

Development of an expert system for the interpretation of serial peak expiratory flow measurements in the diagnosis of occupational asthma

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Abstract

If asthma is due to work exposures there must be a relation between these exposures and the asthma. Asthma causes airway hyperresponsiveness and obstruction; the obstruction can be measured with portable meters, which usually measure peak expiratory flow, or sometimes forced expiratory volume in 1 second (FEV₁). These can be measured serially (for instance 2 hourly) over several weeks at and away from work. Once occupational asthma develops, the asthma will be induced by many non-specific triggers common to non-occupational asthma. The challenge is to identify changes in peak expiratory flow due to work among other non-occupational causes. Standard statistical tests have been found to be insensitive or non-specific, principally because of the variable period for deterioration to occur after exposure, and the sometimes prolonged time for recovery to occur, such that days away from work may initially have lower measurements than days at work. A computer assisted diagnostic aid (Oasys) has been developed to separate occupational from non-occupational causes of airflow obstruction. Oasys-2 is based on a discriminant analysis, and achieved a sensitivity of 75% and a specificity of at least 94%; therefore peak expiratory flow monitoring combined with Oasys-2 analysis is better to confirm than to exclude occupational asthma. A neural network version in development has improved on this. Both have been based on expert interpretation of peak flow measurements plotted as daily maximum, mean, and minimum, with the first reading at work taken as the first reading of the day. Oasys has been evaluated with independent criteria against measurements made in a wide range of occupational situations. Oasys is sufficiently developed to be the initial method for the confirmation, although less so for exclusion of occupational asthma.

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Specific bronchial provocation tests are considered the gold standard in the diagnosis of occu-

pational asthma.¹ The tests are often far removed from the work exposures that they are meant to reproduce—for instance, nebulised allergen extracts are sometimes used. It can be difficult to reproduce some work exposures in the laboratory—for instance, welding fume or the aerosols generated when coolant oil hits a very hot fast revolving piece of metal. Specific challenges can be falsely negative when for instance the particle size of the material is different in the challenge chamber from the workplace, non-specific reactions can also occur if the challenge exposures are inappropriately high.² In the workplace the potential sensitising agent is often accompanied by other exposures which might enhance the reaction—for instance, amines in flux activators might enhance the effect of colophony in solderers.³ Some centres send a technician to monitor lung function during days away from work, and during workdays; this is an expensive approach and has not been adequately validated against gold standards. We set out to validate laboratory based challenges by returning the subject to the workplace and observing the reaction with self measurement over longer periods. Over the past 20 years our work has developed to make physiological monitoring of airflow obstruction in the workplace the primary investigation, with specific laboratory challenges reserved for defining the aetiology rather than the presence of occupational asthma. This paper will review the problems we have encountered, and concentrate on a computer assisted expert interpretation of serial peak expiratory flow (PEF) measurements which has developed from this work. Guidelines on self monitoring of PEFs in the investigation of occupational asthma were published in 1995.⁴ Recommendations for research included the required frequency of daily measurements, the development of computer generated standard graphs, methods of objective analysis less dependant on expert interpretation, comparison with specific challenge tests, assessment of the effects of treatment and the applicability to epidemiological studies. This current review considers all but the last issue.

The measurement of PEF

It is over 150 years since Hutchinson described the measurement of vital capacity,⁵ and more than 50 years since the forced expiratory manoeuvre was described by Tiffeneau and Pinelli.⁶ The first portable device suitable for self measurement of lung function was developed by Wright and McKerrow.⁷ Peak expira-

