In each year after return to work the percentage of time lost from coronary heart disease was calculated according to the following formula :

Total time lost from work on account of coronary heart disease in the year $\times 100$

Total possible time at work in the year

where the "total time lost" is the sum of all periods of absence during the year from coronary heart disease among those under observation at the beginning of the year (including the remainder of the year for those who died during the year); and "possible time" is what would have been possible if there had been no absence—that is $X + Y + Z$ of "Prognosis for Life and Death" if calculated from return to work.

"Time lost" does not refer to the actual working hours. The data merely give the days lost, and these are converted to fractions of a year.

Throughout these calculations exact dates at which absence began and ended, and policies terminated, permitted accurate calculations of the periods of exposure to risk and time off work. The methods would of course not be applicable without adjustment where such complete information was not available. All fractional periods were worked in decimals of a year correct to two decimal places.

The fact that in "coronary thrombosis" a very large proportion of deaths occur in the first few days of the first absence means that what at first seemed a considerable body of data did not give as much information about prognosis for life and death as had been hoped. The information about how prognosis varied with age, for instance, was disappointing. Thirty per cent. of all first attacks result in death within six days and 38% within a month, but, of the 91 recorded deaths amongst the 192 cases presenting as "coronary thrombosis," 74, or about 80%, occurred within the first month.

A disease, like pulmonary tuberculosis, in which the chance of early death is relatively small, and in which the deaths are more evenly spaced in time, would give greater scope for the methods used.

APPENDIX 3

Independent Categorization of Samples of Membership, and of Men having First Attacks of Coronary Heart Disease, from the Records of the National Health Service

The following are the results of the two checks that were applied to test the validity of the categorizations already made (and summarized in Table XI) from the *Medical Directory* of 1946, 1948, and 1949.

Category from Medical Directory	General Practitioners		Hospital Staff	
	No. Checked on N.H.S. Lists for General Medical Services	Proportion Found on N.H.S. Lists	No. Checked on N.H.S. Lists for Hospital Service	Proportion Found on N.H.S. Lists
(1)	(2)	(3)	(4)	(5)
General practitioners, Category 1	485	91%	122	1.6%
Consultants/specialists, Category 2	186	1.6%	87	85%
G.P.-Specialists, Category 3	123	88%	123	66%
Public officials, Category 4	68	13%	68	2.9%

Column 1—The four main categories as described in the opening of Part II of this report.

Column 2—All in the samples aged 45–64, and all cases of first attack alive and at work after July 5, 1948, were checked on the general medical services lists of N.H.S.

Column 3—The proportions of those in column 2 who were found to be providing general medical services under the N.H.S. Act. Most of the public officials who were providing such service were clearly doing so for other members of their own staffs.

Column 4—It was impracticable to classify hospital service as "specialist" or otherwise. The following general practitioners are included in the 122 categorized from the *Medical Directory* as general practitioners who were now checked for hospital service: all in the samples who were not found in the general medical services lists; all in the samples who were resident in Scotland and Northern Ireland; all G.P.s who had first attacks of coronary heart disease in 1947–50 and who were alive and at work after July 5, 1948. The 87 consultants/specialists whose names were now checked included all so categorized who were not on the staff of teaching hospitals; and all the relevant cases of coronary heart disease.

Column 5—The proportions of those in column 4 now found to be rendering N.H.S. hospital service. The 2 of the 122 categorized as general practitioners who were found to be under contract for hospital service were also rendering general medical services. 12 of the 41 "G.P.-Specialists" not found in the N.H.S. lists seemed to have lost their hospital appointments very recently, judging from the changes in the *Medical Directory* between 1946–9 and 1951; 27 still record these appointments in the 1951 *Medical Directory*; 2 had retired. Two "public officials" now found to be clinical specialists were also clearly continuing as public health officers: 2 of 68 is 2.9%.

HERPES ZOSTER VARICELLOSUS

BY

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In 1892 von Bókay, of Budapest, described the simultaneous appearance of herpes zoster and varicella in the same patient, and he advanced the theory that the two conditions were caused by the same virus. Seiler (1949) has estimated that the yearly incidence of herpes zoster in Edinburgh is 2 per 1,000 of the population, and that 3.8% of these zoster cases are complicated by a varicelliform eruption.

