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Recent Experience of Influenza

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Epidemic influenza can cause greater disruption of school life than any other illness. Rugby School with over 700 pupils, part of a town of 55,000 inhabitants, situated in the middle of England at the centre of the country's network of motorways, records outbreaks of influenza in two years out of three. When antigenic shift affects the influenza virus A, attack rates of up to 80 per cent have been observed, and influenza virus B has caused attack rates of up to 50 per cent. Such high rates are not seen in the adult population, except possibly in residential institutions for the elderly. Curiously, the source of infection is not always apparent. Infection seldom spreads from school to town, and rarely, if ever, from town to school. The school's experience frequently differs from that of the maintained schools in the Rugby area, and from that of comparable independent schools in the country. The manner of spread of infection within the school varies from outbreak to outbreak. With a 'new' virus the outbreak is explosive, and the epidemic is over in three to four weeks. If herd immunity is high, influenza may splutter for much of the term or may fade out.

With such an unpredictable illness it is not easy to assess the place of prophylactic vaccination. It is hoped that the experience recorded in this paper may cast some light on this issue, or at least may raise some questions.

Since 1950, Rugby School has experienced 14 outbreaks of virus A influenza and 8 outbreaks of virus B influenza. There have been eight years in which influenza has not been recorded in the school. Virus C influenza has been noted on three occasions, during outbreaks of virus A influenza. All virus C influenza cases have been diagnosed serologically and, no doubt, other cases have remained undiagnosed as they have not been sought.

This paper deals with outbreaks of influenza in the seven school years 1967/68 to 1973/74 inclusive. These were years when laboratory investigations were extensively undertaken.

The clinical picture is not specific, and resembles that of many other infections of the upper respiratory tract. The sudden onset, the unusual prostration of the sufferer, and the rapid spread of infection in the community enable one to make the diagnosis. Complications are uncommon (Table 1). Convalescence is usually brief.

Table 1. Complications of influenza 1950-1975 (2,371 cases).

	No.
Otitis media	57
Asthma	17
Bronchitis	16
Pneumonia	14
Tonsillitis	7
Stomatitis	7
Peripheral neuropathy	5
Meningism	3
Quinsy	2
Arthropathy	2
Appendicitis	2
Encephalopathy	2
Pleurisy	1

LABORATORY INVESTIGATIONS

Virus Isolation

Throat swabs were taken in the first 24 hours of the illness, and transported in ice immediately to the Public Health Laboratory at Coventry. The specimens were inoculated into rhesus monkey kidney tissue culture. Tissue culture negative specimens were inoculated into fertilised hens' eggs. Virus was identified with the current designated type specific influenza antiserum provided by Colindale.

Serology

(*a*) *Paired Sera.* A fourfold or greater rise of complement fixation titre was considered to be positive.

(*b*) *Convalescent Sera.* A complement fixation titre of 1/64 or greater was regarded as evidence of recent infection.

Bacteriology

Throat swabs were examined for bacterial pathogens in more than half the cases. Few were positive.

Virus A Influenza

Table 2 shows the results of laboratory investigations in outbreaks of virus A influenza.

Lent Term 1968. The isolates were identified as A/ENG/68, marking a considerable drift from A/ENG/64, the strain that the school had encountered in 1966, and an even greater drift from A/Singapore/57 and A/ENG/61, which had formed the A component of the oil-adjuvant vaccine used in December 1963.

Table 2. Influenza A.

Date	No.	Virus isolation No.	+	Paired sera No.	+	Convalescent sera No.	+	Throat swab No.	+
Lent term 1968	105	23	13	76	76	8	7	96	15
Lent term 1969	10	9	9	2	2	1	1	10	–
Advent term 1969	6	5	5	–	–	–	–	–	–
Lent term 1972	112	81	63	23	20	31	20	44	5
Lent term 1974	69	61	40	7	7	24	8	14	4
Total	302	179	130	108	105	64	36	164	24

Diagnosis confirmed in 271 patients – 77.2 per cent.

Lent Term 1969. The isolates were identified as A/HK/68.

Advent Term 1969. The isolates were identified as A/HK/68.

Lent Term 1972. The isolates were identified as A/HK/68.