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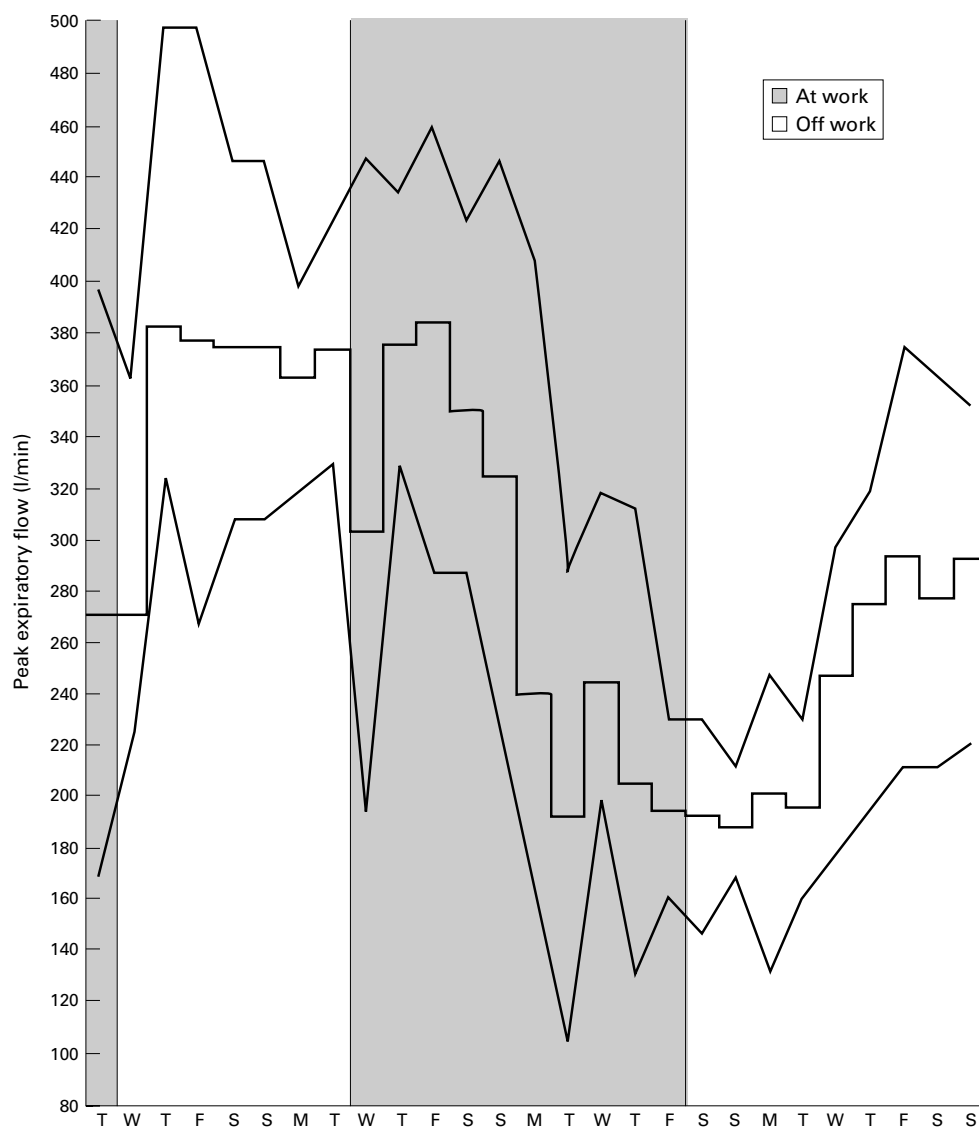


Figure 1 An early PEF record made over the Christmas holiday in 1976, used in the first statistical analyses.¹⁸ The record was made hourly from waking to sleeping in a gravure printer who had previously been sensitised to isocyanates used as a surface coating on his press. Isocyanates were used for laminating two rooms away from his printing press. He had a period off work before the record started, on the first day he visited the medical department and his colleagues, which induced an attack of asthma. He returned to work without direct isocyanate exposure on 15 December. If the record had started on 15 December, the first regular workday, the mean PEF would have been higher on days at work than away from work. The record shows how results are influenced by the work pattern during the record. He had a dual asthmatic reaction after challenge to 0.004 ppm toluene diisocyanate (TDI) for 30 minutes.

tory flow was measured rather than forced expiratory volume in 1 second (FEV_1) for convenience rather than any attempt to develop a superior measurement of forced expiration. Hetzel and Clark investigated and characterised the diurnal variation in PEF found in asthmatic patients,⁸ and Turner-Warwick wrote the first descriptive account of the patterns of asthma seen in chronic asthmatic patients in general.⁹ We have used PEF measurement because of the portability, robustness, and cheapness of the measuring devices available.