Most uncomplicated zoster cases in this region are dealt with by local practitioners, and few are referred to the Infirmary. During the period under review (1947–50 inclusive) the number of zoster cases seen was 79, of which 67 were uncomplicated, 6 suffered from involvement of the eye, and the remaining 6 cases were complicated by a generalized varicelliform eruption. Five of the cases are summarized in the Table on the opposite page, and the sixth is described in greater detail below.

Case Reports

Case 6.—A man aged 69 was suffering from haemorrhagic herpes zoster in the distribution of the ophthalmic division of the fifth cranial nerve on the right side. The condition had been present for seven days. Before the attack of

zoster his health had been excellent and there was no history of his having taken drugs of any sort. Blood examination showed no abnormality. He had never had herpes zoster or varicella previously. The day after the appearance of the zoster lesions a generalized varicelliform eruption developed suddenly. This eruption reached its maximum distribution within 24 hours, and thereafter no fresh lesions developed. He was photographed on the day he first reported, and a biopsy of a vesico-pustule on the right forearm was done by one of the doctors in the department.

Case 7.—The doctor who had done the biopsy on Case 6 complained of general malaise, anorexia, and headache 13 days later, and on the following day a typical varicella eruption developed, beginning in the scalp and on the fauces, and appearing in crops on the trunk, back, face, and arms during the subsequent three days. At its height two days later the rash was profuse, especially on the back, but by this time the constitutional symptoms had subsided. There was no previous history of herpes zoster or of varicella, although the patient had often been in contact with both diseases. He was clear of varicella lesions in 16 days.

Case 8.—The technician who had photographed Case 6 complained of general malaise and had the typical features of varicella 15 days after his one and only contact with Case 6—that is, two days after Case 7 had developed varicella.

FIG. 1.—Case 3, showing haemorrhagic herpes zoster of L1 and L2 and the varicelliform eruption of trunk and limbs.

Seven days later an eruption of herpes zoster appeared over the area of distribution of the twelfth thoracic and first

The technician did not touch Case 6 nor did he handle his clothing. Here again there was no previous history of herpes zoster or of varicella. The rash cleared in three weeks.

Case 9.—A doctor, with whom Case 7 had lunched on several occasions between the first and tenth days of the incubation period of his varicella, developed severe neuralgic pains in the right lumbo-sacral region two days after Case 7 developed varicella—that is, 15 days after Case 7 had been in contact with Case 6.

lumbar nerves on the right side. There was no actual contact by touch between Cases 7 and 9. The doctor in question had often been in contact with cases of herpes zoster and of varicella in the past without contracting either disease, but had not recently been in contact with any other known possible source of infection.

The Diagram illustrates the relationship between the primary zoster and the secondary varicelliform eruption in Case 6 and the spread of infection to three other individuals.

Laboratory Investigation

Histology.—Biopsies were taken from the edge of the zoster eruption and from a secondary vesicle on the trunk in Case 3 and from a secondary vesicle on the forearm in Case 6 (Figs. 2 and 3). The histological features in all

Summary of Five Cases of Concurrent Herpes Zoster and Varicella

	Case 1	Case 2	Case 3	Case 4	Case 5
Sex and age . .	Male; 67	Male; 82	Male; 75	Male; 64	Male; 79
Distribution of zoster	C3, 4, and 5 on left side	Trigeminal nerve on left side	L1 and L2 on left side (Fig. 1)	7th nerve rt. side. Ramsay Hunt syndrome	C3 on left side
Interval between development of zoster and varicella	2 days	1 day	2 days	1 day	Less than 4 days
Previous history of zoster or varicella	Nil	Nil	Nil	Nil	Nil
History of contact with cases of zoster or varicella	"	"	"	"	15 days' contact with a convalescent zoster case
General health	Suffered from chronic lymphatic leukaemia	Diabetic patient	Chronic lymphatic leukaemia treated with x rays	Good	Very good
Duration of zoster eruption	6 weeks	15 days	7 weeks	Residual facial palsy 7 months later	15 days
Duration of varicella eruption	14 days	12 "	18 days	15 days	8 "

FIG. 2.—Case 6. Histopathology of a varicelliform lesion from the anterior aspect of the left forearm. The stratum corneum is intact, and immediately subjacent to it and to the stratum granulosum a thin layer of degenerated rete cells is visible. The basal layer has disintegrated, with the result that balloon cells, giant cells, and cellular debris lie directly on the upper dermis. H. and E. ($\times 60$.)

