more neurotic types of depressive symptoms in patients who suffer from such periodic depressions. These drugs may be given in small doses all through the normal phase, and the dose increased as soon as the depressive phase comes on and until it lifts again. Before the introduction of these drugs there was no real means of helping such unfortunate patients, and even now we may not be able to stop the attacks in deeper recurrent depressions, only the depth of the attack being perhaps lightened or shortened.

Imipramine

Another of the new and widely publicized antidepressant drugs, imipramine ("tofranil"), is not an amino-oxidase inhibitor and is more closely allied to the chlorpromazine ("largactil") group of drugs. On the whole, it is far more effective in the more endogenous types of depression, but is of less value in the neurotic types of depression already discussed. It also generally takes longer to work. The dose needed may vary from 25 to 75 mg. t.d.s., and it can undoubtedly bring some of the milder cases of endogenous depression out of their attacks without the need for electric shock treatment; but one may have to wait for up to a month for this to happen, and in most cases of deeper endogenous depression E.C.T. is still desirable. To put deeply depressed patients on imipramine alone, and to leave them too long on it while awaiting possible improvement, may actually result in a marked worsening of symptoms and in what should have been a quite unnecessary suicidal attempt.

Imipramine can, however, be useful in helping to maintain recovery after the use of E.C.T. and in preventing future attacks. And, as already mentioned, there is now some evidence that the giving of imipramine during the course of E.C.T. may diminish the number of treatments otherwise needed; and this, too, applies to some of the monoamine-oxidase inhibitors, such as phenelzine and isocarboxazid. In cases in which there is doubt regarding which group of drugs is the most efficacious in a particular patient, one can sometimes combine, say, phenelzine and imipramine, and even give both of them together with E.C.T. Here, however, there is naturally a greater risk of postural hypotensive effects and other complications. But some patients do seem to tolerate quite large combined doses, such as imipramine mg. 25–50 t.d.s. and phenelzine mg. 15 t.d.s., very well indeed.

Outlook for the Future

What do all these advances mean for the future? Well, when I first entered psychiatry in 1934 there were no effective treatments of depression, and, just as now, psychotherapy was showing itself to be a most uncertain and very limited form of treatment in this large group of illnesses. But in the past twenty-five years one has seen what has amounted to a total revolution in treatment. Unfortunately, the training of medical students in the recognition of even such common psychiatric illnesses as simple depressions has been so deplorable because of the lack of time so often allowed in the medical curriculum that it will be impossible for some time to come for us to take full advantage of all the significant advances in treatment that have been made in recent years. However, if the various types of depressed patients can only be recognized early and distinguished one from the other by general doctors, numbers of neurotic depressions in people with good previous personalities, and some endogenous ones as well, can now be quickly and effectively treated by the use of some of the new antidepressant drugs in the way I have described.

Other advances such as E.C.T., the provision of better and more varied types of long- and short-acting barbiturates, all the amphetamine drugs, the new tranquillizers, the use of modified insulin, and, when everything else has failed, a consideration of the most successful new and more modified forms of leucotomy—all such advances make the actual position to-day one in which there are very few cases of depression indeed, either acute or chronic, and occurring in good previous personalities which cannot be helped back to renewed efficiency and happiness in living. The skill, however, must still lie in the proper selection of patients for all the varied types of physical treatment now available to us, and a much longer paper would be needed to exhaust this whole fascinating and important topic.

Conclusion

I do believe, however, that all these recent physical advances in the treatment of depression also spotlight what must almost inevitably happen in most other major psychiatric illnesses in the years to come. For we are bound to discover more and more empirical physical methods of treatment to help them, and we shall also continue to learn more about their fundamental physiological nature and causes. I still remain quite unrepentant in my beliefs that a lot of our present-day specialized psychiatric and psychotherapeutic treatments will become more and more unnecessary in the future. And the next twenty-five years will see very many more of our patients able to go back and be treated quite simply and easily by the general practitioner and general physician using ordinary medical methods.

