The natural history of shingles

Events associated with reactivation of varicella-zoster virus

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THE viruses of herpes simplex and varicella-zoster are closely related. Both are DNA viruses with superficially similar appearance under the electron microscope, although there is a difference in the density of the DNA moiety (Goodheart *et al* 1968). There is some cross-reaction between certain of the antibodies of the two viruses (Ross *et al* 1965). The disease caused by both viruses is characterized by a primary infection with appearance of antibodies where there were none before. Following the primary infection with either virus the patient usually makes an apparently complete recovery, but the virus remains dormant in the host, and if the patient lives long enough it may be reactivated, in the case of herpes simplex virus not infrequently many times, in the case of varicella-zoster virus usually only once. The clinical manifestations of the recurren-attack are those of recurrent herpes simplex and of zoster, respectively. It is well estabt lished that a variety of stimuli (mechanical, a rise in temperature, ultraviolet light, emotion—possibly through the release of adrenaline) may provoke a recurrence of herpes simplex lesions (see *e.g.* Juel-Jensen 1969a). It is therefore surprising that some of the larger series of zoster record few instances of a provoking factor in the history of the attack. Hope-Simpson (1965), although making reference to "the classical precipitants of zoster—lead, arsenic, syphilis, spinal trauma and neoplasm . . . leukaemia and x-irradiation . . . and perhaps steroid therapy . . ." in his series of 192 cases found only two in whom he suspected a precipitating cause (a young man bitten by a horsefly, and a girl with an injured leg). Burgoon and others (1957) were very indefinite about precipitating factors. In the course of work on the effect of viral chemotherapy on herpes simplex infections I had been struck by the frequent history of trauma in patients with recurrent lesions. During more recent work on viral chemotherapy in zoster (described elsewhere; Juel-Jensen, 1969b; Juel-Jensen *et al* 1970) I had the opportunity of making a close inquiry into the immediate past history of 100 patients with zoster of recent onset.

Methods

The patients were referred by colleagues on the general medical and surgical services and by the ophthalmic surgeons in the Radcliffe Infirmary, and by general practitioners in Oxford. All patients were seen within four days of the first appearance of the lesion. In all a careful history was taken, including any evidence of a possible precipitating factor within the last fortnight of the first manifestations of shingles. The patients were given a general physical examination; they had a haemoglobin estimation, wbc, and platelet counts done, and a blood film examined. Their immunoglobulins were assayed and their urine examined to exclude possible unsuspected underlying malignant disease.

Results

The segmental distribution of the lesions in this series of patients is given in table I. There was a disproportionately high percentage of patients with ophthalmic zoster, because the ophthalmologists referred most of their cases of zoster to me, and ophthalmic

zosters are more likely to reach hospital than shingles in other sites. The distribution otherwise is like that in other published series, with little evidence of laterality, except perhaps in the cervical region (12 on the right, three on the left). Zoster involving motor nerves occurred at C6 in one patient, and three patients with ophthalmic zoster had associated paralysis of extrinsic eye muscles, and two a seventh nerve palsy, one with clinically obvious zoster of the geniculate ganglion, one without. The age distribution of the 100 patients was like that of other series.

In this series 65 per cent of the patients gave a good history when questioned closely of a possible precipitating event immediately preceding their shingles, usually within a

TABLE I

INCIDENCE OF ZOSTER AT VARIOUS NEUROLOGICAL LEVELS IN 100 PATIENTS (SOME HAD INVOLVEMENT OF MORE THAN ONE SEGMENT)

Left			Right	
	2	III	1	
	2	IV	1	
	35	V[I]	21	
	3	V[II]	1	
		VI	1	
		VII	1	
		C1		
		2	1	
		3	5	
3		4	2	12
	2	5		
		6	3	
	1	7	1	
		T1	1	
	2	2	1	
	1	3	1	
	3	4		
	4	5	1	
13	1	6	1	10
	1	7		
		8	1	
		9	3	
		10		
		11		
	1	12	1	
	2	L1	2	
	3	2		
7	1	3		2
		4		
	1	5		
		S1		
2	2	2		0

