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## Respiratory System: Methods; Gas Analysis

John C. Lilly

Problems in respiratory physiology\* and in clinical research (Fulton;<sup>1</sup> Fenn, Rahn and Otis<sup>2</sup>) concerned with human subjects and mammalian laboratory animals involve analysis of gas mixtures. Most of this work has been done with chemical methods of gas analysis (Peters and Van Slyke<sup>3</sup>). It is the purpose of this article to indicate the new developments in physical methods and to point out the enlarged domain of investigation which these methods bring into physiology and medicine. In addition, it is hoped that the physicist or engineer developing new methods for use in this field will

see the challenging nature of the measurement problems presented (Table 3), for new methods are urgently needed to give accurate results in the situations described. E.g., there is still no completely satisfactory method of rapidly recording gas volumes moving into and out of the respiratory system, with a dead space of less than 1-10 ml and a response time of less than 0.01-0.001 sec; without this device, the dynamics of respiration in extreme states (hyperventilation, coughing and explosive decompression) cannot be adequately investigated.

The generalized situation for the analysis problem is as follows: an animal is inspiring air or a known mix-

\* See Richards—Respiratory System: External Respiration.

ture; it is expiring a complex, unanalyzed mixture, partly inspired gas and partly that changed by gas exchange in the lungs. Each small volume, expired or inspired, may differ in composition and in temperature from the preceding or following volume. The volume flow rate varies in amplitude and direction with time; the linear velocity of each portion of any given cross-section varies with time and location. To solve the problem of the dynamics of this situation, the following measurements must be made: (1) the composition of each small gas volume, including all components ( $O_2$ ,  $CO_2$ ,  $N_2$ ,  $H_2O$  and any other gases which may be introduced, such as anesthetic gases, carbon monoxide, acetylene, methane, etc.); (2) the total volume of gas breathed in or out at each instant; (3) the total pressure at each instant; (4) the gas temperature at each instant. A mere beginning has been made on this problem, with a 1-component analyzer and a rapid volume recorder (Lilly<sup>4</sup>). However, newer methods are being developed which allow a closer approximation to an ideal solution.

New methods for measuring total gas flow and volume moved have been developed which allow accurate recording of rapid changes in these variables (Lee and Silverman,<sup>5</sup> Pappenheimer<sup>6</sup> and Lilly *et al.*<sup>4,7</sup>). Rapid methods for temperature measurement are also available (Billings *et al.*<sup>8</sup>). Changes and absolute values of the total pressure of gases can be determined with an accurate barometer† and some form of rapid differential recording manometer‡ (Lilly *et al.*<sup>7</sup>). These measurements are essential and place definite limits on the accuracy of the results of gas analyses. The methods for rapid and specific analysis of various constituents of the unanalyzed mixtures in the flowing stream entering and leaving the animal will be presented here.

#### GAS SPECIES

**Metabolic Viewpoints.**—As of 1948, the gross over-all picture of animal metabolism stresses the importance of the "chemical viewpoint" in regard to the respiratory gases. In brief, this states that the organism uses oxygen from the atmosphere, discharges carbon dioxide and water vapor into the atmosphere and becomes fairly uniformly saturated, at sea level, with the remaining atmospheric constituents as relatively inert elements. In other words, this viewpoint considers that the body uses oxygen as an elementary substance and treats all its isotopic variants occurring in nature (Table 2) in the same way, irrespective of their varying molecular masses. Similarly, carbon dioxide and water vapor, though occurring in numerous isotopic forms, are metabolically pure "elements." Schoenheimer<sup>9</sup> and others showed that this view is correct in the gross biochemical sense. There are hints that it may not be correct for a more detailed microscopic physical-chemical picture of the cellular metabolism of the body: heavy water, e.g., influences enzyme reaction rates and is toxic for certain animals; protium, deuterium and tritium compounds have different chemical-energy relations (Kamen<sup>10</sup>). Though these results do not give a clearcut argument for recording the isotopic variants of respiratory gases, it is well to point

† Hg manometer FA-135, dial gage FA-126, from Wallace and Tiernan Products Co., Belleville, N. J.

‡ Strain-gage pressure pickups, from Statham Laboratories, 8222 Beverly Blvd, Los Angeles.

out that if it is ever found that isotopic variants do have biologic effects of a specific and fundamental nature, there are methods of recording their concentrations in the gas phase. Similarly, there are methods for recording the various noble-gas species and their changes.

**Analytic Fractionation.**—In an unanalyzed, naturally occurring gas mixture, the various component species are "seen" differently by different methods. The standard chemical methods (Peters and Van Slyke;<sup>3</sup> Carpenter<sup>11</sup>) divide the mixture into various fractional volumes according to chemical reactivity; the resulting chemical fractions for air and expired lung-gas are  $O_2$ ,  $CO_2$ , water vapor and "nitrogen" or "the inert fraction." If the unanalyzed mixture is liquefied by lowering the temperature and increasing the pressure, the methods involving fractional distillation and adsorption divide the mixture into distillation-adsorption fractions (Shepherd;<sup>12</sup> Cady and Cady<sup>13</sup>); atmospheric air produces water vapor, carbon dioxide, oxygen, nitrogen, argon, krypton, xenon, neon, helium, hydrogen. These divisions of atmospheric air are summarized in Table 1.