REFERENCES

Dally, P. J., and Rohde, P. (1961). *Lancet*, **1**, 18.
Sargant, W. (1960). *Psychosomatics*, **1**, 14.
West, E. D., and Dally, P. J. (1959). *Brit. med. J.*, **1**, 1491.

"ACUTE WHEEZY CHESTS"

CLINICAL PATTERNS AND NATURAL HISTORY

BY

JOHN FRY, M.D., F.R.C.S.

General Practitioner, Beckenham, Kent

The management of the patient with a "wheezy chest" is a common problem in British medical practice to-day, as it has been for many centuries past. According to my own estimate and that of others (Goodall, 1958; Fletcher *et al.*, 1959), the family doctor in an average-sized practice (2,500) may expect to see in any year between 100 and 150 patients complaining of wheezing in their chests and shortness of breath, and of these some 40 to 50 will be seen for acute and distressing episodes of wheezing and breathlessness. It is these acute episodes that cause most of the troubles for the patient and most of the problems for the doctor, and it is with this group of cases that the present paper is concerned.

A non-specific term such as "acute wheezy chest" has been used on purpose rather than terms such as "asthma" or "bronchitis," because it was intended to study a clinical syndrome and not a specially delineated group such as "asthma."

The needs to study "acute wheezy chests" are obvious to anyone engaged in active medical practice, for there are many questions to which we have had no clear answers. What do these acute episodes signify and what are their implications? What happens to the individual patients? How many go on with attacks and end up as respiratory cripples and invalids? How many "grow out of" their attacks and become symptom-free? The answers to these questions cannot be found in any standard textbooks, and it is only from years of observation that one gains the experience from which to build up clinical opinions and impressions.

This study was undertaken to record the progress of patients who have suffered from "acute wheezy chests" in a general practice and to analyse their course and progress so that some factual evidence may be available to support clinical opinions and impressions.

Aims and Methods

The importance of defining clinical patterns of "acute wheezy chests" and observing the natural history has already been noted, and it is this that has been attempted in a general practice.

In a general practice a follow-up extending over many years is a relatively easy matter, since the patients and their families are seen regularly, and up-to-date information on the patient under review is always available. The mechanics of the project presented few problems.

A period of 10 years (1949–58) was taken, and during this period all patients with "acute wheezy chests" were picked out, information on them recorded on special cards, and then the patients were followed up over the years. Only those patients were included who had been observed for five years or longer, and who were still in the practice at the end of the period (1959).

During this period 21 children (in addition to the 126 observed) and 12 asthmatics (in addition to the 98 observed) moved out of the area of the practice. Of these asthmatics, only two were severely affected. There was no suggestion of any significant number of asthmatics moving out or changing to another doctor for treatment.

An acute wheezy chest was defined for the purposes of this study as an acute episode with sudden onset, or sudden worsening, of wheezing in the chest accompanied by breathlessness. On auscultation high-pitched rhonchi were heard in all the patients' chests.

When patients suffering from acute wheezy chest were seen, all ages and all types being included, they were included in the study. Details were noted of the attacks, their onset and progression, and of family history and past illnesses. Treatment was noted. The patients' progress over the years was carefully observed and the number of recurrences recorded. At the end of the period of observation the patients were graded functionally. The system of grading was one adapted from Harris (1955) and Bruce Pearson (1958).

Grade 1: no attacks for three years.

Grade 2: minor attacks controlled by simple treatment and causing no interference with normal life and routine.

Grade 3: occasional severe attacks with some loss of time from school or work.

Grade 4: frequent severe attacks causing much interference with school attendance or work.

Grade 5: complete invalids unable to carry out work or attend school, or deaths from pulmonary failure.

The Practice

Information on the practice is naturally of importance as a background of the type of community where the patients lived. It is situated in the south-eastern London suburbs with a typical social grouping as shown in Table I (males only). The average size of the practice is shown in Table II.