FIG. 3.—Case 6. Histopathology of a varicelliform lesion from the anterior aspect of the left forearm. The cells forming the floor of the bulla show varying degrees of degeneration. Intracellular oedema gives rise to the appearance of ballooning of the cells (A); several so-called giant cells (B), consisting of aggregations of degenerated nuclei surrounded by a variable quantity of cytoplasm, are prominent. The infiltrate consists of polymorphs and, to a less extent, of lymphocytes. H. & E. ($\times 450$.)

three sections show an intra-epidermal bulla, the roof of which is formed by stratum corneum, stratum granulosum, and the upper part of the degenerated rete mucosum. It is clearly demarcated laterally from the adjacent epidermis by a few rows of flattened degenerated rete cells. The base is composed of degenerated and disorganized rete and basal cells, around which there is an infiltration of polymorph leucocytes and lymphocytes. In this area there is intercellular and intracellular oedema, giving rise to the appearance of ballooning of the cells, and several so-called "giant cells," consisting of aggregations of degenerated nuclei surrounded by the remains of the cytoplasm of these cells, are apparent. The bulla fluid contains some of these balloon cells, giant cells, and leucocytes. In the upper part of the dermis there is oedema, with a well-marked polymorph and lymphocytic infiltrate, particularly in the perivascular situation.

Bacteriology.—On admission 10 ml. of blood was withdrawn and fluid was collected from bullae on the groin and thigh in Case 3. Large numbers of elementary bodies were demonstrated in the bulla fluid by the methods of Weiss and of Paschen. The bulla fluid was diluted and set up for complement fixation against three sera derived from known severe cases of herpes zoster, including serum from Case 2, and against three normal sera. The antigens in the vesicle fluid combined with the antibodies in the known positive sera to fix 2 M.H.D. of complement when the sera were diluted 1/16. No fixation took place with the normal sera. No antibodies were demonstrated in the patient's serum, against his own bulla fluid, or against fluid from another case of herpes zoster, indicating that the patient had not at that stage produced antibodies to the herpes zoster virus.

Comment on Case Reports

In each of the six cases of herpes zoster complicated by a varicelliform eruption the herpes zoster eruption developed first, and the interval between the appearance of the zoster and the development of the secondary rash was 24 hours to four days. None of the patients had previously suffered from herpes zoster or varicella. The herpes zoster and the secondary eruptions both healed with scarring; the duration of the zoster eruption varied within wide limits, from 15 days to 7 weeks, whereas the secondary eruption, which developed to its maximum extent in 24 hours, cleared within 8 to 21 days. In each instance the secondary eruption had cleared before the primary zoster lesions. In Cases 7 and 8 the incubation period of the varicella was 13 and 15 days, respectively—that is, within the normal incubation period of varicella. The incubation period of herpes zoster is said to lie between 9 days (Kundratitz) and 21 days (Siegl); in Case 5 it was 15 days or less, and in Case 9 it lay between 12 and 22 days.

Although epidemics of zoster have been described the actual mode of spread has not yet been established. In 1900 Haslund noted that herpes zoster was often ushered in with nasal or pharyngeal symptoms, and he regarded the tonsils as the probable portal of entry. He thought that the virus was then carried by the blood stream to a posterior root ganglion and thence via a sensory nerve to the skin. Fenner (1948) has described the mode of spread of the virus causing ectromelia in mice. He has proved experimentally that the virus multiplies at the source of infection—normally minor trauma on the skin surface—and spreads thence to infect the associated lymph nodes, where further reproduction results in a blood infection or viraemia. This primary viraemia is controlled by the phagocytic action of the cells of the liver, spleen, and other tissues. When these cells have been overcome by the virus a secondary and more profound viraemia develops, resulting in the clinical condition. It is possible that a similar sequence of events occurs in zoster and varicella, the virus being neurotropic in the former disease and dermatropic in the latter.