TABLE 1.—DRY ATMOSPHERIC AIR

FRACTION	SYMBOL	SPECIES	VOLUME FRACTION (F) × 10 <sup>4</sup>	
Chemical	$O_2$	oxygen	2094.0	± 0.5*
	$CO_2$	carbon dioxide	3.0	± 0.5
		inert	7903.0	± 0.5
Distill.-adsorp.	$N_2$	nitrogen	7809.6	± 0.5†
		noble gases	93.4	± 0.1‡
	A	argon	93.2	± 0.05
	Ne	neon	0.18	± 0.005
	He	helium	0.050	± 0.005
	Kr	krypton	0.0110	± 0.0003
	Xe	xenon	0.0008	± 0.00015

\* From Carpenter.<sup>11</sup>

† Inert minus noble gases.

‡ From Cady and Cady.<sup>13</sup> No determinations of noble gases in air by the mass spectrometer could be found in the literature; future work may allow more accurate values to be assigned for A, Ne, He, Kr, and Xe.

If a more complete and refined physical method, such as the mass spectrograph (Aston<sup>14</sup>), is applied to the unanalyzed gas mixture, the fractions become far more numerous than in the chemical and distillation procedures. The isotope fractions§ of the chemical and distillation fractions are separated out and measured (*Preparation and Measurement of Isotopic Tracers*,<sup>15</sup> Symposium<sup>16</sup>). The naturally occurring isotopes of the atmospheric-air fractions are summarized in Table 2.

#### PHYSICAL METHODS OF GAS ANALYSIS

The definition of a physical analytic method is seen as a contrast to the chemical methods. The chemical methods generally separate out fractions of an unanalyzed mixture by removing fractional volumes from the gas phase through the formation of non-gaseous compounds (Carpenter<sup>11</sup>). The physical methods, in the sense used here, maintain the gas phase and sepa-

§ See Nier—Isotopes: Stable; Measurement; Keston—Isotopes: Stable; Biologic Applications; Evans—Isotopes: Radioactive; Measurement.

TABLE 2.—RELATIVE ABUNDANCE AND CONCENTRATION OF RESPIRATORY GASES: ELEMENTS, MOLECULES, STABLE ISOTOPES\*

MASS NO.	VARIANT†	RELATIVE ABUNDANCE	DRY AIR, ‡ F × 10 <sup>4</sup>	ALVEOLAR GAS, § F × 10 <sup>4</sup>	VARIANT	RELATIVE ABUNDANCE	DRY AIR, ‡ F × 10 <sup>4</sup>	ALVEOLAR GAS, § F × 10 <sup>4</sup>
1	H <sup>1</sup>	0.9998	0					
2	H <sup>2</sup>	0.0002						
3								
4	He <sup>4</sup>	1.000	0.05					
12	C <sup>12</sup>	0.989	0					
13	C <sup>13</sup>	0.011						
14	N <sup>14</sup>	0.9962	0					
15	N <sup>15</sup>	0.0038						
16	O <sup>16</sup>	0.99757						
17	O <sup>17</sup>	0.00039	0					
18	O <sup>18</sup>	0.00204			(H <sub>2</sub> O) <sup>18</sup>	0.9972	0	616.7
19					(H <sub>2</sub> O) <sup>19</sup>	9.9 × 10 <sup>-4</sup>	0	0.61
20	Ne <sup>20</sup>	0.9000	0.16	0.15	(H <sub>2</sub> O) <sup>20</sup>	2.74 × 10 <sup>-7</sup>	0	1.69 × 10 <sup>-7</sup>
21	Ne <sup>21</sup>	0.0027	4.9 × 10 <sup>-4</sup>	4.6 × 10 <sup>-4</sup>	(H <sub>2</sub> O) <sup>21</sup>	1.22 × 10 <sup>-6</sup>	0	7.54 × 10 <sup>-4</sup>
22	Ne <sup>22</sup>	0.0973	1.75 × 10 <sup>-2</sup>	1.65 × 10 <sup>-2</sup>	(H <sub>2</sub> O) <sup>22</sup>	8.16 × 10 <sup>-11</sup>	0	5.05 × 10 <sup>-8</sup>
28	(N <sub>2</sub> ) <sup>28</sup>	0.9921	7747.9	7262.5				
29	(N <sub>2</sub> ) <sup>29</sup>	0.0075	58.6	54.9				
30	(N <sub>2</sub> ) <sup>30</sup>	1.37 × 10 <sup>-5</sup>	1.07 × 10 <sup>-1</sup>	1.00 × 10 <sup>-1</sup>				
32	(O <sub>2</sub> ) <sup>32</sup>	0.99515	2083.8	1440.3				
33	(O <sub>2</sub> ) <sup>33</sup>	7.78 × 10 <sup>-4</sup>	1.6	1.13				
34	(O <sub>2</sub> ) <sup>34</sup>	4.07 × 10 <sup>-3</sup>	8.5	5.89				
35	(O <sub>2</sub> ) <sup>35</sup>	1.55 × 10 <sup>-6</sup>	3.24 × 10 <sup>-3</sup>	2.24 × 10 <sup>-3</sup>				
36	(O <sub>2</sub> ) <sup>36</sup>	4.16 × 10 <sup>-6</sup>	8.71 × 10 <sup>-3</sup>	6.02 × 10 <sup>-3</sup>	A <sup>36</sup>	3.07 × 10 <sup>-3</sup>	0.286	0.268
38					A <sup>38</sup>	6.1 × 10 <sup>-4</sup>	0.0569	0.0532
40					A <sup>40</sup>	0.99632	92.9	87.0
44	(CO <sub>2</sub> ) <sup>44</sup>	0.9842	2.95	518.0				
45	(CO <sub>2</sub> ) <sup>45</sup>	0.01162	0.035	18.4				
46	(CO <sub>2</sub> ) <sup>46</sup>	4.05 × 10 <sup>-3</sup>	0.012	6.31				
47	(CO <sub>2</sub> ) <sup>47</sup>	4.63 × 10 <sup>-5</sup>	1.39 × 10 <sup>-4</sup>	7.32 × 10 <sup>-2</sup>				
48	(CO <sub>2</sub> ) <sup>48</sup>	4.11 × 10 <sup>-6</sup>	1.23 × 10 <sup>-5</sup>	6.47 × 10 <sup>-3</sup>				
49	(CO <sub>2</sub> ) <sup>49</sup>	4.58 × 10 <sup>-8</sup>	1.37 × 10 <sup>-7</sup>	7.21 × 10 <sup>-6</sup>				

\* The radioactive isotopes occurring in air exist at concentrations very much less than any of these values.