TABLE I.—*Social Class Distribution of Practice (Males Only)*

Social Class:	I	II	III	IV	V	Not Known	Total
No. ..	99	476	1,522	100	109	26	2,432
%	4	18	63	4	5	6	100

TABLE II.—*Average Population at Risk*

Age:	0–	5–	10–	20–	30–	40–	50–	60–	70+	Total
Males ..	199	221	259	349	383	396	321	167	137	2,432
Females ..	189	188	346	362	438	391	327	224	150	2,615
Total ..	388	409	605	711	821	787	648	391	287	5,047

Table III gives some idea of the annual prevalence of all types of acute wheezy chests. This has taken into account all cases, including those who moved in and out of the practice. Some patients were inevitably included more than once because of recurrent attacks. The annual prevalence rate of 20 per 1,000 means that in this particular practice just over 100 episodes were treated every year. The age distribution shows the particular susceptibility of the young and old.

TABLE III.—*Annual Prevalence Rate per* 1,000 *at Risk* (1949–58)

Age:	0–	5–	10–	20–	30–	40–	50–	60–	70+	Total
Rate per 1,000 ..	32	25	15	5	5	15	20	35	75	20

Clinical Groups

Over the 10 years (1949–58) 327 individual patients suffering from an acute wheezy chest were seen and followed up for at least five years. As time went on it was found that these patients, with their attacks, could be classified into three clinical groups: wheezy children, 126; asthmatics, 98; chronic bronchitics, 121. 18 patients were included in more than one group: 12 wheezy children were eventually diagnosed as asthmatic and were also included in that group, and six asthmatics were also considered to be suffering from chronic bronchitis. The criteria for the three groups were as follows:

Wheezy Children.—This group included all acute wheezy episodes in children in their first decade. No attempt was made initially to diagnose "asthma," but it was found on follow-up that 12 of the 126 (nearly 10%) were eventually labelled "asthmatics." Since in 92% of cases in this group the attacks were preceded by an upper respiratory infection, these attacks were probably examples of an acute bronchitis with wheezing.

Asthma.—Although over a period of time it was quite easy to recognize a case of "asthma," a definition of "asthma" is not easy. In this survey asthma was diagnosed when the patient experienced paroxysmal recurrent acute episodes of wheezing that were not always related to an associated acute or chronic respiratory infection.

Chronic bronchitis was recognized to be present when the patient gave a history of cough and sputum had

been present for at least three consecutive months every year for at least three years.

Delineation of these three clinical groups was very useful in practice. Wheezy children and asthmatics are dealt with below, but it was not possible to do this in the case of chronic bronchitics because of difficulties of definition. A separate study of chronic bronchitics is planned.

Wheezy Children

Over the period of 10 years 126 children (aged 0 to 10) out of an average 797 at risk suffered an acute wheezy chest. This gives an incidence rate of 160 per 1,000, or 16%. This figure is not extraordinarily high, as Goodall's (1958) rate was 22% of 1,726 children in his Yorkshire practice. It seems, therefore, that at least one child in five suffers from acute wheezy episode at some time during the first 10 years of life.

These 126 children were observed in 214 attacks, and in no fewer than 198 (92%) of these attacks there was a preceding acute upper respiratory infection. These attacks were probably examples of a descending acute bronchitis in which wheezing was a prominent feature. The attacks were characterized by sudden onset, with malaise, fever, cough, wheezing, and breathlessness. The attacks varied in severity. Boys (70) were more often affected than girls (56). In just over one-third (39%) there was a history of some other allergic disorder such as eczema, urticaria, or allergic rhinitis.

Age at Onset.—The age at which attacks first began is shown in Table IV, and it is evident that in the majority (87%) their attacks had started by the age of 6 years. There appeared to be peaks in levels of incidence in the first year and in the pre-school period.

TABLE IV.—*Age at Onset of Acute Wheezy Chests in Children (0–10)*

Age:	0–	1–	2–	3–	4–	5–	6–	7–	8–	9–10	Total
No.	26	18	11	20	18	17	8	7	1	—	126
% ..	21	14	9	16	14	13	6	6	1	—	100

Frequency of Attacks and Recurrences.—These 126 children suffered 214 attacks. Table V gives the incidence of these attacks at various ages. The peak was in the pre-school period and during the first year at school, with a marked decline after the eighth year, a decline that continued in the adolescent years. The number of recurrent attacks is shown in Table VI. As many as 80

