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Observations on the epidemiology of appendicitis

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EDITORIAL COMMENT During a study of the epidemiology of appendicitis it was found that acute appendicitis is equally common in men and in women. Appendicectomy for non-acute appendicitis is commoner in women, and it is suggested that these patients are suffering from pain originating in the genital organs.

Acute appendicitis in Wales is equally common amongst the Welsh and non-Welsh population. Appendicectomy for non-acute appendicitis is commoner in people of Welsh origin. Acute appendicitis is commoner in the spring but there is no seasonal variation in the case of appendicectomy for non-acute conditions.

Appendicitis is one of the commonest conditions responsible for the admission of patients to hospital for surgical treatment. Admissions to hospital for appendicitis are exceeded only by the total of admissions for all malignant disease, admission for abdominal hernia in the male, for old age and injury in both sexes, and for chronic inflammatory disease of the nose and throat. It is the third commonest operation in the male, being exceeded only by the removal of tonsils and by the repair of hernia, and the second commonest operation in the female, exceeded only by the removal of tonsillar tissue (Ministry of Health and General Register Office, 1964). Approximately one person in seven in the population of England and Wales may expect to undergo appendicectomy at some time in his life. Appendicitis is generally regarded as an inflammatory condition, reflected by the suffix to its name, but it is apparently not influenced by the antibiotics which have come into use during the last twenty years; antibiotics are not used in the definitive treatment of the condition and there has been no apparent fall in the incidence of the disease.

This investigation is based on three approaches to the problem of the aetiology of the disease. First, the age and sex specific incidence of appendicitis was studied in a series of 848 patients who had undergone appendicectomy. Secondly, a genetic study was made of the relative incidence of the disease in the Welsh and non-Welsh moieties of the population of the Swansea area. Finally, an examination of the seasonal incidence of appendicitis was made on a series of 1,325 consecutive appendicectomies during the calendar years 1960 to 1965.

The material on which the investigation was based consisted of specimens of the vermiform appendix removed at operation from patients in this hospital. This is a large acute general hospital into which are admitted a high proportion of the abdominal emergencies occurring in the town of Swansea and in the neighbouring rural and semi-urban districts.

There is no conscious bias in selection of cases for admission to this institution. In 60% of the cases histological examination of the excised appendix showed an acute inflammation. This was recognized by the presence of infiltration with polymorphonuclear leucocytes, always of the submucosa and the mucosa, often of the muscularis and the serosa, and often with exudation of pus in the lumen of the viscus. In many instances there was also ulceration and loss of the mucosal epithelium. The remaining organs did not show an acute inflammatory reaction and are classified together as 'appendix, not acute appendicitis'. In many of these, however, there was evidence of chronic inflammation exemplified by fibrosis in the submucosa and the subserosa, by an increase in the amount of lymphoid tissue in the submucosa, by diffuse infiltration of the submucosa and subserosa by lymphocytes, and occasionally by a lymphocytic exudation into the lumen.

THE AGE INCIDENCE OF APPENDICITIS

Burch (1963) has shown in his studies on the autoimmune diseases how an investigation of the age-specific incidence of a condition, the proportion of cases presenting at defined ages through the normal life span, may help in the understanding of aetio-

logical processes. Similar studies by Armitage and Doll (1954, 1957) have tried to relate the onset of cancers to a series of causal agents and recent studies of my own (1965, 1966a and b) have shown how this technique may be used in the investigation of the problem of latent carcinoma of the prostate and of the biological status of carcinoma *in situ* of the uterine cervix.

ACUTE APPENDICITIS

Cases of acute appendicitis were first selected and divided into age groups and the relative age specific incidence rates were calculated for each group (Table I). The population distribution was that of Swansea and its environs and it was thought that the

