Mackerras and Ercole (1947) found that when proguanil was given in a dosage of 0.1 to 0.3 g. daily to falciparum or vivax gametocyte carriers (New Guinea strains) no effect was observed on the number or microscopical appearance of the gametocytes in the blood. Only when given very early in the attack was gametocyte production affected by proguanil, and then only indirectly, because the primary trophozoite wave was checked before gametogony had started.

In the stomach of the mosquito ingested falciparum or vivax gametocytes may undergo exflagellation and fertilization and even produce small oöcysts, but development ceases at this point and the oöcysts die if proguanil is present even in small quantities in the blood feed. Complete sterilization of the gut infection in mosquitoes results some one to two hours after 0.15 g. of proguanil has been administered to a carrier. In mosquitoes fed on the second day vermicules may form, but in those fed on the third or fourth day of proguanil administration neither vermicules nor oöcysts are detected. The same effect was produced by letting mosquitoes first engorge partially on a normal person taking 0.1 g. of proguanil daily and then allowing them to complete their feed on a carrier with plentiful gametocytes in the blood.

Shute and Maryon (1948) confirmed these findings with the Rumanian strain of *P. falciparum* and suggested it was the female gametocytes on which the drug acted.

These experimental findings imply that it would be difficult for salivary-gland infections to become established in the local anophelines when they are feeding on the blood of people who are taking proguanil regularly. Thus the daily administration of proguanil to a military force in a hyperendemic area would not only be acting as a causal or partial causal prophylactic in individuals inoculated with sporozoites but by inhibiting the development of the sexual cycle in the mosquito it would be a potent factor in limiting transmission and preventing the development of epidemics.

Comment and Conclusions

In conclusion, I would remark that during the past decade we have learnt how to use and when not to use the older antimalarial drugs like quinine, pamaquin, and mepacrine. During this period several potent antimalarial drugs have been discovered or rediscovered and their therapeutic action worked out with considerable exactitude. Proguanil is unique among these owing to (1) its true causal prophylactic action in falciparum malaria, (2) the schizonticidal effect often exerted by a single small dose in overt malaria, and (3) its polyvalent gametocidal properties. Chloroquine is probably the most potent schizonticide yet discovered; it is of great value both as a schizonticidal suppressant given once weekly and in the intensive treatment of the overt attack. For the radical cure of benign tertian malaria pentaquine and iso-pentaquine are now becoming available; just how superior they are to pamaquin when given in combination with quinine future work will decide.

Malaria casualties in non-immune troops operating in hyperendemic areas could be prevented or kept at an insignificantly low level by the routine administration under supervision of such drugs as mepacrine, proguanil, and chloroquine in correct dosage. During military operations it would be advisable to have stock-piles of two such antimalarial drugs for suppressive or prophylactic purposes, since the development of resistance to any particular antimalarial drug is specific and can be circumvented by the substitution of another drug of a different group.

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THE NATURAL HISTORY OF ASTHMA

A REVIEW OF 300 CASES

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It is known that asthma is a disease varied in its causation but unvarying in its mechanism, essentially involving contraction of the smooth muscle of the bronchioles. This contraction may occur in response to any of a wide range of stimuli—inflammatory, allergic, mechanical, reflex, psychological, endocrine. Such factors may be "aetiological" (inducing the first of the patient's attacks) or "aggravating" (being concerned in the precipitation of subsequent attacks). The former may act either centrally, by increasing the patient's sensitivity to asthmogenic agents, or peripherally, by producing a permanent state of irritability of the respiratory mucosa or musculature, whereby an attack of asthma occurs in response to appropriate stimulation. Aetiological and aggravating factors may be identical or they may be apparently unrelated. For example, in many instances asthma may be initiated by some endocrine crisis such as puberty or pregnancy, or by acute respiratory infection, but the same patient may nevertheless have subsequent attacks brought on by a

completely different aggravating factor such as dust, exertion, or psychological shock.

In brief, the genesis of asthma may be said to be a triple phenomenon, depending, first, upon the establishment of the "asthma diathesis," in which a family history of allergic diseases, previous allergic manifestations in the patient, and organic abnormalities in the bronchial tree or upper respiratory tract are also known to be significant. The other essential elements are the presence of aetiological factors and exposure to aggravating stimuli.