† Molecular values calculated from element values (Bethe<sup>17</sup>) and Table 2.

‡ Dry air is assumed to have a water-vapor value of 0.00000.

§ Alveolar gas is assumed to be at 760.00 mm Hg, 37.0 C, and to have partial pressures of CO<sub>2</sub> of 40.000, H<sub>2</sub>O of 47.000 and O<sub>2</sub> of 110.00 mm Hg.

rate out the fractions by means of molecular and/or atomic properties present, without the production of chemical combinations (larger or new molecular forms).

TABLE 3.—DRY ATMOSPHERIC AIR: CONCENTRATION RATIOS\* USEFUL IN ESTIMATING RELATIVE IMPORTANCE OF COMPONENTS AND IN CALIBRATING ANALYSIS METHODS

SPECIES	VALUE OF RATIO	RECIPROCAL RATIO
O <sub>2</sub> /inert fraction	0.2650	3.7736
O <sub>2</sub> /N <sub>2</sub>	0.2681	3.7295
(O <sub>2</sub> ) <sup>32</sup> /(N <sub>2</sub> ) <sup>28</sup>	0.2690	3.7180
CO <sub>2</sub> /O <sub>2</sub>	0.00143	699.
CO <sub>2</sub> /A	0.0322	31.1
(CO <sub>2</sub> ) <sup>44</sup> /A <sup>40</sup>	0.0318	31.4
A/inert	0.01179	84.82
A/N <sub>2</sub>	0.01193	83.82
A <sup>40</sup> /(N <sub>2</sub> ) <sup>28</sup>	0.01198	83.47
A/O <sub>2</sub>	0.04451	22.47
A <sup>40</sup> /(O <sub>2</sub> ) <sup>32</sup>	0.04455	22.45
N <sub>2</sub> /inert	0.98818	1.0120
(N <sub>2</sub> ) <sup>28</sup> /inert	0.98037	1.0200
(N <sub>2</sub> ) <sup>28</sup> /N <sub>2</sub>	0.99210	1.0080

\* Calculated from values in Tables 1 and 2. Isotope ratios between different species are to be carefully distinguished from ion-current ratios in mass spectrometer (Table 4, notes).

The methods capable of high degrees of specificity and high analysis speed use those primary physical processes which occur at a velocity near that of light (absorption and emission of quanta) and near the

maximal velocities of travel of molecules and ions (high-speed flow and acceleration of ions by electric and magnetic fields in a vacuum).

**Analysis Processes.**—In any generalized analytic method, the over-all analytic procedure can be divided into several processes: sampling, transport of sample, sample modification for analysis, analyzing and recording. In any given method these processes may be at different locations or may be so close together as to be indistinguishable. They may be linked together either continuously or discontinuously with respect to the flow of material through each process. In a "continuous method" there is a steady-state flow of gas from the unanalyzed mixtures to and beyond the analysis site, i.e., a flow of material at the input and a flow of corresponding data at the output (see Figs. 2 and 13). In a "discontinuous method" this material flow is intermittent with respect to any 1 or any combination of the above processes. It is obvious that a method can be used intermittently, but be essentially continuous in the above sense.

Discontinuous methods do not offer a uniform solution to the set of problems previously formulated. As the classic analysis methods have, in general, been discontinuous ones, the compromises and rather ingenious technics (Rahn *et al.*<sup>18</sup>) to get around the difficulties of using discontinuous methods are generally known.

Among them are the "closed-volume integration of material" methods (Peters and Van Slyke,<sup>3</sup> p. 161), the use of long tubes and multiple sampling valves (Cotton<sup>19</sup>) and timed sampling valves (Clark-Kennedy and Owen<sup>20</sup>). We shall neglect discontinuous methods as being inadequate for our purpose, except for labeling a given method "discontinuous" or "continuous." It is to be noted, however, that discontinuous methods are still the standards of reference for all other methods (Carpenter;<sup>11</sup> Shepherd<sup>12</sup>).

**Time Factors in Continuous Methods.**—Following the conventions used by Cunningham,<sup>21</sup> it is well to define 2 time factors: the latency interval,  $t_L$ , corresponding to Cunningham's delay time, and the response time,  $t_R$ , corresponding to Cunningham's build-up time. Fig. 1 pictures these factors for 2 extreme cases; Figs. 3