TABLE V.—*Incidence of Acute Wheezy Chest Attacks in Children 0–10 Years*

Age:	0–	1–	2–	3–	4–	5–	6–	7–	8–	9–10	Total
No. of attacks	26	20	15	29	30	28	16	25	19	6	214
% of those at risk	34	24	20	35	43	35	20	30	24	7	27%

TABLE VI.—*Recurrent Attacks of Acute Wheezy Chest in Children (0–10)*

No. Attacks:	1	2	3	4	5	6+	Total
No. of individuals ..	80	25	10	6	3	2	126
Total attacks ..	80	50	30	24	15	15	214

children (63% of total) experienced only a single attack of wheezing with no recurrence during the period of observation, and only 11 children (8%) suffered more than three attacks.

Course.—At the end of the period of observation, in 1959, a functional assessment and grading was made of these 126 children by the method already noted. The results are shown in Table VII.

TABLE VII.—*Functional Grading of Wheezy Children After 5–10 Years of Observation*

Grade:	1	2	3	4	5	Total
No. of individuals	108	12	5	1	—	126
% of total ..	87	9	3	1	—	100

The outlook for these wheezy children was favourable. At the end of 5 to 10 years of observation 87% had ceased to suffer attacks altogether, 9% had very minor and insignificant attacks, 3% still had acute episodes that involved periods away from school, and only one child was in any way severely incapacitated by frequently severe episodes. These children were all treated at home and attended normal schools. The treatment was kept as simple as possible and was based on antispasmodics such as ephedrine and antibiotics (penicillin by intramuscular injection) where indicated. Asthma was eventually diagnosed in 12 (10%) of these children, but, even so, only 6 (5%) continued having attacks after their tenth birthday.

Comments

The fact that approximately 20% of children in two distinct areas suffered from acute wheezy chests during their first decade underlines the importance of the condition. The reasons why it should be so frequent in young children are probably related to special anatomical, physiological, and pathological factors.

The statement made by Chevalier Jackson that "all that wheezes is not asthma" was borne out in these wheezy children, for only 10% were diagnosed as asthmatic.

Observations on the course of these wheezy attacks showed that the prognosis was excellent. Since the treatment given was simple and non-specific, and aimed at relieving the wheezing whenever it occurred, it must be concluded that the satisfactory outcome must have represented the true natural history of the disorder. Only one single attack occurred in as many as 63% of the children, and only 8% had more than three attacks over the 10 years. By the age of 10, 87% of the children had ceased to suffer any attacks at all, 9% had very minor episodes, and only 4% were inconvenienced by the disorder.

Goodall (1958) found a very similar pattern of prognosis—over 80% of children had ceased to wheeze by the age of 10 and 95% by the age of 15.

It is quite justifiable, therefore, to give parents of wheezy children a good prognosis and reassure them that their children are not likely to become asthmatic.

Asthma

Asthma was diagnosed when recurring acute attacks of wheezing and breathlessness occurred paroxysmally and unassociated with either acute upper respiratory infections or chronic bronchitis. This somewhat vague and rather exclusory definition was found to be useful and practical in general practice, where from long periods of observation the diagnosis could always be confirmed with certainty over the years. Some interchange of cases between the clinical groups has already been noted; 12 wheezy children were finally placed in the asthma group, and six asthmatics were thought to be suffering from chronic bronchitis.

Frequency.—Over the 10 years (1949–58) in an average population of 5,047 there were 98 patients diagnosed as suffering from asthma and followed up for at least five years. This represents an incidence rate of 20 per 1,000. The rate would have been higher if those who had moved in and out of the practice over this time had been included. It is a little difficult to compare these figures with others, because our figures covered a period of 5 to 10 years and because there is really only one other reliable source, and that is the report of Logan and Cushion (1958) on a study of one year's records of over 100 family doctors. Here the incidence rate for asthma *over a period of one year* was 10 per 1,000. In the present study of these 98 patients an average of 51 required medical attention in any year, which gives an almost identical *annual* incidence rate of 11 per 1,000.

