a plateau. Less commonly we have also seen apparent plateaux when too high an inspired CO_2 concentration was used. This may occur in patients breathing very shallowly, when it is apparently due to inadequate exchange between the bag and the lungs; the gas in the neck of the bag and in the subject's dead space just passing to-and-fro by the sampling site. An extreme example, of course, is apnoea, which can be excluded by watching the movements of the bag. We have also observed an apparent plateau about 20–25 seconds after the start of rebreathing in subjects who breathe deeply when very high inspired CO_2 concentrations are used (Fig. 1 C). The probable explanation of this late plateau is that there is too much CO_2 to be removed by the blood before recirculation. Equilibration therefore occurs with recirculated blood whose $p\text{CO}_2$ was raised by the very high alveolar $p\text{CO}_2$ present in the first 5–10 seconds.

As a result of these findings we suggest the following modification of Collier's definition of a satisfactory plateau: an inspired-expired CO_2 concentration difference of less than 0.1% which is present in two successive breaths. Plateaux which occur within two breaths of the start of rebreathing or which take more than 15 seconds to appear should be regarded with suspicion.

Conclusions

The mixed venous and arterial CO_2 tensions can be estimated accurately by rebreathing techniques.

The simplest method is to use a continuous CO_2 analyser as described by Collier.

If such an instrument is not available it is still possible to estimate $p\text{CO}_2$ with sufficient accuracy for clinical purposes in 5 to 10 minutes, using the following procedure: (1) Fill a bag with 1.5–2 l. of oxygen. (2) Rebreathe one and a half minutes. During first few breaths partially empty bag if tidal volume is less than half bag-volume. (3) Wait two minutes. (4) Rebreathe 20 seconds or five breaths (whichever is longer). (5) Analyse: bag $p\text{CO}_2$ = mixed venous $p\text{CO}_2$ (arterial approximately 6 mm. Hg less). [Note: (a) If in doubt, make 1 smaller; extend 2 as long as possible; extend 4 to 40 seconds. These should not increase bag $p\text{CO}_2$ by more than 5 mm. Hg. (b) $p\text{CO}_2$ of bag after initial one and a half minutes' rebreathing will give an approximate estimate of mixed venous $p\text{CO}_2$ (Table II).]

Summary

The physiological significance of the measurement of arterial $p\text{CO}_2$ is summarized and previous methods are reviewed.

Collier's rebreathing method for the estimation of the mixed venous and arterial CO_2 tensions is outlined.

A simplification of Collier's method, eliminating the necessity for a continuous record of CO_2 concentration, is described.

An evaluation of the method is described in patients with various disorders of CO_2 and pH regulation showing that the accuracy is to within ± 3 mm. Hg.

Simple routines for the estimation of $p\text{CO}_2$ are described for use both with and without continuous analysis of CO_2 .

We are grateful to Dr. A. Willcox, Professor A. Kekwick, Dr. G. D. Hadley, Dr. F. H. Scadding, and Dr. J. D. N. Nabarro for permission to study patients under their care; and to Professor Kekwick for reading the manuscript.

The irid-o-meter was kindly lent to us by the Infra Red Development Co., Welwyn Garden City, Herts.

ADDENDUM.—Since this paper was prepared the method has been used for detecting the presence or absence of ventilatory failure in the following conditions: chronic bronchitis and emphysema, asthma, pneumonia, poliomyelitis, barbiturate poisoning, carbon-monoxide poisoning, head injury, cerebrovascular accidents, heart failure, myasthenia gravis, peripheral neuritis, post-anaesthetic collapse, post-thoracotomy distress, obesity, hypothyroidism, polycythaemia, and carcinoma of the bronchus. In several patients decisions about the use of artificial ventilation, tracheostomy, or other measures depended on the findings. It has also been used to evaluate the disordered hydrogen ion regulation of patients with diabetic coma, renal failure, pyloric stenosis, Addison's disease, Cushing's syndrome, potassium depletion, uretero-colic anastomosis, steatorrhoea, and tetany. Many of these measurements were made by junior medical staff or students.

REFERENCES

- Bradley, A. F., Stupfel, M., and Severinghaus, J. W. (1956). *J. appl. Physiol.*, **9**, 201.
 Brooks, D., and Wynn, V. (1959). *Lancet*, **1**, 227.
 Campbell, E. J. M. (1960). *Brit. med. J.*, **1**, 457.
 — and Howell, J. B. L. (1960). *pH and Blood Gas Measurement: Methods and Interpretation*, edited by R. Woolmer. Churchill, London.
 Collier, C. R. (1956). *J. appl. Physiol.*, **9**, 25.
 Griggs, D. E., Hackney, J. D., Collier, C. R., and Affeldt, J. E. (1958). *Amer. J. Med.*, **25**, 31.
 Hackney, J. D., Sears, C. H., and Collier, C. R. (1958). *J. appl. Physiol.*, **12**, 425.
 Plesch, J. (1909). *Z. exp. Path. Ther.*, **6**, 484–499.
 Riley, R. L., Campbell, E. J. M., and Shepard, R. H. (1957). *J. appl. Physiol.*, **11**, 245.
 Severinghaus, J. W., and Bradley, A. F. (1958). *Ibid.*, **13**, 515.
 Shepard, R. H., and Meier, P. (1957). *Ibid.*, **11**, 250.
 Suskind, M., and Rahn, H. (1954). *Ibid.*, **7**, 59.