With a view to correlating the rates of incidence of the above factors and assessing their relative significance the case records of some 300 cases treated at the Liverpool Royal Infirmary Asthma Clinic between 1935 and 1940 have been surveyed.

Signs of the "Asthma Diathesis"

Family History.—Previous allergic disease in the family was found in 51% of 147 males, and in 50.6% of 158 females. In this series at least one member of the patient's family (parents, grandparents, brothers, sisters, uncles, aunts, or cousins) had suffered from asthma, hay-fever, urticaria, eczema, migraine, or epilepsy. Sometimes there were many such instances in the family, and it was found that 22.5% of the males, and 24% of the females had two or more members of the family so affected. Of 141 non-asthmatic patients in the same hospital, a group representing the same class of population, only 12.2% gave "positive" family histories. These findings are very similar to those of Coke (1927) but differ from those quoted by Witts (1934), who found a 60% incidence of "positive" family histories, and more significant than those of Pearson (1934) and Vaughan (1933), who quote much higher rates of incidence of allergy in families of normal subjects.

Age Incidence.—The present series comprised in all 294 patients—141 males and 153 females. They were classified into two main groups—"F.H. positives" with an allergic family history, and "F.H. negatives" with no such family history—and the incidence of asthma beginning at different age groups is shown in Table I.

TABLE I.—Incidence of Asthma Related to Sex, Ages of Onset, and Family History

Age Group	Sex		F.H. Positive	
	Male	Female	Male	Female
0-10 years ..	60	36	63.3%	75.0%
11-20 ..	21	40	57.1%	45.0%
21-30 ..	18	35	28.0%	34.3%
31-40 ..	13	24	53.8%	54.2%
41-50 ..	14	9	35.7%	44.4%
Over 50 ..	15	9	26.7%	33.3%
Total ..	141	153	50.0%	50.0%

Possible Effect of Menstruation and Pregnancy in Production of Asthma.—Figs. 1 and 2 illustrate the relative ages at onset of asthma in the two sexes, and in Fig. 1 the incidence of "positive" family histories in each age group is also shown. There appears to be quite a close parallel between the incidence of positive family histories in the two sexes and at similar ages of onset (see Table I), but the female incidence curves C and D (Fig. 1) and A (Fig. 2) cross the male incidence curves A and B (Fig. 1) and B (Fig. 2) respectively at age groups 11-20 and remain higher until the ages at onset exceed 40 years, after which the figures in each case become similar. This suggests the possibility of some factor or factors having a different effect in the two sexes, beginning approxi-

mately at the time of puberty and having in females an aggravating effect upon the asthma. Female endocrine functions seemed significant in this respect, and reference was therefore made to details of female cases in which the onset of asthma occurred between the ages of 14 and 50 years and in which there was a clear history of aggravation by menstruation, pregnancy, or a combination of both. Of 62 cases in which the ages of onset of asthma were stated, the numbers falling into each decade are shown in Table II.

TABLE II.—Incidence of Asthma Aggravated by Menstruation and/or Pregnancy, With Ages of Onset of Symptoms

Age of Onset:	0-10	11-20	21-30	31-40	41-50
No. of patients ..	5	24	21	11	1

If all such patients are excluded from the total number of females in each age group the remainder represents those in which there is no apparent association with pregnancy or menstruation. They are shown in curve C (Fig. 2), a striking feature of which is its close similarity to that found in males (curve B). Statistical analysis of the figures illustrated by the curves A, B, and C in Fig. 2 shows that the difference between A and B is greater than is likely to be caused by chance ($\chi^2=22.1$, $\eta=5$, $P<0.01$) and that curves C and B differ by amounts which cannot exclude chance as a possible cause ($\chi^2=5.9$, $\eta=5$, $P=0.3$). These findings suggest, therefore, that a proportion of cases of asthma in females may be due to causes associated in some way with female reproductive activity. While it is freely admitted that other associated factors such as psychological changes or reflex sensitivity otherwise enhanced may in many patients have a more direct bearing on the association of asthma with menstruation, evidence is not lacking (Zondek and Bromberg, 1947) that allergic hypersensitivity to the patient's own hormones is by no means rare and may be demonstrated by appropriate skin tests.