Age at Onset

Table VIII shows the ages at which attacks of asthma began in these 98 patients. In 53% they started in the first 10 years of life. The apparent paradox that while 53% of asthmatics began their attacks in their first decade and that only 5% of wheezy cases went on to asthma is explained by the different groups of patients that were being considered. The asthmatics were not only children but adults whose attacks had started in childhood and who had not been included in the groups of wheezy children that were being studied. In other words, the asthmatics came from a much larger population at risk (5,047) than did the wheezy children (797).

TABLE VIII.—*Age at Onset of Asthma*

Age:	0–	10–	20–	30–	40–	50–	60+	Total
Males ..	32	4	4	3	4	1	—	48
Females ..	20	4	10	10	2	3	1	50
Total ..	52	8	14	13	6	4	1	98

This early commencement of asthma has been noted by other authors writing from the hospital and consultant fields. Onset in the first 10 years of life was found in 40% by Bruce Pearson (1958), in 33% by Williams and Williams (1949), in 56% by Williams *et al.* (1958), and in 49% by Kauntze *et al.* (1951). It appears that between one-half and one-third of asthmatics begin their troubles in childhood.

Sex Incidence

Another interesting feature was the sex incidence. There was little difference between the sexes over the whole series (48 males and 50 females), but there were appreciable differences in the various periods at which the attacks began. In the first decade asthma began much more frequently in boys than in girls (3:2). Over the age of 20 twice as many females began to have asthma as did males. Similar trends were observed by Williams and Williams (1949), Bruce Pearson (1958), and Williams *et al.* (1958).

Course

What happens to our asthmatic patients? How many go on to become pulmonary invalids? How many cease to suffer attacks? These are important questions, and an attempt is made here to answer them.

All the patients were observed continually for at least five years, but many for much longer periods. Also, many came into the practice some time after having their first attacks, so altogether a good composite picture was obtained. Since there is no satisfactory specific therapy for asthma these patients were treated for the attacks with antispasmodics and antibiotics when necessary. No attempts were made to desensitize the patients or to give any special psychotherapy or other pseudospecific treatment. The follow-up and assessment represents a picture of the natural history of asthma.

A functional assessment and grading was made, using the system described, at the end of the period, in 1959 (Table IX). It will be seen that the peak severity (which occurred some three to seven years from the onset) was associated with a disability rate of approximately 96% —that is, grade 3 or worse. However, 5 to 10 years later this disability rate fell to a mere 10%, showing that there is a natural trend for asthma to improve with time. Of course, there are individual patients who do not improve, who remain disabled or deteriorate or even die, but it is gratifying to note that in only 7% in this series was there any severe disability. This included three patients who died from the effects of asthma, leaving some 4 to 5% still living but considerably disabled.

TABLE IX.—*Functional Assessment of Asthmatics at the End of 5–10 Years' Observation*

Grade:	1	2	3	4	5	Total
Onset	—	19	53	21	5	98
Peak	—	4	30	38	26	98
Follow-up at 5–10 years	45	43	3	1	6*	98

* 3 patients died from asthma.

Deaths

The deaths occurred, surprisingly enough, in three women.

Mrs. M. P., aged 35, died as a result of a sudden tension pneumothorax that developed during a severe bout of status asthmaticus (in 1950, before the days of corticosteroids).

Miss A. W. aged 68. Her asthma started late in life. This was eventually found to be connected with a polyarteritis nodosa, from which she died some years later.

Miss J. G., a frail and anxious spinster, began to suffer from asthma at 55; it was never well controlled, and she died from cor pulmonale at the age of 78.

Other authors, quoting figures from hospital practice, have also noted a good prognosis in asthma, although not as good as in this series (Table X). In both these series—Williams and Williams (1949) and McCracken (1950)—the periods of observation were over 7 to 12 years.