Data quality needs to be as good as possible. At least four evenly spaced readings a day are required to assess diurnal variation¹⁰ and response to occupational exposures.¹¹ Two hourly readings are optimal. Many of the original peak flow meters are non-linear, if so linearisation is needed before analysis.¹² Treatment should be kept constant, and periods with

respiratory infections or other confounding factors removed from the record before analysis. Increased diurnal variation is a hallmark of asthma, but is seriously biased by a low denominator when mean PEF is used when the PEF is low. Use of the predicted PEF overcomes this problem and is the denominator of choice.¹³ Some readings are likely to be fabricated,¹⁴ the most obvious are removed before analysis, but the final record is likely to contain some mistimed or invented readings. The quality of a record may deteriorate with time. Gannon *et al* showed that the PEF fell by a mean 21 l/min during a 3 week record, which could be reversed with encouragement and prevented by further training.¹⁵ A fuller account of the technical problems in acquiring measurements has been published.¹⁶

The analysis of serial peak flow measurements at work and home can be likened to the

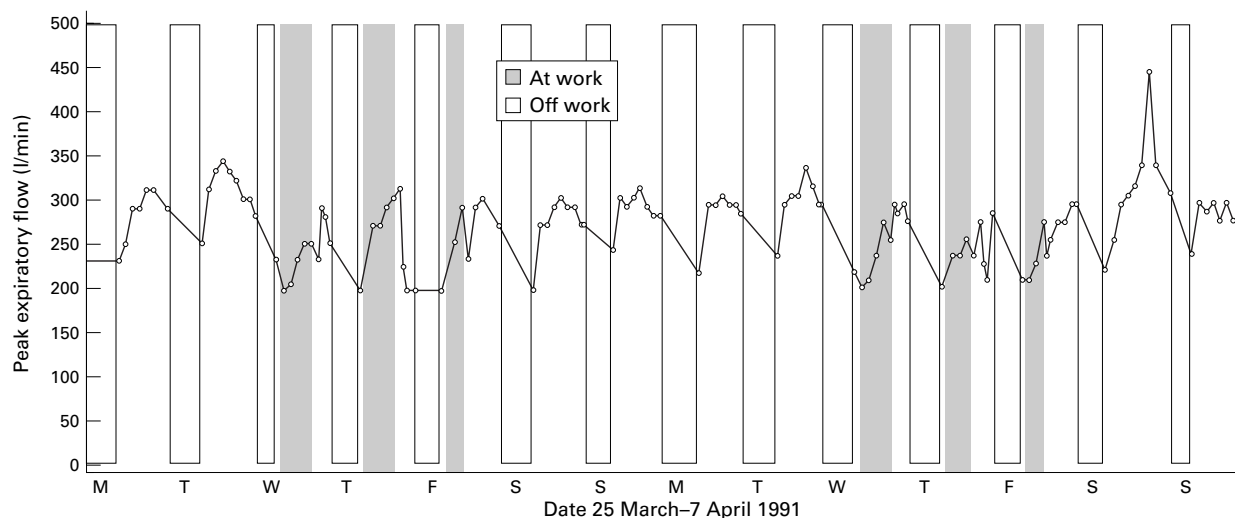


Figure 2 Peak flow records in an endoscopy nurse exposed to glutaraldehyde. She was taking beclomethasone throughout the record. The PEF is plotted sequentially, the periods at work are shaded, the vertical lines show the time of sleeping and waking. On the first workday there is an immediate fall in PEF followed by a rise while at work; the PEF rises during work on all the other workdays, and always falls during sleep. On days away from work the waking reading is higher, but the maximum reading is often similar to workdays. In the last period off work there is a single reading much higher than the others. This may well be a measurement or transcription error. The relation between PEF and exposure to glutaraldehyde is not obvious from this record. Specific bronchial provocation testing showed a dual immediate and late asthmatic reaction after exposure to glutaraldehyde at $0.07\text{mg}/\text{m}^3$.

interpretation of repeated daily specific challenge tests where the exposures are not defined, the lung function measurements not supervised, where often unrecorded additional causes of reduced PEF are distributed throughout the record, and where no stable baseline is achieved before each exposure. On the positive side the exposures will always be realistic.

Early attempts at statistical analysis

The first attempt was to measure PEF hourly on 1 day at and 1 day off work and to plot the PEF as if it was a single specific challenge. The baselines were often different, and the PEF seemed to be much more erratic than recorded in supervised in-hospital challenges, making interpretation very difficult. Extending the records to several days showed that there were often progressive changes on serial workdays and progressive improvements away from work, making single days unrepresentative.^{17–19} We thought that the variability induced by the erratic exposures and unmeasured confounding factors would be compensated by making longer records. The identifiable factors relating to a particular PEF reading was the time of the day (or the time from waking), the number of days with or without previous occupational exposure, exposure on the particular day, and any extra treatment taken. These factors were put into an analysis of variance (ANOVA), running the effect of exposure or no exposure after the other factors.²⁰