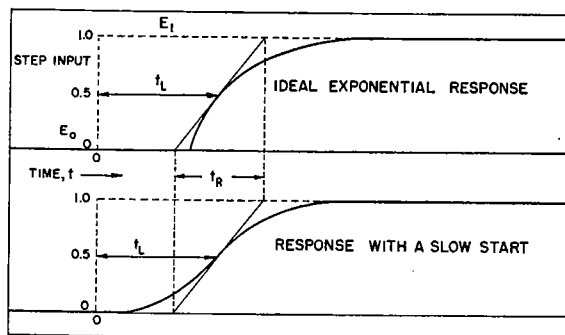


FIG. 1.—Diagram of latency interval,  $t_L$ , and response interval,  $t_R$ . Two response curves of extreme types chosen to give equal response intervals and latencies, which do not include the "overshoot" or "after-vibration" case. The latter occurs but rarely in gas systems, such as with large changes in total pressure or leaks into the system, but can occur in the electric or mechanical recording system. Step input (dashed line) represents the ideal stepwise change of composition. Between the initial level  $E_0$  and the final level  $E_1$ , the response amplitude at a given instant is taken as  $E$ . In the upper, exponential case, the response interval is easily defined in terms of constants of the exponential function:  $t_R = (\text{time at } E/E_1 = 0.865) - (\text{time at start of response})$ . In the lower, slow-start case, the beginning of the change is indefinite; therefore the response interval must be defined independently of the start of the response. Real analyzers usually give a response curve of the slow-start type (see Fig. 14).

and 14 show 2 recorded cases. Visualize a stepwise change in composition of short duration, occurring in the unanalyzed system and flowing past the sampling inlet. This change in composition flowing into the apparatus is ultimately recorded as some form of response curve of deflection versus time. This curve starts at 1 level and some time later reaches a 2d level. The time interval elapsing between the instant that the composition "step" enters the sampling inlet and the instant the deflection record reaches a point halfway between the 2 levels is the latency interval. This overall latency may be thought of as the summed value of the latencies of the sampling, transport, modification, analysis and recording processes.

The response interval is defined as the interval between the intercepts of the tangent to the response curve at the 50% point, with the extended initial and final levels (Fig. 1). It may be thought of as the result of a certain amount of "slowing" in each of the above

processes. An ideal analysis method would have values of latency and response intervals approaching a value very small with respect to the least time interval of the uncontrolled changes occurring in the unanalyzed system.

In respiratory situations involving high linear velocities of inspired and expired gas (large volume exchange and small tubing), an ideal analysis method should have a response interval of about  $10^{-3}$  sec (Table 5). At present this response interval of 1 msec is approached rather than realized, and at that by only 1 method. The latency interval can be larger than this value, if it is known, reproducible, and taken into account in using the records. Usually, however, there is a functional relation between latency and response intervals; they tend to increase and decrease together in a given apparatus.

It is well to emphasize that the investigator sees the gas only through his apparatus and analysis method. He is blind in 2 areas: to changes in unrecorded species and to changes in the recorded species occurring in time intervals short compared with the response interval of his apparatus. No amount of deduction from general gas laws and from previous experimental results will ever allow him to see unrecorded events, and experience with a high-speed continuous method will convince any investigator of the severe limitations of the slower continuous and of the discontinuous methods.

**Physical Properties of Gases Used in Analysis Methods.**—Certain physical properties have unique values for each of the gas species occurring in respiration (Tables 1 and 2). Such properties are mass numbers (molecular weight), ionic mass/charge ratio, atomic and molecular emission spectra, atomic and molecular absorption spectra and certain atomic nuclear properties. Gas-analysis methods based on 1 or more of the properties have been worked out for any or all constituents of air; these are discussed later.

Other physical properties which have less unique values for each species can be used for analysis, with caution. Such properties are heat conductivity, magnetic susceptibility, refractive index using visible light, viscosity, density, velocity of sound, absorption of sound energy, etc. In general, use of these properties requires molecular separation of the species of the unanalyzed mixture by chemical absorption, physical adsorption or condensation before applying the method. These fractionating procedures usually increase the over-all latency and response intervals of the methods. Berg<sup>22</sup> used the thermal-conductivity method for all the respiratory gases. The Pauling oxygen meter<sup>||</sup> takes advantage of the high magnetic susceptibility of  $O_2$  compared with other respiratory gases to give  $O_2$  values in dry mixtures to approximately 0.5% (Pauling *et al.*<sup>23</sup>). Rein<sup>24</sup> developed an  $O_2$  method utilizing the magnetic susceptibility of  $O_2$  in dry and  $CO_2$ -free mixtures in a flow system. The Raleigh type of interferometer<sup>¶</sup> (Edwards<sup>25</sup>) can be used for  $CO_2$  analysis to about 0.01% in dried  $O_2-N_2$  mixtures. However, these methods have long response times, of the order of 6 or more sec, or are discontinuous. The faster methods are of more interest for our situation. The properties of the respiratory gases involving radiation, ionization and molecu-

<sup>||</sup> A. O. Beckman Co., Pasadena, Calif.  
<sup>¶</sup> Baird Associates, Cambridge, Mass.

lar weight are used in certain methods which may be, or have been, made fairly rapid.

#### Methods Using Specific Radiation.—ABSORPTION.

—The spectral regions for maximal radiation absorption of each gas are:  $N_2$ , less than 990 A (far ultra-

sources (Groth<sup>30</sup>), windows\*\* and receivers (Locher<sup>31</sup>) are developed for this spectral region.

Methods of analysis for  $CO_2$  and  $H_2O$  and other polyatomic gases, such as  $CO$ ,  $N_2O$ , ether, ethylene and cyclopropane, utilizing infra-red absorption were reviewed by Williams.<sup>32</sup> The method of Pfund and Fastie<sup>33</sup> is particularly desirable in the sense of relative simplicity and high sensitivity. The response interval is about 6 sec at present. Baird Associates, Cambridge, Mass., manufacture several models of this instrument. There is a reasonable hope that utilization of fast bolometers (Billings *et al.*<sup>8</sup>) developed during the war, or of the new photoconductive films (Starkiewicz<sup>34</sup>), and reduction in gas volumes in the absorbing path may shorten the response interval of these infra-red methods. Such work is at present being done by Fowler<sup>35</sup> for  $CO_2$  in respiratory systems. It is well to be aware that certain anomalies in gas radiation-absorption laws appear in complex mixtures in certain pressure ranges (Coggeshall and Saier<sup>36</sup>).