Lent Term 1974. The isolates were identified as A/PC/73. The H3N2 virus had now drifted twice: first, to A/ENG/42/72, a virus that the country, but not the school, had met, and that formed the A component of the polyvalent vaccine used in December 1973; and secondly, to the A/PC/73. Since 1974 the H3N2 virus has drifted at least annually.

Virus B Influenza

Table 3 shows the results of laboratory investigations in outbreaks of virus B influenza. Virus isolation is less successful for the B virus than it is for the A virus. Additionally, only half the 1971 cases were investigated. The outbreak was explosive, and allowed no time for laboratory studies to be undertaken.

Table 3. Influenza B.

Date	No.	Virus isolation No.	+	Paired sera No.	+	Convalescent sera No.	+	Throat swab No.	+
Lent term 1968	16	14	8	–	–	2	2	16	3
Lent term 1971	161	54	3	2	2	23	23	112	9
Lent term 1974	5	4	1	2	2	2	2	1	–
Total	182	72	12	4	4	27	27	129	12

Diagnosis confirmed in 43 patients – 41.7 per cent.

1967/68

The Lent term began on 16th January 1968. The first case of virus A influenza was admitted to the Sanatorium on that day, the last on 20th March.

This was the fifth outbreak of H2N2 virus influenza in the school since September 1957, and, as it turned out, the last. Only one previous outbreak of H2N2 influenza had occurred in the school lifetime of the then members of the school, an outbreak of 84 cases in the Lent term 1966, two years previously, but it is safe to assume that every boy in the school in January 1968 had already met the H2N2 virus subtype. This may explain the slow development of the outbreak, and suggests some natural herd immunity.

The clinical picture was unremarkable, the only complications of note being two cases of encephalopathy.

The attack rate for the school was 16.4 per cent but only 2.7 per cent for boys who had either been vaccinated with a polyvalent oil-adjuvant influenza vaccine in December 1963, or had had attacks of H2N2 influenza in the Lent term 1966 (Table 4). Although the virus had drifted three times since the vaccination and once since the 1966 outbreak, the difference in the attack rates is significant, $p = <0.000001$ (Fisher's two-tailed exact test).

Table 4. Lent term 1968: H2N2 influenza.

	Number	Cases	Attack rate (%)
Whole school	642	105	16.4
Vaccinated or previous attack	113	3	2.7
Remainder	529	102	19.3

It seems reasonable to suggest that an attack of H2N2 influenza in 1966 or the administration of an oil-adjuvant vaccine in December 1963 conferred good protection on exposure to the H2N2 virus in 1968.

Sixteen cases of virus B influenza were diagnosed in the last week of term. No case was diagnosed in the 18 boys who had had attacks of virus B influenza in the Trinity term 1965, nor in the 54 boys who had received the oil-adjuvant vaccine in December 1963. The attack rate in the remaining 570 boys was 2.8 per cent.

Protection, natural or vaccinal, appears to have been good.

1968/69

In July 1968 a new subtype of the influenza A virus was isolated during an outbreak of influenza in Hong Kong. This was later named the H3N2 virus. The

haemagglutinin antigen differed from that of the H2N2 subtype, but the neuraminidase antigens were similar.

The Committee on Influenza and other Respiratory Virus Vaccines of the Medical Research Council invited the school to take part in a trial of influenza vaccines. The protocol of the trial called for the administration of vaccine by nasal spray or intramuscular injection, using vaccines of different subtypes in a variety of combinations and on a blind basis. After discussion the Committee allowed the school to test a monovalent vaccine containing 7,000 H.A. units of the new virus by itself. Vaccination was voluntary, and the vaccine was given in the first week of December 1968.

At the start of the Lent term 1969, 85.2 per cent of the boarders had had the vaccine, 43.3 per cent by intramuscular injection and 41.9 per cent by nasal spray. The first case of influenza was admitted on 20th January, the last on 10th March. Case-to-case infection was obvious in only a few boys, and it appeared that the H3N2 virus had been introduced into the school on at least four separate occasions.

The attack rate was 5.3 per cent in the unvaccinated, 1.4 per cent in those vaccinated by intramuscular injection, and 0.4 per cent in those vaccinated by nasal spray (Table 5). The attack rate for the boys who had had attacks of H2N2 influenza in 1966 or 1968 was less than half that of the rest of the school (Table 6). Perhaps this was due to the similar neuraminidase antigens. Application of Fisher's two-tailed exact test to the data in Table 5 gives probabilities of <0.04 for the unvaccinated against the intramuscular injection group, <0.006 for the unvaccinated against the nasal spray group, and <0.006 for the unvaccinated against the combined vaccine groups.

