.

Herpes Zoster and Lesions of Deep Somatic Tissues

When zoster is of gangrenous type the lesions extend deeply and lead to much scarring. Glandular swelling and inflammation in the region of the affected skin lesions is usual and may precede the latter (Bichelon, 1907; Lebel, 1920; Ramond, 1923), so that they cannot be due to secondary infection of the skin. The subcutaneous tissues, fat, and muscles may contain painful and swollen areas identical in character with "fibrositis" and "myositis" (see Brain, 1931; Wilson, 1940; Ford, 1946). Synovial effusions occur in the affected areas and the joints may become ankylosed with fibrous tissue. The pericapsular joint tissues are often swollen and painful, and, when the hand is affected, this gives appearances indistinguishable from those of rheumatoid arthritis, so-called "periartthritis chronica rheumatica" (Guillain and Pernet, 1910; Guillain and Rouvillier, 1913). The affected limb may exhibit oedema and cyanosis. When the lower limb is involved, permanent pitting oedema may remain (Wilson, 1940). The muscles sometimes waste either immediately or after a variable period. When a limb is affected, its bones may become osteoporotic (see Schönfeld, 1929), or show Sudeck's atrophy (Sudeck, 1910). Schleicher (1949) describes chronic inflammatory changes in the marrow of the affected bones. Pleural reactions and haemorrhagic pleural effusions may appear beneath zoster of the chest wall (Curtin, 1902; Mann, 1931) or there may be symptoms and signs of irritation of the parietal peritoneum (Ford, 1946).

In cases of ophthalmic herpes sterile inflammatory changes often occur in the eye, resulting in a panophthalmitis and not infrequently in the appearance of haemorrhages and thromboses in the retinal vessels. Afterwards the eyelids may remain permanently oedematous. It is reasonable to suppose that these manifestations in the deeper somatic tissues are produced in a manner analogous to those in the skin—namely, by disturbance in the unmyelinated fibres of the posterior spinal and trigeminal sensory nerve roots.

Herpes Zoster Accompanied by Visceral Lesions

Unmyelinated afferent fibres with their cell bodies in the posterior root ganglia run from the viscera uninterruptedly through the autonomic ganglia and white rami communicantes to enter the posterior nerve roots with those from somatic tissues. The posterior nerve roots through which

the afferent fibres from the various viscera enter the cord are as follows (Lewis, 1942; White and Smithwick, 1947; Kuntz, 1953):

Heart	C 8-D 4 (?)
Lungs	D 2-5
Oesophagus	D 4-5
Stomach and duodenum	D 6-8
Liver and gall-bladder	D 7-8 right
Pancreas	D 8 left
Small intestine	D 9-10
Appendix and ascending colon	D 10-L 1
Epididymis	D 10
Ovary, testis, and suprarenal	D 10-11
Bladder fundus }	D 11-L 1
Kidney }	
Uterine fundus }	L 2-3
Colonic flexure }	
Sigmoid and rectum	S 2-5
Cervix	
Neck of bladder, prostate, and urethra	

It might be expected that irritation of the unmyelinated afferent fibres in the posterior nerve roots or peripheral nerves, or their cell bodies in the posterior root ganglia, would produce changes not only in the skin and somatic tissues, but also in the viscera. In his classical paper on herpes zoster Head (1893) did not specifically mention visceral involvement. In the literature on herpes zoster, however, there are a number of descriptions of localized visceral disturbances accompanying the skin lesions. I have observed this association in numerous cases, of which Cases 1-8 cited below are typical examples. These cases and those taken from the literature are summarized in the Table.