In my patients there was a difference in the prognosis of those whose asthma started in childhood (under 15)

TABLE X.—*Prognosis of Asthma—Other Series*

	No. of Attacks	Improved ++	Frequent Attacks	Death
Williams and Williams (1949)	20%	35%	28%	17%
McCracken (1950)	21%	54%	15%	10%
Average	66%		33%	

TABLE XI.—*Prognosis of Asthma Starting in Childhood—Other Series*

	No Attacks	Improved ++	Frequent Attacks	Death
Flensborg (1945)	41%	38%	16%	5%
Rackemann and Edwards (1952)	31%	40%	26%	3%
Average	75%		25%	

and in those who began attacks in adult life. In the former group the 5 to 10-year disability rate was only 5%, whereas in those whose asthma began in adult life the disability rate was as high as 18%.

Flensborg (1945) and Rackemann and Edwards (1952) also found a good prognosis in asthma in children (Table XI).

Comments

With an incidence of around 20 per 1,000 the average family doctor might expect to be kept busy caring for the 50-odd asthmatics in his practice, were it not for the apparently good prognosis and tendency towards a natural improvement.

A functional assessment of the 98 asthmatics in my practice has shown that in time as many as 90% cease to suffer major attacks. This pattern of improvement is undoubtedly part of the natural history of the condition, for the same trends are noted in the more severe types of asthma referred to consultants in hospitals. In reported series from hospitals between 66% and 75% of these more severely affected patients cease in time to be troubled by their asthma.

The importance and significance of appreciating this feature in the natural history of asthma are obvious. Our whole approach to asthma should focus on this aspect, and we should give our patients and their relatives a good and hopeful prognosis, and the management of our patients should be simple and be designed so that the attacks may be treated as they occur, with the efficient antispasmodics at our disposal, not forgetting the corticosteroids, which have greatly eased the management of severe cases. This non-specific approach must of course be supplemented by caring for various emotional, allergic, and other aspects of the individual patient.

While the course of most of these cases of asthma is towards a steady and natural improvement, it must be stressed that the situation in the 10% minority is potentially dangerous. It is in this small group that fatalities occur, especially in those over the age of 30, and it is these patients who will cause the family doctor and the consultant disproportionate anxieties.

Discussion

When one is dealing with a syndrome whose aetiology is uncertain, whose nomenclature is confusing, whose natural history is forgotten and unappreciated, and whose treatments are manifold, it is useful to start with a clean slate and take the syndrome as a whole and examine afresh possible clinical groupings and natural patterns of progress. This is what has been attempted in the present study in a general practice.

The family doctor is often bewildered by the many cases of "acute wheezy chests" in his practice. What are they? What is their outlook? What is their simplest form of management? Some answers have been suggested as a result of this study.

Three simple clinical groups were defined—wheezy children, asthmatics, and chronic bronchitics—and individual patients in the former two groups followed up for at least five years.

Fortunately, the course in the wheezy children and asthmatics was much better than expected. As the follow-up showed, 96% of wheezy children ceased to have trouble and in as many as 90% of asthmatics either their attacks stopped completely or they were little troubled by them. These figures may seem astonishingly good and other physicians may say, "But I'm sure I have many more bad cases." Unless accurate records are kept over long periods "impressions" and "opinions" are worthless. Inevitably it is the worst and most troublesome cases that are remembered. The asthmatics who proceed to status asthmaticus and the children who pass through the vulnerable years with many attacks of wheezing and other respiratory infections—these are the cases that are remembered rather than the many others that clear up uneventfully. These few problem patients cause us great anxieties and require very careful and individual care.

The history of wheezy children is one of natural and spontaneous improvement, and Goodall (1958) confirms this. The same tendency in asthma has also been noted by Flensborg (1945), Williams and Williams (1949), McCracken (1950), Rackemann and Edwards (1952), Williams *et al.* (1958), and Bruce Pearson (1958). This being so, management must be aimed at tiding our patients through the critical years by the safest and the simplest measures until the natural improvement occurs. When any "new" treatment is introduced and publicized it must be assessed carefully, using these natural patterns as baselines for comparison.

Summary

Considerable confusion exists over the causes, the significance, the course, and the management of acute wheezy attacks. The average G.P. seeing 40 to 50 such attacks each year is faced with many problems. This study has attempted to define simple clinical groups and to clarify the true natural history of these groups.

To carry out these aims 327 patients with such acute wheezy attacks in a practice of over 5,000 patients were observed and followed up for 5 to 10 years, from 1949 to 1958.