CHANGES IN FORCED EXPIRATORY VOLUMES THROUGHOUT THE DAY

BY

H. C. LEWINSOHN, M.B., B.Ch.

Medical Registrar, London Chest Hospital

L. H. CAPEL, M.B., M.R.C.P.

Senior Medical Registrar, London Chest Hospital

AND

J. SMART, M.D., F.R.C.P.

Consultant Physician, London Chest Hospital

The early-morning exacerbation of their symptoms is often the bitterest complaint of patients suffering from chronic productive cough and breathlessness. The important immediate cause of this chronic breathlessness is probably persistent airway obstruction. An increase in the severity of this obstruction may cause the early-morning increase in breathlessness. This study was undertaken to show the magnitude of the change in the airways, and to find out whether it is peculiar to obstructive airway disease or whether it is part of a cycle of changes throughout the day present both in health and in airway disease.

Methods and Results

Five healthy men (mean age 30 years; mean forced expiratory volume 3,270 ml.) and 16 male patients with obstructive airway disease, 12 severely affected (mean

age 57 years; mean forced expiratory volume 760 ml.), and four mildly affected (mean age 48 years; mean forced expiratory volume 2,190 ml.) were tested. In each patient the diagnosis of chronic bronchitis and emphysema, with or without asthma, had been made. The patients were admitted to hospital for 48 hours, usually at the week-end to avoid loss of work if the patient was working.

Two measurements were made with a recording spirometer—the volume of air expelled during the first second and that expelled during the completion of a forced expiration following a full inspiration. These are, respectively, the forced expiratory volume (F.E.V.) and the forced vital capacity (F.V.C.). These were recorded at fixed times during the day, including 10 p.m. and 6 a.m. No medicines were taken.

The results in each case and the mean of the results of each group are shown graphically in Figs. 1, 2, and 3.

At 6 a.m. the F.E.V. and the F.V.C. were lower than at any other time of the day both in healthy subjects and in patients. By 8 a.m. the mean increase in the F.E.V. was 2.9% in the healthy subjects. By 9 a.m. it was 60% and 36% respectively in the patients with mild and with severe obstructive airway disease. Similar changes were seen in the F.V.C.

Relatively large spontaneous variations in the F.E.V. and the F.V.C. occurred between 9 a.m. and 5 p.m. in the patients.

Discussion

The changes in the F.E.V. and the F.V.C. probably reflect changes in the severity of airway obstruction and possibly changes in total lung capacity as well. Total lung capacity may fall because of an increase in the volume of blood in the lungs or a decrease in the number of patent alveoli occurring during sleep. Alterations in expiratory force are probably of minor importance; a greater expiratory force which might increase the F.E.V. would reduce the F.V.C. (the vital capacity of patients with obstructive airway disease is greater when expelled without force). In fact, the F.E.V. and the F.V.C. varied together. Failure to inspire to maximum depth would reduce both the

F.E.V. and the F.V.C. This was prevented so far as possible by carefully briefing the subjects.

Between 10 p.m. and 9 a.m. the pattern of change was the same for each subject—a marked dip and rise of the F.E.V. and the F.V.C. Not all patients expectorated in the morning. In those who did, improvement in spirometry was not related to the volume or character of the sputum, but often followed expectoration immediately.

FIG. 2.—Changes in the F.V.C. during the day in normal, mildly affected, and severely affected subjects. —: Normal. ----: Mild.: Severe.

FIG. 1.—Changes in the F.E.V. during the day in normal, mildly affected, and severely affected subjects. —: Normal. ----: Mild.: Severe.

FIG. 3.—Changes in the mean F.E.V. and the mean F.V.C. during the day in normal, mildly affected, and severely affected subjects. —: Normal. ----: Mild.: Severe.

Between 9 a.m. and 10 p.m. the pattern of change was different in each subject. The F.E.V. of the mildly disabled patients and the F.V.C. of some of the severely disabled patients varied in a regular manner. Other changes appeared random (Figs. 1 and 2). A number of patients showed a distinct fall in the F.V.C. after the midday meal.

These changes were recorded during a day spent in hospital. McKerrow *et al.* (1958) have shown that the F.E.V. of cotton-workers falls during their day in the dust of the mill. In contrast, coal-miners slightly increased their F.E.V. during the shift at the coal-face. These investigators also give experimental evidence for the relationship between the F.E.V. and airway resistance.