The ANOVA for work effect was often significant when visual inspection showed what seemed to be a normal record, with low diurnal variation and no changes related to work exposure. The statistics were very sensitive to slightly lower measurements during the first few days of a record (a learning effect) which were often workdays, and a lower waking PEF due to earlier waking on workdays. The ANOVA was also very sensitive to any delayed recovery pattern—for instance, a severe reaction at work might

lower PEF for several days. If the worker was off sick during these days the PEF would be lower on days away from work. The statistics only worked if full recovery occurred before return to work (fig 1). For these reasons statistical analysis was abandoned. Others subsequently have failed to develop statistical analyses which improve on visual inspection.^{21 22}

Replotting of records to aid subjective interpretation

A problem arose when the workday started at variable times, such as in a shift worker; days were reinterpreted to start with the first reading at work, and to continue until the last reading before work on the next day. This restored the waking reading, which was often the lowest, to the previous day's exposure. There were complicated adjustments needed during shift changes, particularly when changing from night shifts to day shifts. All subsequent analysis has used these adjusted days, now called "day interpreted".

Visual interpretation of a series of PEF measures is facilitated by plotting the daily maximum, mean, and minimum PEF, rather than the sequential PEF measurements, as this tends to accentuate the differences between work and rest exposures. Figures 2 and 3 show the same PEF measurements plotted in each way. All subsequent analyses have used the daily maximum, mean, and minimum plot with day interpretation. The method is illustrated in figure 3. To evaluate serial PEF measurements in the diagnosis of occupational asthma, gold standard tests for positive and negative records are required. Some have used specific challenges as the gold standard; unfortunately as already mentioned these can be falsely negative, and tend to be done only in those with a good history of occupational asthma, and exposures that are reasonably easy to reproduce in the laboratory setting. To overcome some of these problems we have extended the criteria for the