Cutaneous Hypersensitivity.—Cutaneous hypersensitivity tests were performed, using Bencard's intradermal and scratch tests for the usual series of allergens. Results were available in 211 cases, and were positive in 35.5%. No comparable series of normal controls was tested, but other workers, such as Pearson (1943), report 20% of positive findings in normal persons, whilst in asthmatic patients the incidence of positives was 75%. On the other hand, Witts's (1934) figures show 40% of positives only among those affected.

It was found that 26 out of 100 "F.H. -" cases were positive to skin tests, while 44% of 111 "F.H. +" cases were positive also on skin-testing. The standard error of these two proportions being 6.42, this difference in the incidence of positive skin tests appears to be statistically significant.

FIG. 1.—Relative incidence of asthma at different ages and subdivided according to sex and family history.

FIG. 2.—Relative incidence of asthma at different age groups, subdivided according to sex and incidence of menstrual or pregnancy aggravation.

Previous Allergic Manifestations.—Of 246 cases in which the information was available, 40.24% gave a history of one or more of the usually suspected "allergic" manifestations, consisting of the following:

Hay-fever (or vasomotor rhinorrhoea)	39
"Eczema" (including infantile eczema)	54
Migraine	5
Urticaria	12
Epilepsy	2

In 13 cases two of the above conditions occurred together, thus: epilepsy and hay-fever, 1; eczema and hay-fever, 4; migraine and hay-fever, 3; urticaria and eczema, 1; urticaria and migraine, 1; eczema and migraine, 1; urticaria and hay-fever, 2.

It is observed that migraine, though occurring in five patients, does not appear alone, being combined with hay-fever, urticaria, or eczema. Epilepsy occurs once by itself, and once in combination with hay-fever. These findings correspond to those of Witts, in whose series 40–50% of patients had other allergic manifestations, and of Coke, who reports that 22% of his patients had suffered previously from eczema.

Aetiological Factors

Information about factors associated with the onset of asthma was available in 276 cases. The results are shown in Table III. Some light may be thrown on the possible

TABLE III.—Incidence of Alleged Causal Factors

Aetiological Factor	Males	Females	Total
No known associated circumstances ..	50	50	100
Acute respiratory infection (bronchitis, pneumonia, measles, pertussis, etc.) ..	57	57	114
Psychological "shock" or "worry" ..	6	8	14
Pregnancy		10	10
Menstruation		5	5
Irritating fumes or dust	7	6	13
Excessive exertion	7	2	9
Miscellaneous causes (food, change of locality, or change of climate)			11

association of allergic tendencies and the nature of the aetiological factors by the data in Table IV, which compares the incidence of positive family histories (F.H.+), skin-test positives (S.T.+), and histories of previous allergic manifestations (P.A.M.) in the four largest aetiological

TABLE IV.—Incidence of the "Allergic" Features in the Four Principal Aetiological Groups. The Actual Number of Patients in each Group is Shown in Parentheses

	Aetiological Factors			
	Not Known	Respiratory Infection	Psychological	Pregnancy and Menstruation
F.H.+	50% (97)	55.5% (108)	57% (14)	28.4% (14)
S.T.+	36% (80)	27.4% (73)	36% (9)	12.5% (8)
P.A.M.	36.4% (89)	35.5% (93)	36% (9)	45% (11)

groups. These figures show that, although there is very little difference between the respective incidence of these allergic factors in the first three aetiological groups, in the fourth (pregnancy and menstruation) group the incidence of F.H.+ and S.T.+ is strikingly less, but that of other allergic manifestations somewhat increased. While the figures are too small to warrant definite conclusions, this would add further support to a hypothesis that "menstruation asthma" is truly allergic in origin in a high proportion of cases. The low positive-skin-test incidence would then be explained by the absence of hormonal extracts from the test series, and the low family incidence by the "sex-linked" nature of the allergy, which would be expected to reduce the family incidence of the manifestations to females only.