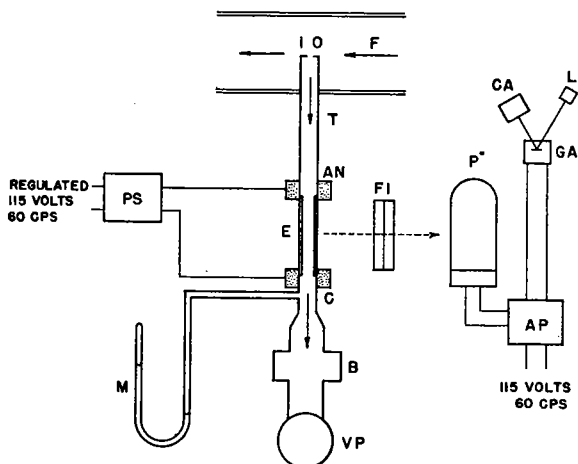


FIG. 2.—Diagram of nitrogen meter. *F*, flowing gas mixture; *IO*, inlet orifice; *T*, inlet-orifice tubing; *AN*, anode; *E*, electrical discharge tube; *PS*, power supply for *E*; *C*, cathode; *M*, oil manometer; *B*, ballast tank; *VP*, vacuum pump; *FI*, filters; *P*, photocell; *AP*, amplifier, power supply; *GA*, oscillograph galvanometer; *CA*, camera; *L*, light.

violet);  $O_2$ , around 1450 A (Schumann ultraviolet) (Boyce<sup>26</sup>);  $CO_2$ , peaks at 2.73, 4.25 and 14.93  $\mu$  (Martin and Barker<sup>27</sup>), and water vapor, peaks at 2.6, 20 and 52  $\mu$  in the infra-red (Dorsey<sup>28</sup>). Neither nitrogen nor oxygen analyses have been done using these absorption bands; yet a layer of oxygen (at 760 mm Hg and

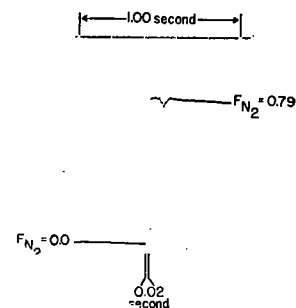


FIG. 3.—Response of nitrogen meter.

EMISSION.—With sufficient electrical excitation at all pressures, gases emit radiation in different ways (spark, arc, glow discharge) in different parts of the radiation spectrum (Harrison;<sup>37</sup> Pearse and Gaydon<sup>38</sup>). Measurement of the emitted radiation can give quantitative values for the elements in mixtures (Dieke<sup>39</sup>). This technique has been developed for use in nitrogen analysis in respiratory gases (Lilly *et al.*<sup>40</sup>), and a diagram of the apparatus is shown in Fig. 2. The gas flow into this

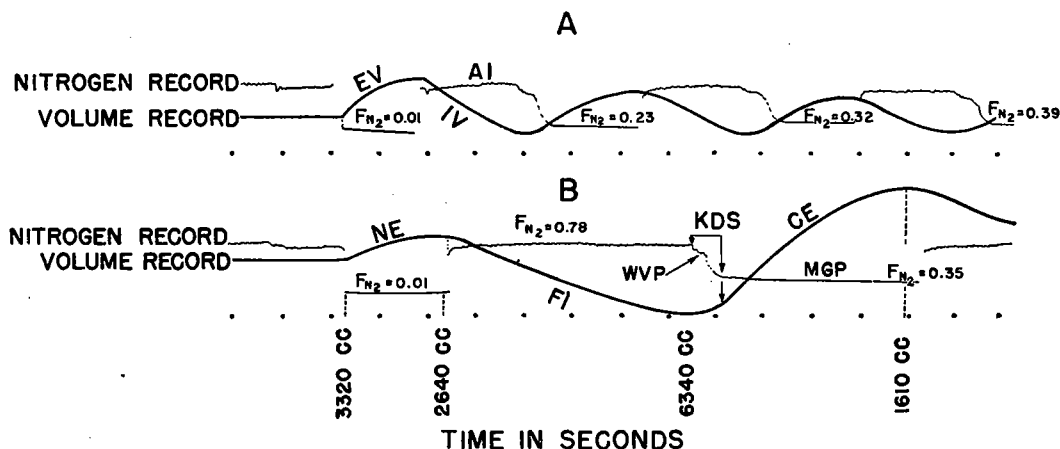


FIG. 4.—Respiratory-gas "mixing" study with nitrogen meter. Records taken after breathing oxygen for 30 min. *A*, normal breathing; *B*, vital capacity maneuver. *EV*, expired volume; *IV*, inspired volume; *AI*, air; *NE*, normal expiration; *FI*, full inspiration; *CE*, complete expiration; *WVP*, water-vapor plateau; *KDS*, "kinetic dead space"; *MGP*, mixed-gas plateau.