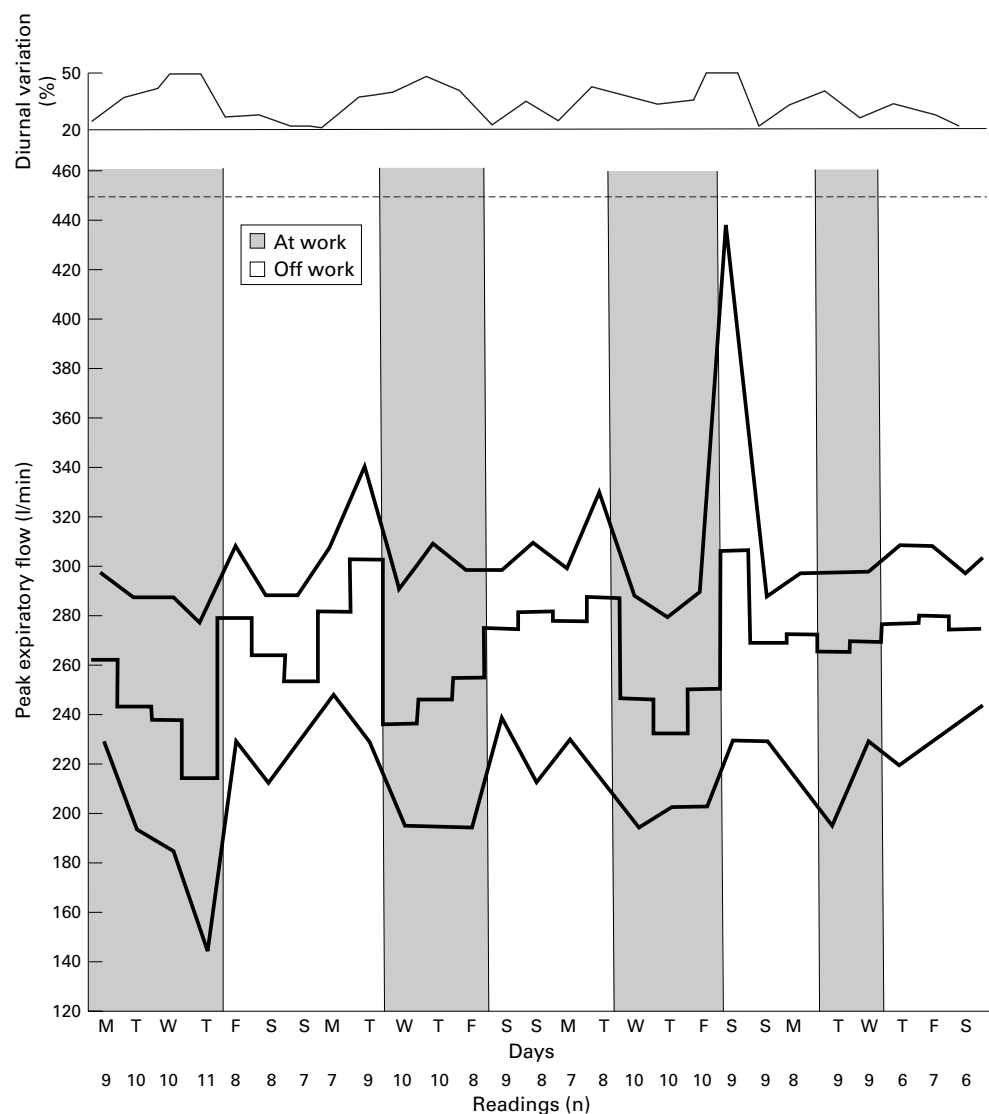


Figure 3 The complete record from the endoscopy nurse shown in figure 2 (which showed the second and third work weeks of this record). The PEF has been linearised; each day starts with the first reading at work rather than the waking reading, and has been plotted as a daily maximum, mean, and minimum, with the diurnal variation in the upper panel, and the number of readings a day at the bottom. Visual scoring compares the first period away from work, with the work periods before and after it (a work-rest-work complex); although the second and third days away from work are not as good as the first, fourth, and fifth, there is a general improvement during this period. The next analysis compares the second 3 day period at work with the period off work before and after this (a rest-work-rest complex). There is clear deterioration during the work period. The analysis moves along the record in a similar manner. The final 2 day period at work is not different from the periods either side of it. The reason is not clear, it could be due to the (relatively) lower readings in the 2 days off work beforehand and afterwards, or to a lack of exposure during the work period. Such variations are commonly seen in records, making short (2 weeks or less) records often unrepresentative. Overall the record shows a clear work related pattern.

diagnosis of occupational asthma to include a suggestive history supplemented by either a fourfold change in non-specific reactivity at and away from exposure (a specific but insensitive criterion^{22, 23}), or a positive specific IgE to a relevant occupational allergen, for instance rat urine in a laboratory animal worker. Gold standard negative tests were more difficult, many studies show that those without occupational asthma are less asthmatic than those with the disease.²¹ We have therefore chosen asthmatic patients of similar severity (often the same people who have occupational asthma), where the record has been made completely away from work. We have called the readings between Monday and Friday workdays, and the weekend readings days off.

Visual interpretation by an expert

The first analysis was subjective expert interpretation of the record plotted as daily maximum, mean, and minimum as described in figure 3. Arbitrary criteria were developed requiring a subjective assessment of deterioration during a work period or improvement during a period away from work on at least 75% of available occasions. The opinion was designed to be specific rather than sensitive, to try and overcome some of the scepticism present about even the existence of occupational asthma at the time. Specificities of 100% for colophony asthma were achieved, but the sensitivity fell from 77% when no prophylactic treatment was being taken, to 42% when inhaled corticosteroids or cromoglycate was

Table 1 Sensitivity and specificity of different methods of PEF analysis in their original assessments, when applied to records not used in the development of the method

	Sensitivity	Specificity
Expert visual inspection	42*-72†	100
Statistical analysis (ANOVA)	50*-93	67
Discriminant analysis (Oasys-2)	75	94
Discriminant analysis (Oasys-3)	82	94
Neural net (Oasys-N1)	80.6	100

*Taking inhaled corticosteroids or cromoglycate.

†No treatment.

taken regularly¹⁷ (table 1).

Bright (personal communication) studied the factors related to certainty and reproducibility of expert opinion. In all 131 individual complexes were scored by an expert on four occasions at least 2 weeks apart, on the first occasion each complex score was prefixed with the degree of expert certainty in his opinion (certain, fairly certain, or uncertain). The weighted κ score for the single expert repeatability was 0.68. Factors associated with uncer-