TABLE I

AGE INCIDENCE OF ACUTE APPENDICITIS

Age	*Male*		*Female*		*Male and Female*	
	No.	*Rate/1,000*	*No.*	*Rate/1,000*	*No.*	*Rate/1,000*
0-2	3	0·57	1	0·2	4	0·39
3-4	6	1·83	7	2·2	13	2·05
5-9	40	5·1	32	3·44	72	4·55
10-14	49	5·4	49	4·6	98	5·50
15-19	60	7·8	51	6·63	111	7·20
20-24	30	4·6	33	5·02	63	4·80
25-29	23	3·18	23	3·4	46	3·28
30-34	18	2·45	16	2·26	34	2·36
35-39	24	3·15	20	2·64	44	2·90
40-44	11	1·43	13	1·68	24	1·55
45-54	20	1·27	28	1·73	48	1·50
55-64	15	1·17	11	0·76	26	0·95
65-74	5	0·715	5	0·51	10	0·6
75	3	0·9	1	0·165	4	0·425

rates by age, while not absolute as some cases were admitted to other hospitals, nevertheless represented the pattern of the disease in this area. There was no significant difference in age incidence between males and females at any age. It can be concluded from this that the female sex hormones, which come into prominence shortly before the time of puberty, are not important aetiological factors, and it may further be concluded that explanations of immunological and genetic behaviour based on the activities of the X chromosome can be excluded. The curve shows a steady rise from birth up to the late teens in a manner proportional with the age; there is a peak incidence between 15 and 20 years, and there is then a rapid fall so that the disease becomes a rarity after the age of 55. The distribution fits one of the family of curves derived by Burch and Rowell (1963). The curve rate, which varies as $T \exp. -\frac{KT^2}{2}$ with a peak age of 18, is drawn on the graph to show the way in which the points fit (Fig. 1).

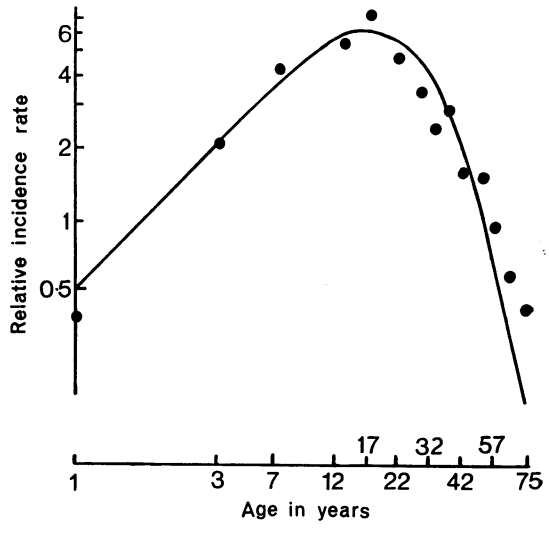

FIG. 1 *Age incidence of acute appendicitis, the curve showing the rise and fall in relation to age.*

Burch's curves were derived from a mathematical consideration of the possible aetiological factors in certain autoimmune diseases. His premises are: 1 The disease is restricted to a carrier subpopulation. 2 The onset of the disease requires the accumulation in a carrier individual of at least two discrete changes, which (3) are random in character and their average probability of recurrence is constant with respect of time. 4 The penetrance of the inherited tendency to the disease approaches unity within the normal life span, *i.e.*, any individual who is susceptible to the disease will, sooner or later, develop it. 5 The average age specific mortality rates are the same in the general population and in the carrier subpopulation before the onset of the disease.

The slope of the curve, particularly the first part of the curve, corresponds to the mathematical model involving a series of two discrete events. It is of interest to try and fit our clinical knowledge of this disease with the premises which Burch puts forward.

1 The fall-off of incidence after a maximum before the age of 20 suggests that there may be a subpopulation at risk to this disease and that the remainder of the population may be inherently insusceptible. The size of the subpopulation may be roughly estimated. In the Hospital In-patient Enquiry of 1961, which was based on a 10% sample of hospital admissions, it was noted that there were 5,767 admissions of males and 6,496 admissions of females for appendicular disease and that 5,431 appendices were removed from male patients and 6,165 from females. Assuming that the survey covers

a reasonably unbiased group of all hospital admissions simple multiplication shows that about 55,000 males and 62,000 females per year are admitted to hospital for appendicular disease. The number of births each year is about 370,000 males and 350,000 females, and, in each sex, of those born about 3% die before the age of 20. Comparison of the number of cases of appendicitis with the total birth rate suggests that some 15% of males and 18% of females are subjected to appendicectomy. Tables I and II show that about four-fifths of the appendixes removed from male patients show histological evidence of acute appendicitis and that two-thirds of those from female patients do so. Hence it can be inferred that in either sex 12% of the population are susceptible to this disease.