Table 5. Lent term 1969: H3N2 influenza.

Category	No. at risk	Cases of influenza	Attack rate (%)
Unvaccinated	95	5	5.3
Vaccinated			
Injection	279	4	1.4
Nasal spray	270	1	0.4
Total	644	10	1.6

Reporting on the MRC vaccine trial Tyrrell *et al.* (1970) stated: 'It was a real disappointment to have found so little evidence for protection in these studies.' Sir Charles Stuart-Harris has written (1976): 'In the MRC trial conducted by Tyrrell *et al.* (1970) both polyvalent (Asian) and H.K. vaccines were used. However, neither vaccine induced clinical protection even in schools where high attack rates were experienced.'

Table 6. Lent term 1969: H3N2 influenza.

		No.	Cases	Attack rate (%)
(*a*)	Boys who had had H2N2 influenza 1966 and/or 1968			
	Unvaccinated	16	–	–
	Intramuscular vaccine	54	1	1.85
	Nasal spray vaccine	54	–	–
	Total	124	1	0.81
(*b*)	Remainder			
	Unvaccinated	79	5	6.33
	Intramuscular vaccine	225	3	1.33
	Nasal spray vaccine	216	1	0.46
	Total	520	9	1.73

In September 1957 the H2N2 (Asian) influenza virus had appeared in Rugby School. The community was unprotected and within 22 days 78.5 per cent of the boys had been attacked.

Why did the school not suffer a comparable experience in January 1969? This must have been due in large part to the protection afforded by the H3N2 vaccine administered six weeks previously. Of the boarders, 85.2 per cent had had the vaccine and, more importantly, half had had the vaccine by nasal spray. Natural infection probably begins through droplet spread via the nasopharynx. In the presence of high local antibody levels the influenza virus cannot thrive, and an epidemic will not develop. This agrees with a phenomenon frequently noted in the school; it is always easier to isolate the influenza virus at the start of an outbreak than it is in the closing stages. An outbreak ceases when the antibodies of the community attain levels hostile to virus survival.

Four other schools took part in the MRC vaccine trial. One school reported no cases of influenza in the Lent term 1969; figures are not available for the vaccine acceptance rate. A second school gave a polyvalent H2N2/B vaccine in November 1968, and the H3N2 vaccine on 21st February 1969, in an unsuccessful attempt to influence an already established outbreak.

Three schools remain, and their experiences are shown in Table 7. Rugby and

Table 7. Lent term 1969: H3N2 influenza.

School	No.	Vaccination rate (%)	Attack rate (%)
Rugby	644	85.2	1.6
Haileybury	575	68.3	20.3
Trent	203	36.5	59.1

Haileybury gave the H3N2 vaccine alone but Trent observed the full trial protocol, 25 boys had the H2N2/B vaccine intramuscularly and saline intranasally, 25 had the H2N2/B vaccine intramuscularly and the H3N2 vaccine intranasally, 24 had the H3N2 vaccine intramuscularly and saline intranasally, and 129 boys were unvaccinated. In these three schools the protection was directly proportional to the vaccination rate.

1969/70

In December 1969 six cases of virus A influenza were diagnosed in the last week of the Advent term. Virus isolation was positive in all five attempts. All isolates were of the H3N2 subtype, and resembled those of the previous Lent term. Retrospective analysis identified a further 55 cases in the school. These cases had occurred in the last week of term or early in the holidays (Table 8).

Table 8. Advent term 1969: H3N2 influenza.

		No.	Cases	Attack rate (%)
	Unvaccinated	201	16	8.0
	Intramuscular vaccine	208	16	7.7
	Nasal spray vaccine	205	29	14.1
	Total	614	61	9.9
H3N2 'Flu 1969	Unvaccinated	4	–	–
	Intramuscular vaccine	5	–	–
	Nasal spray vaccine	1	–	–
	Total	10	–	–
H2N2 'Flu	Unvaccinated	16	–	–
	Intramuscular vaccine	37	4	10.8
	Nasal spray vaccine	39	5	12.8
	Total	92	9	9.8
Rest	Unvaccinated	181	16	8.8
	Intramuscular vaccine	166	12	7.2
	Nasal spray vaccine	165	24	14.5
	Total	512	52	10.2

About a third of the 614 boys had not had the monovalent H3N2 vaccine a year previously, a third had had the vaccine by intramuscular injection, and the remaining third by nasal spray. The attack rates were similar for the unvaccinated and the intramuscularly vaccinated groups, but higher in the group vaccinated by nasal spray. The more effective form of vaccination for immediate protection possibly had a detrimental effect a year later.