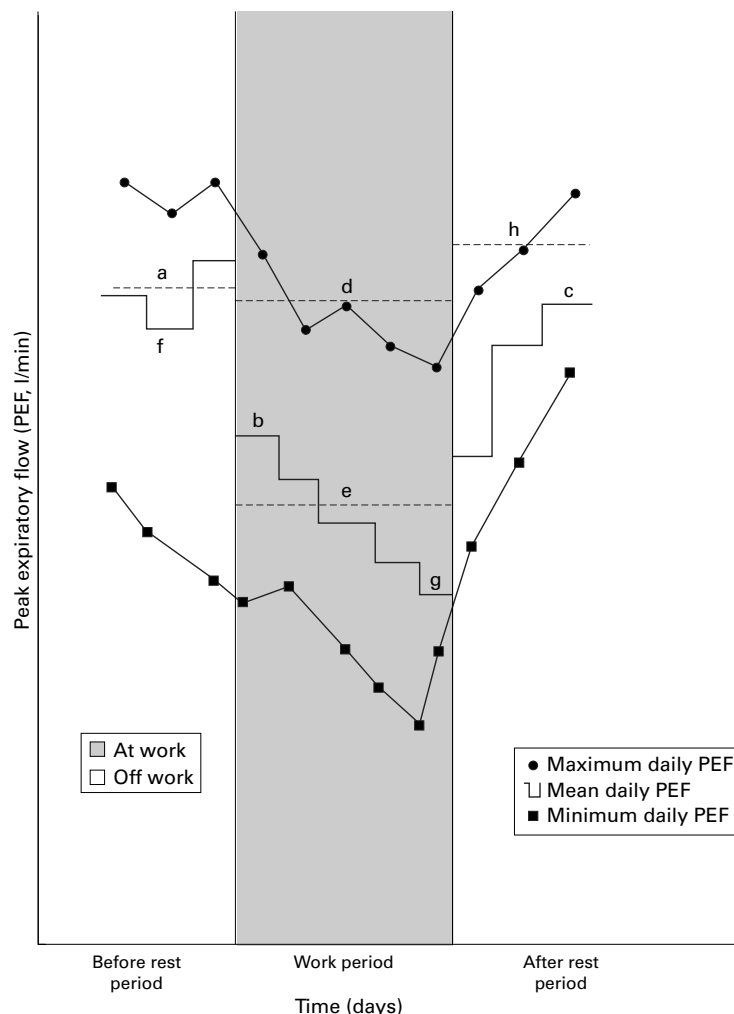


Figure 4 (Adapted from Thorax 1996;51:487, figure 2) Measurements from periods at work found to be independent predictors of the expert opinion in the development of Oasys-2. They are: a-b (average of daily mean PEFs in preceding rest period minus the highest daily mean PEF in the next work period); c-d (the highest rest period PEF in the next rest period minus the average of the maximum daily PEFs in the preceding work period); e-g (average of daily mean PEFs in preceding rest period minus the average of the daily mean PEF in the next work period); f-g (lowest daily mean PEF in the preceding rest period minus the lowest daily mean PEF in the next work period); h-d (average of the daily maximum PEFs in the next rest period minus the average of the maximum daily PEFs in the preceding work period)

tainty included records with a high PEF and complexes with large differences between daily mean PEFs. By contrast, Oasys-2 was less certain for low diurnal variation complexes, and ones with a short central section. Not all experts can be relied on to agree when interpreting occupational peak flow records. In one study, 35 original peak flow records from patients under investigation for suspected occupational asthma were reviewed (Baldwin, personal communication). Records included details of the nature of the work, intercurrent illness, drug treatment, predicted PEF, rest periods, and holidays. Both consecutive plots of PEF (fig 2) and the record plotted as daily maximum, mean, and minimum (fig 3) were available. Eight experts in occupational asthma from three continents were given 1 hour to review 35 records and were asked to score each work-rest-work period and each rest-work-rest period for evidence of occupational effect. Then they scored the whole of each record between 0 (none) and 100 (certain) for evidence of asthma and occupational effect. All eight experts completed 13 records and seven completed 24. If agreement was defined as scores within 20%, the κ values for agreement on an occupational effect was 0.58, agreement as to the presence of asthma was worse at 0.29. The level of agreement between experts depends on the records used. When the work related changes are large and consistent agreement is high (and statistical analysis more helpful²⁴). In practice, work related changes are often much less consistent, which is likely to explain the different results for expert repeatability between studies^{11 25 26}; experts from each of these groups contributed to the three continent study described above. An objective reproducible scoring system is therefore needed.