Author	Site of Zoster	Visceral Disturbance
Case 1, present series	C 3-4	Redness, oedema, inflammatory changes, and bleeding on right side of larynx and trachea
Andréassian (1934)	L. cervico-scapulo-thoracic	Endocarditis and tachyarrhythmia
Turner (1909) ..	D 2	Paroxysmal tachycardia during and following attack
Mann (1931) ..	D 3-4	Marked bradycardia
Case 2 of Spillane and White (1939)	C 8-D 2, and D 4-6	Followed 3½ years later by progressively severe anginal pain at site of zoster, cardiac enlargement, and E.C.G. changes
Curtin (1902) ..	D 7-8	Pleuritic pain, friction rub or pleural effusion
Mann (1931) ..	D 7-8	" " "
Brain (1932) ..	D 7-8	" " "
Ryle (1932) ..	D 3-4	Gastro-intestinal disturbance
Variot (1907) ..	Intercostal	Disturbance of passage of food down oesophagus
Curtin (1902) ..	Upper abdominal	Anorexia and constipation
" " " " " "	Lower thoracic margin	Bowel atony and abdominal distension
Rayer (1935) ..	Abdominal	Gastro-intestinal disturbance preceding, during, and following rash
Frisch (1908) ..	"	" " "
Bielschowsky (1914)	"	" " "
Fuchs (1840) ..	"	" " "
Case 2, present series	D 6-8	Severe spasm of prepyloric region of stomach (Fig. 1) with reddening of gastric mucosa, symptoms being partly relieved by atropine
Case 3, present series	D 7-8	Nausea, vomiting, and anorexia, followed by haematemesis and appearance of gastric ulcer on lesser curvature (Fig. 2)
Hess and Faltischek (1925)	D 6-10	Gastric hyperacidity cured by paravertebral sympathetic block
Stone (1948)	D 9-10	Haematemesis
Fitzpatrick (1948)	D 9-10	Nausea, anorexia, burning epigastric sensation, haematemesis, and achlorhydria. Radiographs showed no peptic ulcer. Symptoms unrelieved by alkalis and gradually disappeared with skin eruptions
"Surgeon" (1950)	D 8-10	Intestinal paralysis and vomiting. Colon radiologically normal, "the disturbance presumably being in the small intestine"
Donaldson (1948)	D 9-11	Anorexia, nausea, and haematemesis, the symptoms disappearing with the skin changes
Curtin (1902) ..	D 10-11	Fever and symptoms resembling appendicitis
Case 4, present series	D 11-L 1	Intense constipation and local spasm of ascending colon with dilatation distal to this, symptoms being partly relieved by atropine
Case 5, present series	D 11-L 1	Intense constipation, though taking no drugs. Laparotomy revealed inflammatory changes in ascending colon
Curtin (1902) ..	Over kidney and passing to abdomen	Persistent haematuria

Author	Site of Zoster	Visceral Disturbance
Grossmann (1932)	D 10-L 2	Renal colic. No urinary disturbance or evidence of calculi
Van der Scheer (1913)	D 12	Polyuria and severe persistent constipation
Nieuwehuise (1914)	D 12	Ileus
Case 6, present series	D 11-L 2	Spasm of ascending and transverse colon and dilatation of distal colon. Inflammatory changes in bladder mucosa, especially on left. Symptoms partly relieved by hyoscyamus
Darget (1929) ..	Inguinal	Cystitis and haematuria. Cystoscopy showed a raised inflammatory area on bladder wall
Volk, quoted by Schönfeld (1929)	Buttock	Zoster of bladder and haemorrhagic cystitis
Ford (1946) ..	Abdominal	Symptoms of bladder irritation
Watts (1948) ..	Upper lumbar root zone	Disturbance of bladder function and haematuria
Siding (1909) ..	L 1	Rectal and bladder disturbance
Case 7, present series	D 12-L 2	Transient severe inflammatory changes in bladder mucosa. Spasm of descending colon and rectum and dilatation of transverse colon above (Fig. 3)
Case 8, present series	L 2-3	Inflammation of mucosa of sigmoid colon, spasm of descending colon (Fig. 4). Inflammation of neck of bladder. Symptoms partly relieved by hyoscyamus
Dubois (1926) ..	Buttock	Frequency, dysuria, and eventually urinary retention. Cystoscopy showed vesicles on left side of base and lateral wall of bladder
Wolbart, quoted by Dubois (1926)	"	Herpes of ureteric orifice
Satani (1926) ..	"	Zoster of bladder on same side and suppuration of large intestine
Rouyer (1903) ..	Gluteal region	Frequency and dysuria
Chesterman (1932)	"	Lesions of bladder
Belgodere (1924)	Buttock	Uterine cervicitis and enlargement
Davidsohn (1890)	Gluteal and sacral	Transient paralysis of bladder and rectum
Bernhardt (1890) ..	" " "	" " "
Oppenheim (1911)	" " "	" " "
Tomey (1909) ..	Sacral	Frequency and disturbance of bowel emptying
Parsat (1910) ..	Gluteal region, scrotum, and perineum	Urinary and faecal retention for 14 days
Frankl-Hochwart (1913)	R. genital area	Dysuria and disturbance of bowel emptying
Spitzer (1925-6) ..	Buttock and one leg	Severe urinary disturbance lasting 3 weeks
Mann (1931) ..	Sacral	Rectal and bladder disturbance