No boy who had had an attack of H3N2 influenza in the previous Lent term had a further attack.

Ninety-two boys who had had attacks of H2N2 influenza in 1966 or 1968 remained in the school. Sixteen of them had not been vaccinated with the monovalent H3N2 vaccine. None had H3N2 influenza in December 1969. The experiences of the other 76 boys did not differ significantly from those of their fellows.

An attack of H3N2 influenza gave solid protection at 9 to 12 months.

An attack of H2N2 influenza gave protection to the unvaccinated on exposure to the H3N2 virus 2½ to 4 years later, but an H3N2 vaccine gave no protection at a year.

1970/71

This was a year in which there was little influenza in Great Britain. In the school 161 cases of virus B influenza were diagnosed between 21st January and 13th March 1971. There were no complications.

There had been only one virus B outbreak in the school lifetime of any boy at Rugby in 1971 – 16 cases in March 1968. Two boys who had had attacks in 1968 remained in the school. Each had a further attack in 1971.

The attack rate for the school was 24.8 per cent and varied little in the different age groups, the lowest attack rate being 22.1 per cent in the 13-year-olds, the highest 27.1 per cent in the 14-year-olds; the 14-year-olds usually have the highest attack rate.

The B virus had drifted considerably in the three years since it had last appeared in the school, but most boys must have met a B virus previously.

1971/72

The H3N2 virus made its third appearance in the school in January 1972. The first attack in January 1969 had been thwarted by prophylactic vaccination, while the ending of the school term had averted a potentially explosive outbreak in December 1969.

Antigenic variation due to drift had been negligible in the four years' prevalence of the H3N2 virus. So, in the Lent term 1972, the current H3N2 virus differed little from its predecessors. The cases were diagnosed between 13th January and 25th February 1972. Three boys developed otitis media, two developed pneumonia. No case of influenza occurred in those boys who had had influenza in 1969 or been vaccinated in 1971 (Table 9).

In this outbreak it appeared that an attack of H3N2 influenza three years previously, or the administration of an H3N2 vaccine three months previously, provided solid protection.

This was an interesting and puzzling epidemic. The school took part in a double blind trial of Amantadine, used therapeutically rather than prophylactically, and for the first time met the problem of rigid diagnostic criteria. There were

Table 9. Lent term 1972: H3N2 influenza.

	No.	Cases	Attack rate (%)
Whole school	641	112	17.5
Vaccine 1971	21	–	–
Influenza 1969	25	–	–
Remainder	595	112	18.8

several virus positive seronegative cases, unacceptable by the trial criteria but in all other respects typical. Seronegative cases are not uncommon in influenza and deserve further study.

1972/73

No case of influenza was diagnosed in Rugby School in this year. However, the number of influenza virus strains sent to the Virus Reference Laboratory in London was easily the highest for the period under review. The 1,290 A viruses had all drifted markedly to A/ENG/42/72. Ninety B viruses were also identified.

1973/74

In the autumn of 1973, for the first time since 1968, the whole school was offered prophylactic influenza vaccine. It was a commercial one containing the A/ENG/42/72 strain which had been widely isolated in Great Britain in 1972/73 and which the school had not met, and two current B strains.

At the start of the Lent term 1974, 294 of the 652 boarders had been vaccinated six weeks previously, a vaccination rate of 45.1 per cent.

In the event, the influenza strain that reached the school on 11th January 1974 had drifted from the A/ENG/42/72 of the previous year's British isolates and of the A vaccine component. The infecting strain in January 1974 was the A/Port Chalmers/1/73.

In the five weeks from 11th January 1974, 68 cases of influenza were diagnosed, and after an interval of a month, one further case. There were no complications.