2 and 3 The nature of the two changes necessary remains obscure. It is conceivable that one of them is related to the diet; there is an observed variation in incidence of appendicitis in different parts of the world, and may be associated with differences in genetic status of the peoples or with differences in the dietary and culinary habits. The other remains obscure: it is unlikely that it is a specific infection, an infection with an identifiable constant micro-organism, as such infections are among the better understood aetiological agents in human pathology, and it seems unlikely that a specific infection as common as this could have escaped attention for so long. This second factor could possibly be vascular or might be the consequence of a second dietary factor or a non-specific virus infection.

4 The penetrance of the inherited tendency may be presumed to be approaching unity: there is, however, no method on the basis of this type of data by which this conclusion can be verified or refuted.

5 With present-day methods of treatment the mortality experience of patients who do or who do not develop appendicitis seems to be similar.

This concept of the aetiology of this condition may explain our failure to prevent it as we have failed to prevent so many conditions, such as the degenerative and neoplastic diseases, which are probably due to the culmination of the effects of a series of inter-relating causal agents.

NON-ACUTE APPENDICITIS

Two hundred and seventy-five cases in which there was no histological evidence of acute appendicitis were analysed. In this group there is an excess of such cases among females (Table II). Analysis of the two sexes separately, by age, shows that the excess of appendixes removed from women is in the age groups 10-14, 15-24, 25-34, and 35-44. The differences between the two sexes at the age 15-24 is significant

TABLE II

AGE INCIDENCE OF 'NON-ACUTE' APPENDICITIS

Age	*Male*		*Female*	
	No.	*Rate/1,000*	*No.*	*Rate/1,000*
0-4	2	0·235	1	0·12
5-9	9	1·14	15	1·96
10-14	16	1·75	30	3·30
15-24	22	1·54	66	4·60
25-34	8	0·535	20	1·34
35-44	8	0·535	18	1·2
45-54	11	0·70	22	1·35
55-64	6	0·47	7	0·48
65	5	0·48	9	0·57

($P < 0{\cdot}001$) and between the ages of 25 and 45 is significant at the 5% level ($0{\cdot}05 > P > 0{\cdot}02$).

The ages, 10-44, when there is an excessive number of 'non-acute' appendixes removed from females as compared with males corresponds to the age when the female sexual cycle is being initiated and beginning to decline. It is reasonable to suggest that in many cases the abdominal pain from which the patient suffers is due to causes in the female reproductive organs and that many innocent appendixes are removed for gynaecological reasons. The age specific incidence of appendicectomy for non-acute lesions of the appendix in males shows a similar curve to that for acute appendicitis in the male and female (Fig. 2), and may indicate that chronic appendicitis is a real disease entity and causally related to acute appendicitis; this is a problem which has still not been solved clinically. An alternative explanation, however, is that the age distribution of

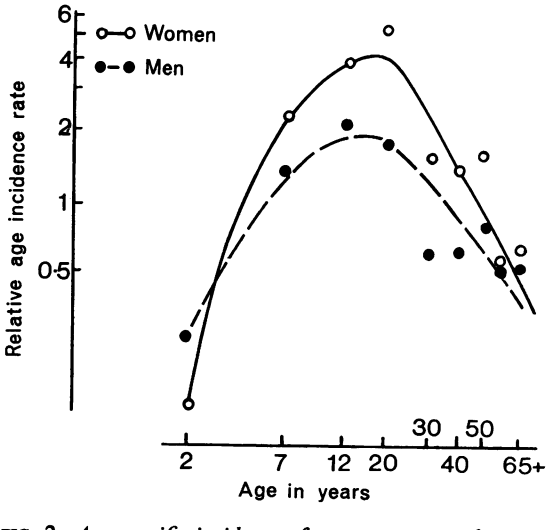

FIG. 2. *Age-specific incidence of non-acute appendicitis in men and women.*

appendicectomy in these patients reflects the clinical impression, gained from dealing with the acute disease, that pain in the lower abdomen is best treated in relatively young patients by removal of the appendix.