Montgomery (1921) considers that the more probable route of entry is via the sensory nerve endings in the skin, and this view is upheld by van Rooyen and Rhodes (1940). It is difficult to conceive how this theory can find acceptance, as prior to the onset of zoster there is rarely any history of trauma over the area affected, and the application of vesicle fluid to the unbroken skin has failed to produce either local or generalized reactions or to stimulate the development of immunity. Furthermore, aberrant vesicles are seen quite often in herpes zoster, and their presence would be difficult to explain on the basis of this theory. Case 7 had been in close contact with Case 6 while doing the biopsy, but infection in Cases 5, 8, and 9, where contact was not close, was in all probability by droplet infection, and the portal of entry may well have been the nasopharynx.

Two cases in this series suffered from chronic lymphatic leukaemia, one of them having been treated with wide-field x-ray therapy six months before the zoster attack. A series of 45 such cases developing zoster following irradiation is described by Ellis and Stoll (1949).

Brief Review of the Literature

The following clinical observations have been advanced in support of the theory that herpes zoster and varicella are caused by the same virus: (a) Varicella often occurs in children in contact with cases of herpes zoster. Adults who have not previously had chicken-pox or herpes zoster are also liable to infection. (b) Herpes zoster is occasionally followed, within five days of the vesicular phase, by a generalized varicelliform eruption (see Cases 1–6). (c) Cases of herpes zoster associated with a varicelliform eruption are not infrequently followed by cases of varicella in contacts, the incubation period being 12–16 days (Cases 7 and 8). (d) A few cases have been reported in which varicella has been followed by herpes zoster in contacts (Case 9).

A common origin for the two diseases is supported by the experimental work of Lipschütz and Kundratitz (1925) in Vienna and of Bruusgaard (1932) in Oslo. These authors reported that when infants or young children were vaccinated with zoster vesicle fluid varicelliform lesions developed locally around the site of inoculation; in a few cases a generalized varicelliform eruption made its appearance, and some of the contacts of these cases developed varicella. Cross complement-fixation reactions have been demonstrated between the serum of convalescent herpes zoster cases and the vesicle fluid or crusts of varicella cases, and vice versa, important work in this respect being that of Netter and Urbain (1924) in France and that of R. T. Brain (1933) in this country. Hassko *et al.* (1938) were unable to confirm these findings, and Thomsen (1934) failed to demonstrate any fixation between zoster serum and varicella antigen in 83 cases, the converse reaction with varicella serum and zoster antigen being also negative.

R. T. Brain considers that zoster may be regarded as a neurotropic modification of the dermatropic virus of chicken-pox. He points out that the virus in question most readily attacks young children who have no natural immunity, giving rise to the characteristic eruption of chicken-pox in varying degrees of severity, some of the milder cases passing unnoticed as subclinical infections. In either event the virus is widely disseminated throughout the body and must reach the central nervous system, where it may persist, without causing symptoms, for many years. After a short or long interval the dormant virus is provoked to activity by some autogenous factor or as the result of trauma, a toxic drug, or other infection.

Chicken-pox is a common disease and herpes zoster is relatively common, and those who uphold the dualistic theory contend that their association is not more frequent than might be expected in the case of any two diseases whose aetiology is quite distinct. In favour of this view the following points have been advanced: (a) Herpes zoster has often been described in patients who have had varicella

at an earlier date, and it does not therefore appear that a high degree of immunity exists between the two diseases. (b) The experiments of Lauda and Stöhr (1926) did not support those of Lipschütz and Kundratitz. They inoculated 55 children with herpes zoster vesicle fluid, but failed to obtain a positive local reaction in a single case. Nevertheless, three of the children developed varicella 14 days after the inoculation. (c) Zoster has been described in isolated communities where varicella is unknown, as in Cantor's (1921) report on Christmas Island and Woolley's (1946) report on three cases on Tristan da Cunha. The numbers involved in both these instances were very small, and so the reports should be treated with reserve.