The attack rate for the 652 boarders was 10.6 per cent (Table 10); 78 boys who had had attacks of H3N2 influenza in 1972 remained in the school. None had

Table 10. Lent term 1974: H3N2 influenza.

	No.	Cases	Attack rate (%)
Whole school	652	69	10.6
Influenza 1972	78	–	–
Remainder	574	69	12.0

Table 11. Lent term 1974: H3N2 influenza.

	No.	Cases	Attack rate (%)
Unvaccinated	310	53	17.1
Vaccinated	264	16	6.1

a further attack in 1974. Thirty of them had been vaccinated in December 1973, 48 had not been vaccinated. The attack rate in the remaining 574 boys was 12.0 per cent.

These 574 boys divide into the 310 unvaccinated, and the 264 vaccinated (Table 11). The attack rates were significantly different – 17.1 per cent in the unvaccinated and 6.1 per cent in the vaccinated (Chi^2 15.4), $p = <0.0002$, demonstrating that an attack of H3N2 influenza two years previously gave solid protection, while an H3N2 vaccine gave worthwhile protection at six weeks.

Five sporadic cases of virus B influenza were also diagnosed in the Lent term 1974. None of the 53 boys who had had an attack of virus B influenza three years previously had a further attack in 1974. Excluding these 53 boys, there were no cases of virus B influenza in the 276 boys who had been vaccinated in November 1973, the five cases all occurring in the 323 unvaccinated boys, an attack rate of 1.5 per cent.

DISCUSSION

Analysis of the outbreaks of influenza at Rugby School suggests views on the quality and duration of the protection conferred by natural attacks and vaccination.

An attack of influenza gives substantial protection for three years. The oil-adjuvant vaccine of December 1963 gave protection comparable with that of a natural attack. However, oil-adjuvant vaccines are no longer used owing to the occasional development of deep, sterile abscesses in the vaccinees.

Saline-killed vaccines can give good protection from 6 to 16 weeks after administration. Experience in 1953/54 had already suggested that such vaccines gave little protection at six months. Experience in 1968/69 suggested that saline vaccines are ineffective at a year and, when administered by nasal spray, may actually increase the vulnerability of the vaccinee at a year.

Saline-killed vaccines are the only vaccines currently in use in the western world. One can reasonably induce two corollaries to their use –

1. If an outbreak of influenza occurs within four months of vaccination the transient vaccinal protection may prevent the development of the more persistent natural protection that follows an attack.
2. If an outbreak of influenza does not occur in the six months after vaccination the vaccine-induced antibody levels will wane and will be ineffective at a year.

The Medical Officers of the Schools Association have for the past seven years advocated the policy of annual vaccination against influenza (*Handbook of School Health*, 1975). Turtle (1968) reviewed the experiences of 139 schools with 40,000 pupils in the influenza outbreaks of the Lent term 1966. Schools practising annual vaccination had the fewest and the smallest outbreaks; schools practising occasional vaccination had more frequent and larger outbreaks, while schools that did not vaccinate had the most and the largest outbreaks.

Hoskins and his associates have produced three papers on trials of influenza vaccines at Christ's Hospital. These trials began in 1970. The diagnosis of influenza was strictly determined by laboratory control.

Their first paper (Hoskins *et al.*, 1973) showed that vaccine given 6 weeks before an outbreak of H3N2 influenza in December 1972 conferred substantial protection against attack, although antigenic drift had occurred. Antibodies against the new strain (A/ENG/42/72) developed in 75 per cent of the vaccinated boys whose original A/HK antibodies had developed naturally, but less frequently in those with vaccine acquired A/HK antibodies. Their second paper (Hoskins *et al.*, 1976) dealt with a complex outbreak of A/Port Chalmers, B/Hong Kong, and B/intermediate strains in March 1974. Influenza B vaccine almost halved the virus B attack rate, but A/HK vaccine, by having prevented infection with A/ENG/42/72 in December 1972, increased the vulnerability of boys to A/Port Chalmers/1/73 in March 1974. In the author's opinion revaccination with the most recent A strain is crucial; naturally acquired antibody is more effective than vaccine acquired antibody.

Their latest paper (Smith and Davies, 1976) shows that children very rapidly acquire natural experience of new antigenic variants of influenza A viruses. Naturally acquired antibody is remarkably persistent. Possession of appropriate neuraminidase antibody alone alters the quality of infection so that a subclinical attack enables the subject to update his antibody status.