WELSH AND NON-WELSH NAMES IN PATIENTS WITH APPENDICITIS

Recent investigations in this laboratory have shown that genetic differences can be identified between the Welsh and the non-Welsh people of this part of South Wales when the parameter used to decide on 'Welshness' is the surname. Further work has shown that there are differences in disease incidence between the Welsh and non-Welsh people of Wales and that there is an excess of stomach cancer, prostatic hyperplasia, and coronary artery disease which can be explained, in part at least, by differences in the gene pools of the Welsh and the non-Welsh (Ashley, 1966c, 1967; Ashley and Davies, 1966a, 1966b).

The data from cases of appendicitis were analysed by comparing the observed and expected numbers of individuals with Welsh surnames (Table III). The surnames used were those in a list of 96 names previously used in similar studies (Ashley and Davies, 1966a, 1966b). The control data comprises a sample of the names on the electoral registers. The individuals selected for study were those in whom the surname was that of their father, *i.e.*, males and young unmarried females. The group was further divided into two, cases of 'acute' appendicitis and cases of 'non-acute' appendicitis, on histological grounds.

TABLE III

WELSH NAMES IN APPENDICITIS

Home	*Total*	*Welsh Names*	
		Observed	*Expected*
Acute appendicitis			
Swansea	152	61	66
Glamorgan	151	85	81·5
Carmarthen	80	57	58
	383	203	205·5
Non-acute appendicitis			
Swansea	130	72	57
Glamorgan	62	50	33·5
Carmarthen	60	38	41·5
	252	160	132·0
All cases	635	363	327·5

There was no difference between the observed and the expected numbers of individuals with Welsh names in the group with acute appendicitis. There was an excess of patients with Welsh names in the group who had no histological evidence of present acute appendicitis in the excised viscus. This excess was statistically significant. Comparison of the two groups, acute and 'non-acute' appendicitis, showed a statistically significant difference between the two in the proportion of patients with Welsh surnames.

The lack of an excess or deficiency of Welsh names among the patients with acute appendicitis indicates that the genetic differences between the Welsh and the non-Welsh do not include factors which affect susceptibility to acute inflammation of this organ. The significant excess of patients with Welsh names in the other group may be explained in several ways. There may be another disease state, clinically leading to the operation of appendicectomy, in which genetic factors, present in the Welsh to a greater extent than in the non-Welsh, contribute to the susceptibility of the individual. Secondly, the Welsh may be more prone to present abdominal symptoms in such a way that exploratory operation is indicated and the appendix is removed *en passant*. Thirdly, there may be an unconscious bias on the part of the surgeons towards appendicectomy in the Welsh.

SEASONAL INCIDENCE OF APPENDICITIS

The distribution of operations for removal of the appendix throughout the year was studied in a rather larger series of 817 instances of acute appendicitis and 508 instances of 'non-acute' appendicitis recognized at this hospital during the calendar years 1960 to 1965. The cases studied have been divided into the two groups, acute appendicitis and non-acute appendicitis, on the basis of the histological appearance of the excised organ, and the second group has been subdivided into males and females.

Acute appendicitis is seen throughout the year (Table IV). There is an excess of cases in February, March, April, May, August, and October, and a

TABLE IV

SEASONAL INCIDENCE OF APPENDICITIS

Month	*Acute*		*Non-acute Appendicitis*			
			Males		*Females*	
	Observed	*Expected*	*Observed*	*Expected*	*Observed*	*Expected*
January	64	69·4	19	15·1	26	28·0
February	86	62·7	19	13·7	33	25·3
March	80	69·4	24	15·1	29	28·0
April	74	67·2	12	14·6	29	27·1
May	73	69·4	14	15·1	21	28·0
June	52	67·2	22	14·6	31	27·1
July	66	69·4	10	15·1	27	28·0
August	77	69·4	11	15·1	32	28·0
September	63	67·2	11	14·6	21	27·1
October	77	69·4	15	15·1	26	28·0
November	54	67·2	9	14·6	32	27·1
December	51	69·4	12	15·1	13	28·0

deficiency of cases in the other months. The deviations are greater than would be expected by chance. Three hundred and thirteen cases were seen in the months of February, March, April, and May when 268·7 would be expected; 258 cases were seen in the summer months of June, July, August, and September when 273·2 would be expected; and 246 were seen in October, November, December, and January when 275·4 would be expected. There is a significant excess of operations for acute appendicitis in the four months from February to May and a significant deficit of cases in the four months from October to January.