Case 1.—Male, aged 42. Ten days before he attended hospital severe pains began in right side of neck and shoulder, followed after three days by rash over right shoulder and front, back, and side of lower part of neck. Three days afterwards he complained of cough, thick mucoid expectoration streaked with blood, and some hoarseness. **Examination:** Typical painful zoster eruption in distribution of right C3 and 4 segmental zones with hyperaesthesia. No abnormal physical signs in other systems. Radiographs of chest normal. Laryngoscopy: redness and oedema of right vocal cord. Bronchoscopy: marked oedema and redness, strictly limited to right side of tracheal mucosa, extending downwards to carina. With fading of the skin lesion the cough, expectoration, and hoarseness gradually ceased.

Case 2.—Female, aged 41. Three weeks before coming to hospital she developed hemigirdle pain in the right lower chest and between the shoulder-blades. Four days later zoster appeared in this region with a sensation of substernal pressure and epigastric aching immediately on swallowing, as though food was stuck. The aching was not improved by taking alkalis. **Examination:** Typical zoster eruption in right D 6-8 segmental areas. Barium meal: marked spasm in the prepyloric region as shown in Fig. 1. Fractional test meal: high acid curve. Gastroscopy: spasm of pyloric antrum, the mucosa of which was reddened and swollen. Vomiting relieved by belladonna, 12 min. (0.7 ml.) t.d.s.; it reappeared if drug omitted. The skin lesions and digestive disturb-

FIG. 1.—Case 2. Right D 6-8 zoster. Barium meal radiograph showing spasm of pyloric antrum.

ance died down in course of the next three months, by which time the spasm had disappeared radiologically. Fractional test meal now showed some fall in acid secretion.

Case 3.—Male, aged 72. No previous digestive disturbance. He developed herpes zoster of right D 7 and 8 zonal areas. At height of attack he complained of nausea, vomiting, and severe anorexia, which lasted for several months. Skin lesions, followed by post-herpetic pain of two types, a constant ache, and a sharp stabbing pain brought on by movement of trunk; pain varied in severity, but worse in damp and cold weather. Two months after onset two severe haematemeses, each of about 1 pint (570 ml.). A barium meal one month later showed an ulcer crater on the lesser curvature of the incisura (Fig. 2). Despite various antacids the digestive symptoms persisted.

FIG. 2.—Case 3. Radiograph taken during barium meal, showing gastric ulcer on lesser curvature developing with zoster of right D 7-8 zonal areas.

sation and tenderness in region of right hip when he lay on it, and a week later this region became painful. Within a few days a segmental zoster eruption appeared in the painful region, extending from 1½ in. (3.8 cm.) below the umbilicus to groin and round to back in distribution of right D 11-L 1 nerve roots. With onset of rash complete constipation set in. A barium enema showed marked spasm of ascending colon with dilatation of gut distal to this. Constipation partly relieved by administration of atropine by mouth. With healing of rash marked post-herpetic pain remained, but more normal bowel function gradually returned. Two years after onset of herpes bowels still remained sluggish.

Case 5.—Female, aged 62. Developed herpes in right D 11-L 1 distribution. With onset of rash absolute constipation developed and persisted for three weeks, during which time no response to enemata was obtained. Laparotomy performed, but no obstructive lesion found in bowel. The ascending colon was, however, oedematous and engorged, and was excised. Histologically it showed non-specific inflammatory changes in all coats for a distance of 25 cm. Rash faded and the scars healed within six weeks, but pain persisted with some severity for nearly two months. For next 10 years the affected region remained tender and bowel function extremely sluggish. Emptying never occurred without use of purges. One month after development of the herpes her two daughters developed chicken-pox.