In a recent letter, Hoskins wrote: 'As far as pre-1976 is concerned we have shown that vaccination has been worthwhile in preventing epidemics which would have brought the school to a standstill.'

Priday practised annual vaccination at Stowe, starting in 1967. In November 1971, 64.5 per cent of the boys were vaccinated. Influenza attacked the school in the Lent term 1972; the attack rates were 25.9 per cent in the vaccinated and 35.5 per cent in the unvaccinated. Priday commented: 'In the school's environment vaccination did not have a very marked protective effect ... Annual vaccination for up to five consecutive years did not show any apparent improvement in the protective effect' (Priday, 1972).

The annual use of influenza vaccine undoubtedly lessens to a variable extent the impact of influenza viruses in schools. It is difficult to be objective on the real purpose of vaccination programmes. Is it to protect the individual pupil, or is it to prevent disruption of normal school life? These two aims do not necessarily

coincide. One cannot help wondering if the annual use of influenza vaccine may not do the individual a disservice in the long run by preventing his acquiring persistent natural antibodies. What happens to the individual after he leaves school – does he fare better or worse than his unvaccinated contemporary?

Polyvalent H3N2/B saline vaccines were offered in Rugby School in 1973, 1974, and 1975. Compared with earlier years, acceptance rates were disappointingly low – 42.5, 56.8 and 62.1 per cent respectively. The number of parents refusing permission was higher than in previous years, when acceptance rates of 80 to 90 per cent were usual. In the Lent term 1976 the school had a mixed outbreak of influenza, caused by A/ENG/864/75, A/VICTORIA/3/75, and B/HK/73.

After allowing for natural protection the attack rates were 31 per cent in the 201 unvaccinated pupils, and 21 per cent in the 379 vaccinated pupils. The protective effect of the vaccine seemed to be insufficient to justify an annual vaccination programme. Influenza vaccine was not offered to the school in the winter 1976/77.

Any vaccine programme has two requirements: a clear protective effect, and an acceptably low level of adverse effects. Hoskins has based his annual vaccination programme at Christ's Hospital on a reaction rate of less than 1 per cent. The 1976 vaccines have had reaction rates of 8 per cent in the adolescent, and up to 50 per cent in the 8 to 12-year-olds (Hoskins, 1977). These rates are unacceptably high, and jeopardise future programmes.

Both influenza vaccines available in Great Britain in the winter 1976/77 contained an H3N2 strain and an Hsw1N1 strain, and a B strain. It was surely unwise to include virus A components of different subtypes in one vaccine. The antigen/antibody response must have been conjectural. Schools that gave an H2N2 vaccine and then an H3N2 vaccine within a short time of each other in 1968/1969 had negligible vaccinal protection in H3N2 outbreaks in the Lent term 1969. It is even illogical to include two variants, although of the same subtype, in one vaccine. It is sensible, but not essential, to include the most recently circulating variant.

Several new types of influenza vaccine are being investigated. Live vaccines, sub-unit vaccines or adjuvant vaccines may prove to be more effective than currently available killed-saline vaccines. There is still much to be learned before the status of prophylactic influenza vaccines is established.

This article is based on the Milroy Lecture read at the Royal College of Physicians in March 1977.

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THE BATTLE OF EDGEHILL

William Harvey's papers, together with his goods, in his Lodgings at Whitehall, were plundered at the beginning of the Rebellion, he being for the King, and with him at Oxon; but he often sayd, That of all the losses he sustained, no griefe was so crucifying to him as the losse of these papers, which for love or money, he could never retrieve or obtaine.

When Charles I by reason of the Tumults left London, he attended him, and was at the fight of Edge-Hill with him; and during the fight, the Prince and Duke of Yorke were committed to his care. He told me that he withdrew with them under a hedge, and tooke out of his pockett a booke and read; but he had not read very long before a Bullet of a great Gun grazed on the ground neare him, which made him remove his station.

He told me that Sir Adrian Scrope was dangerously wounded there, and left for dead amongst the dead men, stript; which happened to be the saving of his Life. It was cold, cleer weather, and a frost that night; which staunched his bleeding, and about midnight, or some houres after his hurte, he awaked, and was faine to drawe a dead body upon him for warmeth-sake.

(From John Aubrey's *Brief Lives*)