It is still undecided whether the two conditions are due to the same virus, to distinct but antigenically similar viruses, or to a mutation of a reversible nature in the structure of the organism. Under the electron microscope the virus of herpes zoster is indistinguishable from that of varicella; from the clinical and pathological viewpoints this organism has an affinity for skin and nerve tissue. In children and in adults who have not previously had either disease or have not been exposed to subinfection of the virus, the tendency is for an infective dose of the virus to result in varicella, as a result of which a high degree of immunity to the organism is usually established. In the majority of adults repeated exposure to and subinfection by the virus seem to result in partial immunity of the individual. W. Russell Brain (1931) considered that the sensory neurone had a tissue immunity feebler than that of other parts of the body, or that its immunity might be temporarily diminished by a preceding lesion, so that an infective dose of the virus in adult life tended to produce herpes zoster.

Summary

Six cases of herpes zoster varicellosus are described. In one of these cases two contacts developed varicella within the incubation period of that disease, and during the incubation period one of these two varicella cases was responsible for conveying the infective agent of herpes zoster to another contact. The literature on the subject is briefly reviewed. It is concluded that herpes zoster and varicella are very closely allied; the definition of the exact relationship of the organisms must be left to the bacteriologist.

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PULMONARY ASPERGILLOSIS FOLLOWING POST-INFLUENZAL BRONCHOPNEUMONIA TREATED WITH ANTIBIOTICS

BY

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The association of fungus infections with antibiotic therapy is now well recognized. Although many references are to be found in the American literature, few examples have been recorded in this country. We therefore think the following case of pulmonary aspergillosis is of interest.

Case Report

A housewife aged 51 was admitted on February 9, 1951, during an influenza epidemic, with a diagnosis of post-influenzal bronchopneumonia and toxic purpura. Her symptoms, which began three weeks previously, were typical of the prevalent influenza. The cough became worse, though the sputum was scanty, mucopurulent, and never blood-stained. She remained febrile, and three days before admission developed a purpuric rash.

Clinical Examination.—The patient was slightly cyanosed, dyspnoeic, and febrile—temperature 99.5° F. (37.5° C.), with a dry mouth—and obviously very ill. There were petechiae and haemorrhagic bullae on her face, arms, and legs which were considered to be typical of a "sedormid" eruption. She had taken three tablets before this rash appeared. There was slight impairment of the percussion note at the right base, and diffuse moist sounds were heard over both lower lobes. She had a regular tachycardia of 120, slight venous engorgement, and a little oedema of the ankles suggesting mild congestive failure. The blood pressure was not recorded because of bullae on the arms. A radiograph of the chest on February 9 showed obliteration of the right costophrenic angle with heavy lung shadows and only slight mottled opacities in both lower zones.

Special Investigations.—A blood count showed: Hb, 94% (Haldane); white cells, 18,000 (neutrophils 95%, lymphocytes 1.5%, monocytes 3%, metamyelocytes 0.5%); platelets, 230,000 per c.mm.; clotting-time, 5 minutes (capillary tube); bleeding-time, 3½ minutes (Duke). The urine contained: albumin, a trace; sugar, a trace on occasions; pus cells, 1–4, and red cells, 0–3, per ¼ field. Blister fluid was sterile. Direct examination of the sputum on February 12 showed numerous pus cells and a few yeast forms; no acid-fast bacilli were seen. Culture yielded a heavy growth of *Bact. coli* sensitive to streptomycin and chloramphenicol, and a heavy growth of *Candida albicans*.

Progress and Treatment.—Treatment was begun at once with crystalline penicillin, 500,000 units eight-hourly. Two days later the patient was afebrile, the pulse rate had fallen, and she was much improved. On the fifth day, however, despite the absence of fresh physical signs in her chest, the temperature rose, penicillin was discontinued, and chloramphenicol was given, 3 g. initially and 0.5 g. six-hourly. By the tenth day her temperature was 100° F. (37.8° C.); she had a pleuritic pain in the right chest, auricular fibrillation had developed, and the sputum, still scanty, became purulent and streaked with blood.