TABLE II

CAUSE PROVOKING ZOSTER IN 100 SUCCESSIVE PATIENTS	*Per-cent*
Physical trauma..	*38**
Frontal sinusitis	*9*
Malignancy	*4*
Ultraviolet light..	*3*
Diabetes—no injury	*3*
Chemical	*2*
Severe emotional upset	*2*
Rheumatoid arthritis	*2*
Steroid cream rubbed into area ..	*2*
All probable causes	*65*
No cause discovered	*35*
*One of these patients also had malignancy, one rheumatoid arthritis	

week (table II). In 35 per cent no obvious associated cause was discovered. Physical trauma to the affected part was common, (38 per cent, table III), and the histories were convincing, although the patients often only remembered the trauma on the second or third visits. Typical was the history of my youngest patient, a little girl of six, who was brought to the hospital with ophthalmic zoster by her mother. Mother adamantly denied that the child had been injured. The child suddenly burst into tears: "It is not true, but I daren't tell mummy. I was playing with Sally and she threw me on the ground and jumped up and down on my head". In none of the 100 patients was unsuspected

TABLE III
TRAUMA AND ZOSTER

Patient No.	*Site*	*Trauma*
1	LV^1	hit head on beam
2	LV^1+	bang on head
3	LV^1	exposure to icy wind
4	RV^1+	prop fell and crushed spectacles
5	LV^1+	fell off motor bike and hit head
6	RV^1	cold blast on face during car-ride
7	LV^{1-11}	prolonged severe draught on face
8	RV^1+	operation under general anaesthesia
9	RV^1	fell on right forehead
10	LV^1	knock on left side of face
11	LV^1+	friend jumped on her head at play
12	LV^1	fell on head during play
13	LV^{1-11}	fell and hit head on fender
14	RV^1	icy draught in car
15	LV^1	blind, fell and hit head
16	LV^1	knock on head
17	RV^1	knocked head on lintel (reticulosarcoma)
18	RV^{1-11}	glasswool forced in area by accident
19	LV^1+	bump on left ear
20	LV^1	burnt by permanent waving machine
21	RC4	bumped into pole in garden
22	LL2	fell downstairs
23	RT6	lower respiratory tract infection with severe cough
24	LL2	slept on ground without groundsheet in tent on cold night
25	LL3	hefty gardening, not taken exercise for years
26	LC5	helped in shop lifting shoeboxes from top shelf for several days
27	RT8-9	osteoporosis, collapsed vertebrae
28	RT2	jerked arm hauling tree trunk out of ground
29	LT2	Caesarian section
30	RC3	drove for 12 hours in icy cab
31	LL5	acute prolapsed intervertebral disc
32	RC4	bumped neck
33	LT2	worked hard in first garden. Unused to physical exertion
34	RC6	fell on crutches and hurt himself (had rheumatoid arthritis)
35	LT5	blind, fell and hurt chest
36	LT6	fall, fractured femur, and bruised herself
37	LT7	wore new dress like sackcloth
38	LV^1+ +gen. ganglica	wore new cap playing golf, burnt by sweatband

A + after V^1 indicates that the naso-ciliary branch is involved.

TABLE IV
ZOSTER AND MALIGNANCY

Patient No.	*Site*	*Provocation*	
(1)	RV^1	Knocked head on hatch-reticulosarcoma	
2	RT3	Carcinomatosis	
3	LS2	Multiple myeloma	Same patient,
4	LL2	,, ,,	very low im-
5	RT9	,, ,,	munoglobulins

malignancy found. In three patients with known malignancy zoster developed (table IV). In one of these patients it may well have developed as a consequence of physical trauma. I have subsequently seen a 51-year-old woman with thoracic zoster in whom I found adenopathy which had been present for six months. On biopsy the lesion turned out to