Discriminant analysis

Each work-rest-work and rest-work-rest complex was scored by one expert for the probability of a work effect. A linear discriminant analysis was developed from the plot of daily maximum, mean, and minimum PEF with 50 likely measurements from two adjacent periods. Five measurements from work periods and seven from rest periods were shown to be independent predictors of the subjective expert score, those identified for work periods are shown in figure 4. The mean PEF was the factor identified most often in the analysis, with little emphasis placed on the daily minimum PEF. The discriminant analysis tended to underscore compared with the expert, agreement falling from 73% for complexes scored as definitely no occupational effect, to 55% for complexes judged to have a definite occupational effect. However, the overall score developed from a weighted combination of individual scores had a sensitivity of 75% when applied to records not seen by the analysis before, which was an improvement on the original subjective assessments, particularly as regular inhaled corticosteroids were taken during most records. This version is known as Oasys-2 and is available for general use.²⁷

The expert uses three adjacent periods to decide whether the central period is different from the other two. We thought we could improve the underscoring of complexes judged to show a definite work related effect by developing a discriminant analysis with measurements from all three periods simultaneously. In all 729 measurements were entered into the model, together with the 50 originally used in Oasys-2. There was a marginal improvement in sensitivity and the scoring of definite work related complexes, but the differences were not significant, and the number of variables entered into the analysis, compared with the 268 records used, was of questionable validity. The resulting equations put more emphasis on daily maximum than daily mean PEF.

Development of a neural network

Neural networks are designed to recognise patterns in sets of data, which do not need to be defined beforehand. A separate neural network would be needed for every combination of days at work and days at home, making the method impractical without earlier data manipulation. Every record was adjusted so that there were 5 days at work then 2 days away from work. For instance 3 days at work then 4 days away from work was adjusted as follows. The three work days were divided to be the 1st, 3rd, and 5th workdays; the 2nd workday was constructed as the mean of days 1 and 3; the 4th workday as the mean of days 3 and 5. The first 3 rest days were meant as the new 1st rest day, the last rest day remained as before. Separate neural networks were constructed for rest-work-rest and work-rest-work complexes. The neural network was taught on complexes scored by an expert, calibrated on records from workers whose diagnosis had been made independently of PEF measurement, and tested on records not used in its development, similarly to the discriminant analyses.

NeuralShell 2 was used to construct a four layer back propagation neural network. The input layer contained nodes for the maximum, mean, and minimum PEF for each day of the work-rest-work or rest-work-rest complex, there was one node in the output layer. The best match with expert interpretation has been achieved with twice as many nodes in the first hidden layer as in the input layer, and half as many in the second hidden layer. The input layer had linear scaling and the other layers logarithmic activation functions. Matching of individual complexes assessed as definitely no occupational effect by the expert was 89%, falling a little to 81% for complexes assessed as having a definite occupational effect. This was an improvement on the previous versions of the discriminant analysis. The first gold standard set was used to set a level for 100% sensitivity (a mean score of 2/4) and 100% specificity (3/4), intermediate scores were deemed indeterminate. When these scores were applied to a new gold standard set, a mean score ≥ 3 had 100% specificity and 80.6% sensitivity. A mean score ≤ 2 had a specificity of 78.6% and a sensitivity of 100%. It is not yet clear whether these improved results are partly related to the

Table 2 Sensitivity, specificity, and accuracy of Oasys-2, Oasys-3, Oasys-N1, and the Coté analysis, when applied to the same data set of 32 positive and 56 negative gold standard records (not used in the development of any system)

	Sensitivity %	Specificity %	Accuracy %
Oasys-2	69	94	86
Oasys-3	64	98	86
Oasys-N1	81	100	93
Coté	100	50	60

data manipulation used before entry to the first layer of nodes, or to the neural network itself. The neural network placed more weight on the daily mean PEF than the maximum or minimum, and placed more weight on the central section of each complex than the flanking areas. This is comforting as it is similar to the weight placed during expert interpretation.

Comparison between different methods of PEF analysis for an occupational effect

The best statistical method for the interpretation of occupational PEF records has been described by Coté *et al.*²⁸ They used the six best measurements for each day, the average of the minimums on workdays and the average of the maximums on rest days were calculated. A positive record had a difference >58 l/min. This method was compared with the Oasys programs with a gold standard set of PEF records not used in the set up of any of the systems. The records came from workers with a wide range of exposures typical of those presenting clinically. The sensitivity, specificity, and accuracy (true positives+true negatives/all records) are shown in table 2. Oasys-N1 has the best accuracy.