Three clinical groups were defined—wheezy children (126), asthmatics (98), and chronic bronchitics (121). Because of special problems a separate study is being made of the chronic bronchitics.

Wheezy Children.—There were 126 such children out of 797 at risk, a rate of 16%. In 87% the attacks first began before the age of 6. The peak periods for the attacks were in the first year of life and in the pre-school and early school periods. Single attacks were noted in 63% and only 8% had more than three attacks. At the end of the follow-up it was found that 87% had had no attacks for the previous three years and 9% were having very slight and insignificant attacks. Only 5% continued to wheeze after the age of 10.

Asthma.—The frequency was 98 cases out of 5,047 at risk—that is, 20 per 1,000 over five years. The annual incidence rate was around 11 per 1,000. In 53% the onset was in the first 10 years of life. In the history there were emotional illnesses in 24%, other allergies in 32%, a positive history in 15%, and an associated respiratory infection in 17%. At the peak (reached three to seven years from onset) there were 96% disabled. At the end of 5 to 10 years of observation the disability rate was only 10%, and in 90% the attacks had either ceased completely or caused very slight trouble. In those whose attacks began before the age of 15, 95% were free from trouble; in those whose

asthma began after the age of 15 there were 82% who were clear and not disabled from asthma.

REFERENCES

Flensborg, E. W. (1945). *Acta Paediat. (Uppsala)*, **33**, 4.
Fletcher, C. M., Elmes, P. C., Fairbairn, A. S., and Wood, C. H. (1959). *Brit. med. J.*, **2**, 257.
Goodall, J. F. (1958). *J. Coll. gen. Pract.*, **1**, 51.
Harris, A. (1955). *Lancet*, **1**, 376.
Kauntze, R., Shire, T. H., and Southwell, N. (1951). *Guy's Hosp. Rep.*, **100**, 69.
Logan, W. P. D., and Cushion, A. A. (1958). *Morbidity Statistics from General Practice*, vol. 1. (General Register Office: Studies on Medical and Population Subjects, No. 14.)
McCracken, D. (1950). *Brit. med. J.*, **1**, 409.
Pearson, R. S. B. (1958). *Acta allerg. (Kbh.)*, **12**, 277.
Rackemann, F. M., and Edwards, M. C. (1952). *New Engl. J. Med.*, **246**, 815.
Williams, D. A., Lewis-Faning, E., Rees, L., Jacobs, J., and Thomas, A. (1958). *Acta allerg. (Kbh.)*, **12**, 376.
Williams, E. O., and Williams, G. E. O. (1949). *Brit. med. J.*, **2**, 897.

ORAL TREATMENT OF PERNICIOUS ANAEMIA: FURTHER STUDIES

BY

F. S. MOONEY, M.D., B.Sc.
Consultant Pathologist, St. Helens Hospital, St. Helens, Lancashire

AND

J. G. HEATHCOTE, Ph.D., B.Sc., F.R.I.C.
Biochemist, Distillers Co., Biochemicals Ltd.

During the past two and a half years the results have been published of 11 cases of pernicious anaemia treated with the oral vitamin-B_{12}–peptide complex, H.P.P./1, which was derived from a fermentation of a streptomyces mutant (Heathcote and Mooney, 1958a, 1958b; Mooney and Heathcote, 1960a). As a result of these findings we formulated a new hypothesis concerning the aetiology of pernicious anaemia—namely, that the disease is due to failure of gastric proteolysis and that intrinsic factor, as currently understood, does not exist. Table I summarizes the present state of 10 of these same patients. Case 39 (Mooney and Heathcote, 1960a) has been withdrawn from the series because he received, inadvertently, an injection of crystalline vitamin B_{12}. Nine of the remaining cases are still maintained on a daily dose of 10 μg. of vitamin B_{12} (78 μg. H.P.P./1) or less. Case 30, however (Mooney and Heathcote, 1960a), was barely maintained on a daily dose of 10 μg., and this has been increased to 20 μg. with satisfactory results (Table I). Haematological remission remains complete in all cases. No neurological complications have developed and there is no refractoriness. The duration of treatment now ranges from 476 to 1,409 days.