273 K) only  $1/1000$  in. (25  $\mu$ ) in thickness absorbs 90% of the incident radiation at 1450 A (Ladenburg and van Voorhis<sup>29</sup>). This is the strongest absorption for any known gas in any known spectral region; it possibly will be used for  $O_2$  analyses in the future as suitable

instrument is about 0.5 ml/sec STPD. This is the fastest instrument (shortest response time, approximately 0.02 sec) for gas analysis at present known to the

\*\* Synthetic fluorite ( $CaF_2$ ), from Harshaw Chemical Co., 1945 E. 97th St., Cleveland.

writer. The unanalyzed mixture is given as flowing gas mixture; the continuous sampling is through the inlet orifice; sample transport is through the inlet-orifice tubing; modification for analysis process occurs as the gas enters the Pyrex tube between the anode and cathode and is electrically excited to emit radiation; the measuring process starts with separation of specific radiation by the filters and activates the photocell; the photocell current is amplified; the oscillograph galvanometer, light, and camera are used in the recording process. With an input of a step change in composition, the latency is proportional to the length of the inlet-orifice tubing; the response interval is the sum of the effects of fore-and-back mixing of the sample in the inlet-orifice region, in the inlet-orifice tubing and in the discharge tube; it is also a function of the length of the discharge tube seen by the photocell, which determines the length of time the front is emitting radiation to the photocell. Total pressure, measured by the oil manometer, varies with flow rate and linear velocity of the sample; hence, the latency and response intervals vary with this pressure reading (the higher the pressure the shorter the intervals, in the operating range). The galvanometer and amplifier are chosen to have very short response intervals ( $10^{-3}$  sec) with respect to that of the above processes.

An over-all response curve of this device (Fig. 3) was obtained on suddenly pulling the inlet orifice out of a stream of tank oxygen into the room air. The response time (measured on the original record with a microscope method) is approximately 0.02 sec. The small perturbations of the final level after the response step can be shown to be due to air- $O_2$  eddies which surround the edge of the flowing  $O_2$  stream (turbulent-flow effect).

A nitrogen record (Fig. 4) is given by the apparatus adjusted to give latency and response intervals of 0.02 sec each. A volume record is given by an electrical manometer (Lilly *et al.*<sup>7</sup>) connected to a rigid, 3000-l reservoir (small altitude chamber) to record the pressure difference between the reservoir and the atmosphere. The subject is outside the reservoir, with nose plugged and mouth sealed to a tube,  $1\frac{1}{2}$  in. in diameter and 1 in. long, communicating with the reservoir's interior. The nitrogen-meter inlet orifice is in the center of the gas stream in the tube, about  $\frac{1}{4}$  in. from the subject's mouth. The change of pressure record was calibrated in terms of the volume of gas added or removed from the reservoir (10 mm  $H_2O/3$  l). The calibration curve is linear to about  $\pm 1\%$  over the full range. A fan in the reservoir rapidly mixed the expired gases. After the subject has breathed tank oxygen for 30 min and is connected to the apparatus, the recording is started; the subject then expires to give the control level of nitrogen in his lungs (volume fraction 0.01 on both records). He breathes normally (Fig. 4, A) and does a vital-capacity maneuver (Fig. 4, B) (Lilly<sup>4</sup>). The lung-volume figures of 3320, 2640, 6340 and 1610 ml were calculated by assuming (1) that all residual gas remaining in the respiratory system had a nitrogen concentration equal to that (0.35) at the end of the full expiration of the lower record and (2) that the nitrogen taken in and given out was all recorded. Presumably this system can give valuable data on the mechanics of gas mixing in normal lung systems and in those im-

paired by disease (asthma, bronchiectasis, pulmonary tuberculosis, laryngeal stenosis, pneumonia, etc.).

With great care in design, use of sensitive receivers, sharp cut-off and narrow pass-band light filters and the hollow cathode discharge tube (McNally *et al.*<sup>41</sup>),  $CO_2$ ,  $O_2$  and  $H_2O$  might also be measured by this method. However, the most promising method for all respiratory gases is that of the mass spectrometer.

#### Methods Depending on Ionic Mass/Charge Ratio.

—The elementary respiratory gases can be ionized at

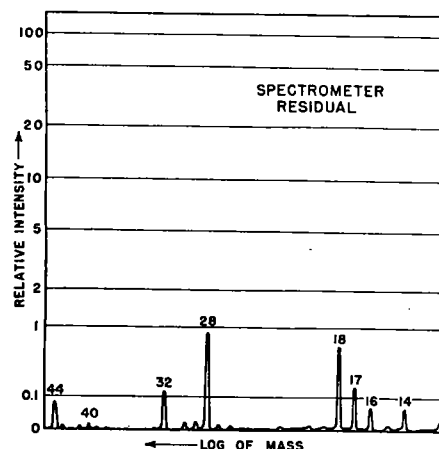


FIG. 5.—Residual gases in mass spectrometer. Values in this record are to be subtracted from those in subsequent records to obtain most accurate results. For species corresponding to these mass numbers (mass/charge ratios for ions) see Tables 2, 3, and 4. The gases giving this record are mainly those of air (Fig. 6). (Figs. 5-12, courtesy of A. O. C. Nier.)

low pressures, accelerated by electric and magnetic fields and spread out in a mass/charge spectrum. This

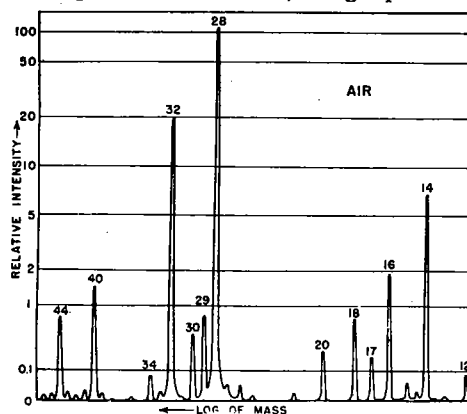


FIG. 6.—Mass-spectrometer record of room air. With suitable calibration with pure gases, records such as this can give very accurate measurements of composition values. Mass number 28 is mainly  $(N_2^+)^{28}$  but contains (1) a zero correction value (Fig. 5), (2) a small amount of  $(CO^+)^{28}$  which can be derived from  $CO_2$  (Table 4 and Fig. 8) and from possible CO in the sampled gas. Mass number 14 is mainly  $(N^+)^{14}$ , derived mainly from  $N_2$ , but contains  $(N_2^{++})^{28}$  and  $(CO^{++})^{28}$  in smaller degree and may contain  $(N^+)^{14}$  and  $(N_2^{++})^{28}$  from, say,  $N_2O$  in the sampled gas.