Case 6.—Female, aged 60. Two weeks previous to attendance at hospital she developed painful irritation of left lower abdomen followed by a herpetic rash passing to loin and back. Two days prior to attendance sudden severe frequency and burning micturition began, and on day of attendance some haematuria occurred. She was severely constipated. **Examination:** Typical herpetic rash and hyperalgesia in left D 11-12 segmental areas of abdomen and loin. Urine: albumin and blood; catheter specimen: numerous R.B.C. and pus cells; no organisms present. Cystoscopy: marked redness and oedema of bladder fundus, chiefly on left side. Barium enema: marked spasm of ascending and transverse colon and dilatation of descending colon. Treated with tincture of hyoscyamus, 30 min. (1.8 ml.) t.d.s., with some relief of urinary symptoms and constipation. With healing of the skin lesions urinary symptoms and constipation gradually diminished, though both these and pain persisted during the next six months.

Case 7.—Male, aged 50. Two months prior to attending hospital he developed severe left lumbar pain spreading into left loin, iliac fossa, and front of thigh. Three days later zoster appeared in this area. At the same time he complained of difficulty in defaecation and constipation, considerable frequency of micturition, difficulty in emptying the bladder, and burning pain in penis when bladder was full and during micturition. Symptoms at first severe, but diminished somewhat in severity in course of next two months. Visceral symptoms varied with pain. **Examination:** Site of zoster scabs very hyperalgesic and corresponding to left

D 12-L 2 segmental areas. Cystoscopy: marked congestion and submucous haemorrhages in the floor and roof of the bladder mucosa, which bled easily and appeared inflamed. Urine: no organisms, but some pus cells present. Barium enema: markedly spastic descending colon and rectum, with dilatation of transverse colon above (Fig. 3). Cerebrospinal fluid: normal. Repetition of barium enema four weeks later showed much diminution in spasm. Over the next two years he was subject to bouts of pain with inability to empty the bladder.

Case 8.—Male, aged 52. Two weeks previous to attending hospital he developed pain in front of left thigh and knee, extending to outer side of left hip. Four days later a rash appeared in painful area and after another four days he developed severe constipation with a desire to empty the bowels; he passed dark blood-stained mucus and had some difficulty and pain on micturition. **Examination:** Typical herpes zoster and hyperalgesia in left L 2-3 segmental areas. Urine: pus cells but no organisms. Rectal examination: normal. Sigmoidoscopy: swollen reddened mucosa at uppermost limit to which the instrument could be passed. Barium enema: severe spasm of descending colon. Cystoscopy: neck of bladder intensely red and oedematous. Intestinal and urinary symptoms considerably relieved by administration of tincture of hyoscyamus, 30 min. (1.8 ml.) t.d.s. Pain, skin lesions, and intestinal disturbance gradually disappeared in the next three months.

FIG. 3.—Case 7. Left D 12-L 2 zoster. Barium enema radiograph showing spasm of descending colon.

Comment

After reference to the course of the afferent visceral fibres shown in the Table it will be observed that the visceral disturbance in cases of herpes zoster occurs particularly in those viscera, or parts of viscera, supplied with afferent fibres by the posterior nerve roots corresponding to the zonal skin areas affected. As in the skin and deep tissues, so the effects on the viscera are to produce vasodilatation, oedema, haemorrhages, and inflammatory changes, and to predispose to vascular thromboses. The affected gut exhibits local hypermotility and spasm. The evidence suggests that, apart from the parasympathetic and sympathetic, the viscera receive a third type of nerve supply which may affect their activity. The bipolar cell bodies lie in the posterior root ganglia, and their peripheral axons pass to the viscera without relay through the autonomic ganglia. They are, in fact, the so-called visceral "afferent" fibres. This perhaps explains to some extent the frequently reported variable and uncertain effects on the viscera of stimulating the rami communicantes of the spinal nerves and the sympathetic chain in which such fibres run. It further raises the problem of whether "antidromic" centrifugal impulses are normally conducted by the "afferent" unmyelinated fibres.