The main purpose of the present paper, however, is to describe the clinical results obtained in cases of pernicious anaemia, using a new peptide complex derived from fermentations of propionibacterium and to discuss these results and the others obtained from the streptomyces preparation in the light of present knowledge.

Properties of the Complex.—Six batches of a vitamin-B_{12}–peptide complex derived from fermentations of propionibacterium have been used in the clinical studies. These have been designated H.P.P./4, H.P.P./7, H.P.P./9, H.P.P./12, H.P.P./16, and H.P.P./17. The spectrophotometric curves of these preparations were similar to one another and to that of H.P.P./1 (Heathcote and Mooney, 1958a), having maxima at 277, 361, and 550 mμ. Amino-acid analysis of the preparations was also similar to that for H.P.P./1. The vitamin-B_{12}–peptide ratio of the batches varied, on a weight basis, from 1:3.7 to 1:7.1, thus showing that the preparation was not a chemical compound in the strict sense but rather a loose combination of peptide and vitamin which can occur in different proportions. Ultracentrifuge studies, carried out at the Microbiological Research Station, Porton, with one of these batches (H.P.P./7) have shown that it produces a single peak corresponding to a molecular weight of about 1,200–1,400—that is, of the same order as vitamin B_{12}. These and further ultracentrifuge studies at the Biochemical Laboratory, Cambridge, have clearly shown that there is no protein in the complex. Furthermore, the batches are dialysable.

Maturation of Megaloblasts.—It has previously been shown (Heathcote and Mooney, 1958a) that the vitamin-B_{12}–peptide complex H.P.P./1 matured megaloblasts *in vitro* in 18-hour cultures as rapidly as folic acid. This property is not shared by crystalline vitamin B_{12} alone, nor by gastric juice alone (Callender and Lajtha, 1951). Of the present vitamin-B_{12}–peptide batches only H.P.P./4 was tested in this way, but it also proved to be approximately as effective as folic acid in bringing about the maturation of megaloblasts.

Clinical Studies

Fourteen newly diagnosed uncomplicated cases of pernicious anaemia were treated with the propionibacterium complex. Three patients were males and 11 were females. The ages range from 36 to 80 years. Case 6A was used as a control, and Cases 11 and 14 in maximum response experiments. As all three of these received

TABLE I.—*Uncomplicated Cases of Pernicious Anaemia Treated Exclusively with Streptomyces Complex (H.P.P./1)*

Case No.*	Age	Sex	Duration Treatment (Days)	Vitamin-B_{12}–Peptide Complex (as μg. Vitamin B_{12})			Initial Blood Picture			Current Blood Picture			
				Total Dose	Mean Daily Dose	Current Maintenance Dose	Hb %	P.C.V. %	M.C.H.C. %	Hb %	P.C.V. %	M.C.H.C. %	Serum Vitamin B_{12} $\mu\mu$g./ml.
1	48	M	1,409	15,370	10·8	10	66	22	44	100	48	32·5	48
2	75	F	1,354	15,450	11·4	10	48	19	37	93	40	34	62
3	67	M	1,316	13,270	10·1	10	39	15	38	98	43	34	66
4	66	M	1,262	14,020	11·1	10	76	27	42	112	46	36·0	90
5	44	M	1,156	12,040	10·4	10	53	19	42	114	53	32	49
25	58	F	912	4,560	5·0	5	66	30	32	101	51	29·5	46
26	55	M	825	2,890	3·5	3·5	50	25	30	100	49	31·5	—
27	61	M	821	3,046	3·7	3·5	56	26	32	100	43	35·5	13
30	66	M	740	10,870	14·9	20·0	56	22	37	110	46·5	35·0	140
38	70	F	476	2,200	4·6	4·0	29	14	31	81	39·0	30·5	23
Average	61		1,026		8·6	9·0	54	22	36·5	101	44	34	60

* The numbers here refer to those same cases reported in the papers by Heathcote and Mooney (1958a) and Mooney and Heathcote (1960a).