method is used in the mass spectrograph (Aston<sup>14</sup>), in the mass spectrometer (Nier<sup>42</sup>) and in the mass spectrograph (Siri<sup>43</sup>). Each gas species, including the isotope

variants, can be separated from the others. The positive-ion current derived from 1 mass/charge position in the mass spectrometer is a measure of the concentration of that species in the entering gas. Since the instrument

ment: the air record and the lung-gas record show the differences in (CO<sub>2</sub>)<sup>44</sup>, (O<sub>2</sub>)<sup>32</sup> and (N<sub>2</sub>)<sup>28</sup> expected in respiratory work (Table 2). Use of the instrument in analysis of anesthetic gases is shown in Figs. 9-12. In

TABLE 4.—PREDOMINATING ION SPECIES FORMED IN MASS SPECTROMETER WITH RESPIRATORY GASES

MASS/CHARGE RATIO	PARENT MOLECULES						
	CO <sub>2</sub>	N <sub>2</sub> O	A	O <sub>2</sub>	N <sub>2</sub>	CO	H <sub>2</sub> O
44	CO <sub>2</sub> <sup>+</sup>	N <sub>2</sub> O <sup>+</sup>					
40			A <sup>+</sup>				
32	O <sub>2</sub> <sup>+</sup> ...		...	O <sub>2</sub> <sup>+</sup>			
30		NO <sup>+</sup>					
28	CO <sup>+</sup>	N <sub>2</sub> <sup>+</sup>			N <sub>2</sub> <sup>+</sup>	CO <sup>+</sup>	
22	CO <sub>2</sub> <sup>++</sup>						
20			A <sup>++</sup>				
18			...				H <sub>2</sub> O <sup>+</sup>
17			...				OH <sup>+</sup>
16	O <sup>+</sup> , O <sub>2</sub> <sup>++</sup>	O <sup>+</sup> ...	...	O <sup>+</sup> , O <sub>2</sub> <sup>++</sup>		O <sup>+</sup>	O <sup>+</sup>
15		NO <sup>++</sup>					
14	CO <sup>++</sup>	N <sup>+</sup> , N <sub>2</sub> <sup>++</sup>			N <sup>+</sup> , N <sub>2</sub> <sup>++</sup>	CO <sup>++</sup>	
12	C <sup>+</sup>					C <sup>+</sup>	
9							H <sub>2</sub> O <sup>++</sup>
8	O <sup>++</sup>	O <sup>++</sup>		O <sup>+</sup>		O <sup>++</sup>	O <sup>++</sup>

NOTES:

1. The relative ratio of production of ionic fragments from a given parent varies from 1 instrument to another; calibrations with pure gases give these ratios accurately, and apply to mixture studies. For representative values, see Figures showing records.
2. In general, the most abundant ion, in the case of these relatively simple gases, is the parent with a single positive charge.
3. Only the most abundant isotopic variants of Table 2 are represented here; the other variants ionize in a constant relative-abundance ratio with respect to those given.
4. At low pressures (large mean free path) in the mass spectrometer, no new combinations (such as CN<sup>+</sup>) are formed.
5. Inspection of Table 2 shows "overlaps" at a given m/c ratio other than those given above (e.g., H<sub>2</sub>O and Ne). Many of these overlaps can be resolved into separate "lines" by special design for high mass-number resolution (Aston<sup>14</sup>).

TABLE 5.—APPROXIMATE EXTREME VALUES\* OF RESPIRATORY VARIABLES FOR HUMAN SUBJECTS

ITEM	VARIABLE	REST	SEVERE MUSCULAR WORK	EXPLOSIVE DECOMPRESSION †
1	Total gas volume moved/half-cycle, ‡ liters	0.5	4	9
2	Peak volume flow velocity, l/sec	0.5	4	130
3	Peak rate of change of item 2, l/sec <sup>2</sup>	0.5	20	>1000
4	Total time/half-cycle, ‡ sec	2	0.5	0.07
5	Least time interval to be resolved, ideally (1% of item 4), sec	0.02	0.005	0.0007
6	Total geometric lung-volume range, l	3-3.5	2-6	2-6
7	O <sub>2</sub> consumption, l/sec, STPD	5 × 10 <sup>-3</sup>	5 × 10 <sup>-2</sup>	
8	Maximal CO <sub>2</sub> output, l/sec, STPD	5 × 10 <sup>-3</sup>	5 × 10 <sup>-2</sup>	
9	Range of expired F <sub>O<sub>2</sub></sub> (STPD)	0.10-0.14	0.12-0.17	unknown
10	Range of expired F <sub>CO<sub>2</sub></sub> (STPD)	0.05-0.06	0.04-0.07	unknown
11	Maximum expired P <sub>H<sub>2</sub>O</sub> (assumed 37 C), mm Hg§	47	47	unknown
12	Range of inspired F <sub>O<sub>2</sub></sub> , STPD, all experiments	0.10-1.00		
13	Range of inspired F <sub>CO<sub>2</sub></sub> , STPD, all experiments	0.000 to about 0.10		

No data are available on variables during coughing, severe or otherwise.