Summary

In cases of herpes zoster the inflammatory skin lesions are thought to result from disturbance of the ganglion cells of the posterior or trigeminal root ganglia or of the "afferent" fibres of the posterior nerve roots or the peripheral nerves. Similar nerve fibres originate or end in the viscera. Evidence is adduced which seems to indicate that, accompanying the segmental skin lesions, there occurs disturbance of the viscus, or part of the

viscus, innervated by the corresponding nerve roots, which results in inflammatory lesions and spasm in the case of the hollow organs. This suggests that, in addition to the sympathetic and parasympathetic pathways, there exists a third nerve pathway by which visceral activity may be altered.

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In a booklet entitled *Health Services in Britain* (H.M.S.O., 3s. net) the Central Office of Information has added another useful publication to its series of "Reference Pamphlets." Starting with water supply and sewerage, the booklet proceeds to describe the other public health services, the National Health Service, and industrial health. There are additional sections on the health services in Scotland and Northern Ireland, on the Medical Research Council, and on professional training in Britain; a bibliography of Government publications; and a useful list of the names and addresses of health departments and organizations. Some statistics are given of the National Health Service. About 97% of the population of Great Britain uses the Service; 98% of general practitioners, the "great majority" of specialists, 94% of dentists, and almost all chemists are taking part in it. The cost of the Service amounts to about 3½% of the total national resources, and four-fifths of the gross cost (£570m.) falls on the Exchequer to be met from general taxation.

INFLUENCE OF HYDROCHLORIC ACID ON GASTRIC SECRETION AND EMPTYING IN PATIENTS WITH DUODENAL ULCER

BY

J. N. HUNT, M.D., D.Sc.

Physiology Department, Guy's Hospital Medical School,
London

There are at least three possible ways of accounting for gastric hyperfunction in patients with duodenal ulcer. They are: (1) an increased number of cells which secrete acid (Meyers, 1948; Guiss and Stewart, 1948; Hunt, 1950; Cox, 1952; Card, 1952; Hunt and Kay, 1954); (2) an increased vagal drive to the gastric mucosa (Dragstedt, 1956); and (3) a failure of the duodenal mechanisms which inhibit gastric activity; this hypothesis embraces both gastric secretion and emptying (Shay, 1944). The present paper is concerned with the last of these possibilities.

Methods

The main purpose of the present experiments was to examine the influence on gastric secretion of low concentrations of acid added to test meals. Such acid might be expected to have three effects: it should stimulate duodenal receptors which slow emptying and thus prolong gastric distension by the meal. Since gastric distension is a stimulus to secretion in man (Hunt and Macdonald, 1952; Macdonald and Spurrell, 1953) such slowing of emptying should increase gastric secretion; on the other hand, acid should depress secretion via the duodenal inhibitory mechanism or possibly by inhibiting the release of gastrin (Woodward, Lyon, Landor, and Dragstedt, 1954). Thus whether added acid increases or decreases gastric secretion will depend upon the balance between the increased stimulus of distension and the inhibition of secretion from the duodenum. It has been found that in most normal subjects adding sucrose to test meals delays emptying and reduces secretion, but in two the addition of sucrose caused an increase of secretion. On further examination it was found that in these two subjects increasing gastric distension produced an unduly large increase in gastric secretion (Hunt, 1954).

For the present experiments, which were mainly concerned with inhibition of secretion, it was decided to use a solution of glucose as the control meal to which acid could be added as a variable. By slowing the emptying of the meals with glucose it was hoped to minimize the effect of the added acid on emptying. A further advantage of adding glucose to both meals is that it minimizes (Bandes, Hollander, and Glickstein, 1940) the absorption of water from the stomach which occurs to some extent in man (Hunt, 1949), so that phenol red added to the meal may be used as a reliable marker to determine the volume of original meal remaining.

The methods used have been described (Hunt, 1954). In essence the technique involves giving a test meal containing a dye which is not absorbed in the stomach. After 30 minutes the gastric contents are recovered, and from the amount of dye remaining the volume of the original test meal in the stomach at the time of recovery may be calculated. Further, the volume of the gastric contents which has passed into the duodenum may be assessed, together with the total amounts of acid, chloride, and pepsin secreted. From the amounts of acid and chloride secreted the outputs of hypothetical parietal component and non-parietal secretions may be found. Twenty-seven volunteer students were studied and 18 tests were made in 16 patients with a diagnosis of duodenal ulcer without pyloric stenosis. The patients were under treatment in the medical and surgical wards, and the