The pattern in the case of 'non-acute' appendicitis is less clear. There is a small excess of cases in both sexes in February and March and in June and a marked deficiency of cases during the month of December which includes the Christmas period. The significant excess of cases in the four months February to May, which is seen in acute appendicitis, is not observed, but there is a significant excess in the months of February and March.

These findings suggest that some seasonal extrinsic factor or factors may be involved in the aetiology of acute appendicitis, and also in some of the cases in the rather heterogeneous group which has here been labelled 'non-acute' appendicitis. The clustering of cases in the spring months lends a little support to the observation of Tobe (1965) that in appendicitis a raised titre of antibodies to adenovirus and to viruses of the Coxsackie B group may be observed, and that evidence of the presence of these viruses in the tissues of the appendix can be demonstrated by immunofluorescent methods. Reports from Great Britain show that viruses cannot generally be isolated from the excised appendix (Jackson, Gardner, Kennedy, and McQuillin, 1966; Bell, 1966) and the specific viral antibodies described by Tobe were not seen (Jackson *et al.*, 1966), although a number of the children had antibodies to mumps V virus.

DISCUSSION

This type of investigation cannot produce final answers but it does lead the way to further investigations: first, whether or not there is a genetically characteristic subpopulation which is liable to develop appendicitis; secondly, what the relation of removal of the non-acute appendix has to gynaecological disorders; and thirdly, what is the biological nature of chronic appendicitis, particularly in the male.

The suggestion that only 12% of the population are susceptible to appendicitis leads to the concept that the operative, life-saving treatment of this disease, which became popular following the famous operation on King Edward VII, has removed a selection pressure against the gene or genes responsible for susceptibility to the disease by allowing those who, in the days before routine appendicectomy would often have died of peritonitis, to survive and reproduce. It will be interesting in years to come to see whether the frequency of appendicitis increases still further.

The recent report by Ludbrook and Spears (1965) of a cohort analysis of all forms of appendicitis in New Zealand shows a similar picture, although the overall frequency of appendicectomy in that country is rather higher in the male than in England and Wales. The people of New Zealand are of similar stock to those of Great Britain and the comparability of the two series reflects the genetic similarity between the two populations.

The use of the Welsh surnames as a genetic marker showed no difference between the Welsh and the non-Welsh in the case of acute appendicitis but an excess of cases of 'non-acute' appendicitis in the Welsh. These observations suggest that there may be genetic factors involved in the aetiology of one or more of the conditions which lead to the removal of an appendix which is not acutely inflamed. The equality between the observed and expected numbers of patients with acutely inflamed appendixes who had Welsh names does not, however, exclude the possibility of a genetic component in this condition but merely shows that there is no genetic difference between the Welsh and the non-Welsh in this respect.

The seasonal concentration of cases of acute appendicitis in the spring months of February to May suggests that some seasonal environmental factor may be involved in the causation of the condition. A non-specific virus infection could be such a factor or an allergic reaction to the release of pollen might be involved. The spread of cases throughout the year indicates that there is no essential environmental factor involved and it may well be that the clinical condition of appendicitis, acute and non-acute, is a reaction pattern which may be set off by any number of aetiological agents. The lack of seasonal distribution in non-acute appendicitis suggests that these patients may be suffering from some intrinsically different disease process.

SUMMARY

The epidemiology of acute appendicitis has been studied in three ways.

The age-specific incidence of acute appendicitis suggests that there is a subpopulation amounting to about 12% of the general population who are susceptible to this disease and that two external factors are necessary for the disease to develop. In

the case of non-acute appendicitis there is a marked excess of pubertal and menopausal females. It is suggested that these patients are suffering from pain originating in the genital organs.

Genetic analysis using the surname as a parameter of Welshness shows no excess of cases of appendicitis among the Welsh of this area compared with the non-Welsh. There is, however, an excess of Welsh people among those whose appendixes did not show acute inflammation and it is suggested that genetic factors, which are different in the Welsh and the non-Welsh, are concerned in the aetiology of this condition.

Study of the seasonal incidence of the disease shows a preponderance of cases of acute appendicitis in the spring but no seasonal variation in the case of non-acute appendicitis. It is suggested that some extrinsic agent, possibly a virus or an allergen, may be responsible for the high frequency of acute appendicitis during the months of February to May.

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