TABLE V

ZOSTER AND PROVOCATION OTHER THAN TRAUMA

Patient No.	*Site*	*Provocation*
		Chemicals
1	LV[1]	Shampooed hair with fierce new shampoo
2	RV[1]	Accidentally sprayed "Repello" dog repellant in right face
		Ultraviolet light
1	LV[1]	Excessive sunbathing
2	RC3	Excessive sunbathing
3	LV[1]	Skiing in brilliant sun at high altitude
		Rheumatoid arthritis
1	LV[1]+	No trauma
(2)	RC6	Fell on crutches and injured himself
3	LS2	No trauma, developed encephalitis
		Sinusitis
1	LV[1]+	left frontal sinusitis
2	RV[1]+	right frontal sinusitis
3	RV[1]+	right frontal sinusitis
4	RV[1]	right frontal sinusitis
5	LV[1]	left frontal sinusitis
6	RV[1]	right frontal sinusitis
7	LV[1]+, LIII, IV	left frontal sinusitis
8	RV[1], RIII, IV, VI, VII	right frontal sinusitis
9	LV[1]+	left frontal sinusitis
		Severe emotional upset
1	LT12	major family catastrophe
2	RV[1]+	house invaded by hooligans
		Diabetes
1	RT6	No trauma
2	RV[1]	No trauma
3	LT5	Acute onset of diabetes
		Steroid
1	LV[1]	Treated scalp with steroid cream for bad seborrhoea
2	RC2-3	Rubbed steroid cream into skin of area for lichen planus

be lymphosarcoma. Associated factors other than physical trauma are recorded in table V. The coincidence with diabetes is probably no more than one would expect from chance. The association of frontal sinusitis and ophthalmic zoster is striking; nine per cent of all zoster patients, or 16.1 per cent of all ophthalmic zosters (56) in this series. Chemicals and ultraviolet light seem to play a part. The association with rheumatoid arthritis is much more dubious. Two patients gave a striking history of having rubbed steroid cream into the skin where the lesion subsequently developed. In two patients a severe emotional upset was possibly related. In all patients except one the immunoglobulins were within normal limits. Apart from temporary depression of the white cell count and platelets in the acute phase of the illness, no haematological or

biochemical abnormalities were found, except in the patients with known malignant disease.

Discussion

The observations recorded in this series of 100 patients suggest that there is a definite association between trauma of whatever kind and reactivation of varicella-zoster virus. The association between the definite history of an insult to the part that subsequently developed a characteristic zoster lesion is too definite to be accounted for by chance. The association with malignancy (at most three per cent) was no higher than that expected by chance (2.5 – 3 per cent for the age-group over a comparable period in the Oxford Region from which the patients were drawn). Second attacks of zoster are uncommon. Head and Campbell (1900) noted four in more than 400 cases, Hope-Simpson (1965) nine in 192, and I found five in my 100 cases (table VI). Of these one

TABLE VI
PATIENTS WITH HISTORY OF PREVIOUS ATTACKS OF ZOSTER

Patient No.	*Age and sex*	*Site*	*Provocation*	*Site of previous attack*	*Interval*
1	F 86	RV^{1}+	trauma	RT10	one month
2	F 58	LV$^{1-11}$	trauma	thoracic region	32 years
3 (Aug. 1969)	M 59	LT10-11	multiple myeloma	LL2, LS2, RT9	Aug. 1967, July 1968, Feb. 1969 four attacks low immunoglobulins
4	M 62	RV^{1}	sinusitis	LV^{1}	18 months
5	F 44	RT9	unknown	LV$^{1-11}$	7 years

patient had four attacks of zoster from August 1967 to August 1969. He suffered from multiple myeloma and had very low immunoglobulins, alone among all the patients.

It is suggested that recurrent clinical attacks of varicella-zoster are due to reactivation of the virus in the host by trauma in the majority of patients who develop zoster. It is possible it may happen through the same common final pathway. The common process may be hyperaemia, an analogy to the hyperaemia that occurs in the kidney after administration of pyrogen or prednisolone and which may lead to a flare-up of bacterial infection (Pickering 1968).

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