Aggravating Factors

An attempt was made to compare factors associated with the onset of individual attacks of asthma with those believed to have been concerned in the aetiology of the condition. The results are shown in Table V. These figures

TABLE V.—Incidence of Aggravation by Certain Factors, Grouped According to Aetiology. The Actual Numbers of Patients in Each Subgroup are Indicated in Parentheses

Aggravating Factors	Aetiological Factors				
	Unknown	Respiratory Infection	Pregnancy and Menstruation	"Dust"	Psychological Trauma
Respiratory infections ..	14.3% (85)	14.4% (91)	0 (12)	0 (13)	25.0% (12)
Food ..	34.1% (85)	32.2% (91)	16.7% (12)	15.4% (13)	33.3% (12)
Psychological disturbances ..	25.0% (85)	25.5% (91)	18.3% (12)	0 (13)	66.7% (12)
Pregnancy and menstruation ..	28.7% (40)	59.4% (45)	83.3% (12)	66.7% (6)	29.4% (12)
"Dust" ..	22.4% (85)	21.1% (91)	25.0% (12)	92.4% (13)	16.7% (12)
Climate ..	70.6% (85)	55.5% (91)	33.3% (12)	53.9% (13)	50.0% (12)
Exertion ..	35.3% (85)	37.0% (91)	41.5% (12)	15.4% (13)	16.7% (12)

show that three out of the four known aetiological factors also aggravate the asthmatic condition in a high percentage of patients. These are, pregnancy and menstruation (aggravated in 83.3%), "dust" (92.4%), and psychological disturbances (66.7%). Respiratory infections, on the other hand, differ markedly in that in only 14.4% of patients was the asthma aggravated by further respiratory infections. Thus it would appear that, while acute respiratory infections have initiated asthma so often that their association is unlikely to be fortuitous, subsequent attacks of asthma are surprisingly seldom occasioned by recurrences of respiratory infection. This might perhaps be explained on the assumption that the respiratory centre, or some other portion of the mechanism governing the tone of bronchiolar muscle, may have received a non-specific sensitization from the original infection which has facilitated an "asthmogenic" response to other stimuli, and may, in fact, establish the "asthma diathesis."

The relationships of aetiological to exacerbating factors may be summarized provisionally by their classification as follows:

Class A.—Factors which initiate the asthmatic condition and exacerbate asthma in a high proportion of cases. These are pregnancy and menstruation, "house dust," pollens, and psychological disturbances.

Class B.—Factors which are apparently associated with the aetiology of the asthma, but not with its subsequent aggravation, such as acute respiratory infection.

Class C.—Factors which frequently aggravate asthmatic attacks, but seldom seem to have played a part in the aetiology of the condition. These are food sensitivity, climatic conditions, and exertion. Together with dust and emotional upsets, such stimuli are well-known aggravators of any respiratory disturbances, particularly cough and dyspnoea.

Clinical and Other Findings in Cases of Asthma

No obvious abnormality was found on clinical examination in 122 out of 251 patients. As might be expected, where physical signs were present the vast majority of patients showed rhonchi. Obvious emphysema was found in 15 patients in this series. Only five of the patients had gross chest deformity (pigeon-breast, kyphosis, or "sunken chest"), the onset of asthma occurring in early life in four of them.

Radiologically, out of 196 patients whose films were available, 66 showed some abnormality—50 had chronic inflammatory changes only, four had old healed tuberculosis,

one active tuberculosis, four pulmonary fibrosis, three emphysema, two pleural thickening, and two cardiac dilatation.

Of 260 patients in whom the upper respiratory tract had been examined, no abnormality of nose, throat, or sinuses was found in 120. Of the rest, 66 had inflammatory lesions of the sinuses, throat, or nose, and 74 showed evidence of changes attributable to allergy only, such as vasomotor rhinitis, simple mucosal oedema, or polyp formation.

Progress

A questionnaire was circulated to 150 patients who had attended the asthma clinic between 1935 and 1940. Of these, 64 replied; their general progress is shown in Table VI.

TABLE VI.—Results as Compiled from a Questionnaire

Result	Males	Females	Total
"Cured" (i.e., no attacks for at least one year)	7	5	12
Died	7	4	11
Improved	13	9	22
Unchanged	4	2	6
Worse	4	9	13

Recoveries.—In the 12 instances of recovery the condition resolved suddenly in six, and gradually in the remainder. The mean duration of asthma in these cases was nine years. The alleged causes of cessation of the attacks are shown in Table VII. In two patients recovery was attributed to more than one cause.