Future developments

There is still scope for increasing the sensitivity of the records. Data quality might be improved by the greater use of logging meters, the current development will have included a number of misrecorded and invented readings which should be reduced with logging meters, provided they are as convenient to carry around and use as the manual peak flow meters. The removal of confounding factors, particularly measurements made with respiratory infections, should help, provided these can be reliably identified. The existing Oasys-N1 does not use the average hourly PEF on days at work or at home, these being lost in the daily maximum, mean, and minimum. Analyses including these hourly readings might improve the results. Indeterminate records can be clarified by measurements before, during, and after a 2 week period off work, methods for the objective analysis of these periods need development.

Oasys identifies work related changes in PEF, asthma being the most common cause for this. There are, however, many records with consistent work related changes in PEF where the diurnal variation is within the normal range (figure 5). Whether these represent asthma, or other lung pathology, is unclear, and whether this distinction alters prognosis also needs to be determined.²⁹

The development of Oasys was initially based on the subjective opinion of an expert. However, the development and evaluation has been

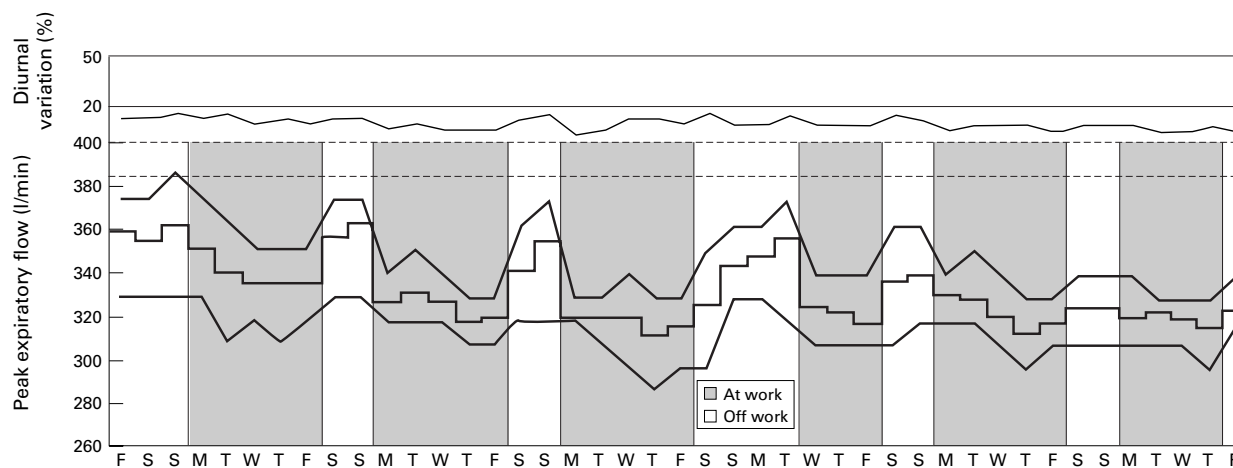


Figure 5 Oasys plot of another endoscopy nurse with exposure to glutaraldehyde showing consistent work related declines in PEF with a diurnal variation <20% throughout. Some would argue that the low diurnal variation implies that the disease is not asthma. The significance in terms of mechanism and prognosis of such records needs clarification. The changes in the first 3 weeks are greater than in the last 3. Such changes may occur when the workers tires of putting effort into the readings, or when the disease becomes more severe. Four weeks is the optimal duration of a record to minimise lack of enthusiasm. Specific bronchial provocation testing showed a late asthmatic reaction to glutaraldehyde 0.07 mg/m³.

against independent criteria. It is possible that other experts might identify further features which distinguish occupational from non-occupational asthma, or that the neural network can be taught with whole records rather than components of the record. So far we have achieved a specific and reasonably sensitive tool to analyse the separation of occupational asthma from other non-occupational causes of airflow obstruction, and have made this available in a form which should provide a consistent opinion wherever it is used. It remains a diagnostic aid, rather than an absolute test, and does not identify the aetiology of the occupational asthma, for which specific immunology, specific bronchial provocation tests, or epidemiological studies are required.

PSB initiated and developed the project and wrote the paper. CFAP has chaired the Oasys research group and supervised the software engineering. DTN wrote the first Oasys program, CBSGB is the software engineer for current development. PFGG did the clinical development of Oasys-2, and PB developed Oasys-3 and Oasys-N1. JB is our statistical and mathematical advisor. JMcC and DRB have contributed to the data quality and expert reproducibility studies. The work has been funded by the National Asthma Campaign, the Health and Safety Executive, the Colt Foundation, the Trustee Savings Bank, the Medical Research Council, the Occupational Lung Disease Trust (Birmingham) and the North Staffordshire Respiratory Trust Fund.

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