Patients shown by spirometry to have severe airway disease may be but moderately disabled by effort breathlessness. A comparatively small increase in the airway obstruction may then cause severe disability (Capel and Smart, 1959). Such an increase occurs during sleep. The severity of the morning breathlessness may therefore reflect the magnitude of the permanent airway obstruction rather than the magnitude of the morning deterioration alone.

Conclusion

Relatively large spontaneous variations in the F.E.V. and the F.V.C. of patients with obstructive airway disease may occur between 9 a.m. and 5 p.m. This might affect the interpretation of results when serial changes in these volumes are used to measure the action of drugs on the bronchial tree.

The early-morning decrease in the F.E.V. and the F.V.C. was found to be part of a cycle of changes occurring throughout the day both in health and in generalized obstructive airway disease. The decrease was greater in patients with airway disease. The severity of the resulting increase in breathlessness probably reflects the magnitude of permanent obstructive airway disease rather than the magnitude of the temporary decrease in the F.E.V. and the F.V.C.

We thank Dr. K. F. W. Hinson for his help in the preparation of the manuscript.

REFERENCES

- Capel, L. H., and Smart, J. (1959). *Lancet*, **1**, 960.
McKerrow, C. B., McDermott, M., Gilson, J. C., and Schilling, R. S. F. (1958). *Brit. J. Industr. Med.*, **15**, 75.

A scheme for the disposal of radioactive wastes used in Edinburgh for medical and research work has been agreed upon by the university, the Department of Health for Scotland, and the trade unions representing employees who will handle the waste. It covers disposal into sewers, municipal tips, and ocean dumping. Liquid wastes are kept in store until their radioactivity has exhausted itself, and then they are disposed of in the city sewers—with the safeguard that the maximum level of radioactivity is the same as that permitted in drinking-water. A further dilution takes place immediately the wastes enter the sewers, which discharge into the Forth estuary. Solid wastes of short-lived materials are wrapped securely in a strong paper bag and placed in a padlocked dustbin. This is taken to a corporation rubbish tip, where the dustbin is unlocked and the parcel dropped into a pit; this pit is then filled in. Materials much more "hot" in the radioactive sense are used in the university, chiefly for experiments. When these have to be disposed of the Department of Health will arrange for their dumping in the Atlantic. (*Glasgow Herald*, February 4.)

SYSTEMIC AND LOCAL CORTICOSTEROID THERAPY IN ULCERATIVE COLITIS

BY

S. C. TRUELOVE, M.D., M.R.C.P.

*Nuffield Department of Clinical Medicine,
University of Oxford*

(From the Radcliffe Infirmary, Oxford)

During the past decade it has been established that corticosteroids improve the chance of obtaining clinical remission when an attack of ulcerative colitis is being treated medically. However, there are two main ways of using corticosteroid therapy in this disease. On the one hand, cortisone and its analogues may be used systemically. On the other, they may be applied locally within the colon with the intention that their action shall be chiefly a direct one upon the inflamed mucosa.

Both these methods of employing corticosteroid therapy in ulcerative colitis have been shown to be beneficial. So far as oral cortisone is concerned, a large-scale "blind" controlled trial carried out with the co-operation of a number of physicians showed that patients receiving cortisone were nearly three times as likely to be in clinical remission within six weeks of starting medical treatment as were patients in the control group (Truelove and Witts, 1954, 1955). Local corticosteroid treatment has likewise been shown to be of value. Two independent controlled studies, using the water-soluble compound, hydrocortisone hemisuccinate sodium, as a nightly rectal drip, have provided convincing evidence that rapid remissions are often obtained in the less severe attacks of ulcerative colitis (Truelove, 1958; Watkinson, 1958).

There is plainly a need to know which of these two methods of using corticosteroids is to be preferred. Though neither has been shown to reduce the risk of subsequent attacks of ulcerative colitis, it is of consequence to know which is the more likely to bring an attack to an abrupt halt. If attacks of the disease can be checked promptly, many of its dangers disappear even though no permanent cure has yet been found.

Objects of the Present Study

The first object was to assess the relative efficacy of oral and local corticosteroid therapy in ulcerative colitis. The second object was to test a personal clinical impression that combined therapy with both systemic and local corticosteroid is better than either used alone. This impression was based on experience with a number of patients whose symptoms were unchanged by systemic and local corticosteroid treatment used singly but who went into clinical remission when the two methods were combined. The following may be taken as a typical example.

A medical student aged 22 was seen in August, 1957, because of bloody diarrhoea for the previous two months. There was a history of a bad attack of bloody diarrhoea 10 years previously which lasted for three months. In between he had been well. Sigmoidoscopy showed typical ulcerative colitis with hyperaemia, granularity, and contact bleeding. A barium enema showed contour irregularities of the rectum and sigmoid colon. Local hydrocortisone hemisuccinate sodium for two weeks gave no benefit, either