TABLE VII.—Alleged Causes of Recovery

Causes	No.	Ages at Onset	Duration
"Grew out of the asthma"	3	15, 2, 3 years	2, 10, 11 years
Change of environment (war evacuation)	3	2, 2, 1 year	8, 14, 12 "
Cautery of nose	2	21, 48 years	23, 10 years
Specific protein desensitization	1	25 years	8 years
Tonsillectomy	1	2 "	8 "
Breathing exercises	1	2 "	14 "
Senility	1	57 "	24 "
Unknown	2	44, 29 years	10, 8 years

Eight of the above 12 patients therefore seem to have recovered without any active therapy, six of these being children. Analysis did not reveal any correlation between age of onset of asthma and ultimate prognosis.

Remedies Found Effective in Attacks.—From the nature of the information received from patients no accurate account could be compiled of the details of treatment found most helpful. It is of interest, however, to find that among the patients who did give a reasonably clear answer the use of one or more proprietary inhalants was considered to have been more effective than medicine from a bottle or than ephedrine tablets.

Discussion

From the above results several points emerge. First, there is support for the accepted view that most cases of asthma are of allergic origin, differences being dependent more upon variations in the nature of the allergic stimuli and their mode of action than upon departure from the allergic process. Secondly, the evidence implicating hormonal activity in the production of asthma is strongly suggestive and lends support to more conclusive findings by other workers regarding the allergic nature of this association (Zondek and Bromberg, 1947).

Clinical abnormalities in the chest (apart from wheezing) were remarkably few, and more interesting still was the

rarity of any gross deformity of the chest, particularly when it is considered that in approximately 30% of this group of patients the asthma began in the first decade of life.

Unfortunately our records are not informative enough to enable conclusions to be drawn on the efficacy or otherwise of treatment of nasal sinuses or tonsillar abnormalities in relation to asthma. These conditions appear to fall into two main categories. The first, occurring in 25% of patients, consist of oedema of the nasal mucosa, polyp formation, and other non-inflammatory conditions, which are all possibly of allergic origin, and therefore probably symptomatic of the allergic state of which asthma is but another manifestation (Rackemann, 1937). The second group, including true sinusitis, infected tonsils, and chronic (infective) nasal catarrh, occurred in about 28% of all cases of asthma, and may be aetiologically significant. Although the results of active treatment of upper respiratory diseases has generally been found disappointing (Witts, 1934), it is possible that better results might follow treatment if it were confined to those in the latter group.

Mortality and Morbidity.—This series of cases is spread over a period of between seven and twelve years. It would therefore not be of value to compare the mortality here with that of groups observed over a much shorter period (e.g., Coke, 1927). An adequate follow-up of hospital patients is not always possible, for many drift elsewhere, and others for various reasons do not reply to letters. Of the 64 patients of whom later information was obtained 11 had died within the period—a somewhat surprising mortality of 17.2%; three had developed phthisis in the course of their asthma and died of the disease; three died as a direct result of their asthmatic attacks, and three others died of secondary cardiac failure. That asthma is potentially a fatal disease is too often overlooked, and the above figures underline the importance of long-term treatment in an attempt to safeguard the patient's future. While it is true that the patient must "learn to live with his asthma," it is clear that life would be both happier and longer in its absence.

Summary and Conclusions

Clinical and other findings in 294 cases of asthma have been examined with the object of analysing the natural history of the disease, its aetiology, and its prognosis. Evidence was obtained of the importance of the allergic factor, particularly of the relevance of hormonal allergy in the production of asthma in women. Comparison of the incidence of aetiological factors relative to those aggravating the condition suggests that the factors involved in the production of the asthmatic state may be of three kinds: aetiological and aggravating, aetiological but not aggravating, and aggravating but not apparently connected with aetiology.

From a relatively small series of cases which were followed up over a period of seven to twelve years, 19.4% had apparently fully recovered, while 17.2% had died. This mortality rate, though occurring in a series too small to warrant statistical analysis, nevertheless suggests that asthma as a potentially fatal disease has received rather less attention than it deserves.

We are particularly indebted to our former teacher and chief, Dr. Robert Coope, both for his permission to use the records of the Liverpool Royal Infirmary Asthma Clinic and for his kindly advice and helpful criticism during the production of this paper.

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