\* Items 1-4: data for rest and work at sea level from L. Silverman (Lee and Silverman<sup>5</sup>); 7, 8, 11: from *Handbook of Respiratory Data in Aviation* (National Research Council<sup>60</sup>); 9, 10: using a discontinuous, chemical method (Galdston and Wollack<sup>61</sup>).

† No experimental data available. Example is calculated for pressures less than 1 atm, for initial/final pressure ratio of 5/1, allowing a maximal lung-volume expansion from an initial of 3 l to a final of 6 l, a minimal air-way cross-section of 2.0 cm<sup>2</sup>, and a maximal linear-flow velocity in this section of 2.2 times a sound velocity of 3 × 10<sup>4</sup> cm/sec. Values are given at final pressure.

‡ One-half cycle is either inspiration or expiration; in explosive decompression it is expiration.

§ Common assumption, not investigated by rapid methods of measurement.

can be "tuned" over an extreme range of mass/charge ratios, all respiratory gases can be measured with an instrument calibrated with known mixtures. Figs. 5-12 show the great range and specificity of a standard instru-

these records, a number of "mass positions" corresponding to isotopic variants can be seen.†† These change their "heights" in a constant, relative fashion (within

†† See Nier—Isotopes: Stable; Measurement.



1 chemical species) as the concentration changes at the input. Other mass numbers corresponding to ionic fragments (Table 4) of the primary molecules, e.g.,  $C^+$  from  $CO_2$  are also shown; in general, these also change their heights, in a given instrument, in a constant fashion relative to the primary spike for the chemical species (cf. 12 and 44 for  $C^+$  and  $CO_2^+$ ).

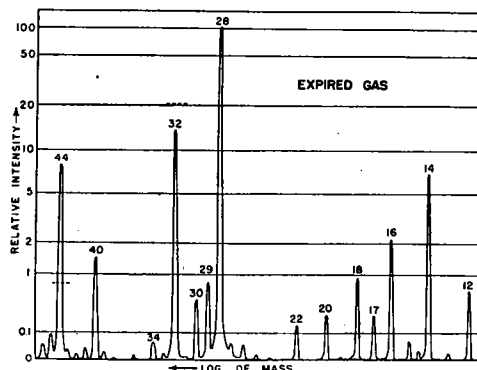


FIG. 7.—Record of gas obtained at end of a full expiration. Dashed horizontal lines at mass numbers 44 and 32 correspond to air values of Fig. 6. Detectable changes occur (Fig. 6) at mass numbers 44, 32, 22, 18, 16 and 12, presumably due to  $(CO^+)^{44}$ ,  $(O_2^+)^{32}$  (from  $O_2$  and  $CO_2$ ),  $(CO_2^+)^{44}$ ,  $(H_2O^+)^{18}$ ,  $(O^+)^{16}$  and  $(O_2^+)^{32}$  (from  $O_2$ , water vapor and  $CO_2$ ), and  $(C^+)^{12}$  (Tables 2 and 4). Relative quantities of each species at each mass number can be calculated.

Doubly charged ions, such as  $A^{++}$ , fall at a mass/charge position (20 for  $A^{++}$ ) of  $1/2$  the singly charged position (40 for  $A^+$ ). However, between species, the instrument does not give exactly proportional heights; a mixture of 50%  $O_2$  and 50%  $N_2$  does not necessarily give spikes, at 32 and 28, of exact equality. However, the height produced for a given species at a given

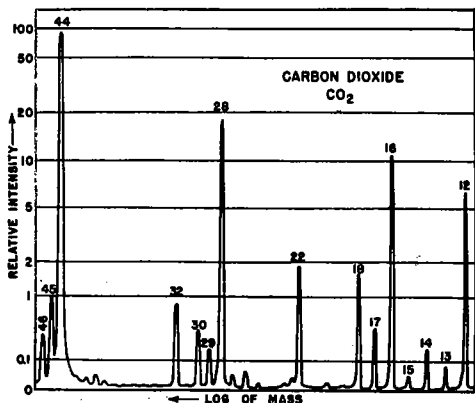


FIG. 8.—Record of carbon dioxide, given by the  $CO_2$  isotope variants (Table 2), the various ionic fragments of these species (Table 4), and the spectrometer residual (Fig. 5). Relative occurrence ratios for these mass-number peaks for this particular instrument can be calculated from data for this figure and that for Fig. 5.

concentration in a given instrument is constant, regardless of other gases and their changes in mixtures at constant total pressure; thus the instrument can be accurately calibrated with standard mixtures. Honig<sup>44</sup> gives the flow conditions necessary to accomplish this result with the highest accuracy. The required gas flow

for analysis is about  $10^{-4}$  to  $10^{-5}$  ml/sec, STPD (Nier;<sup>42</sup> Siri<sup>43</sup>).

An ingenious development of the mass spectrograph allows it to be applied to the analysis of the respiratory

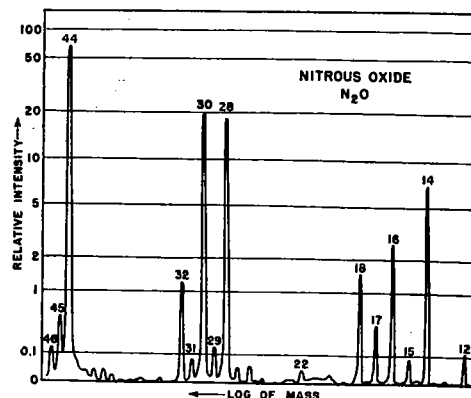


FIG. 9.—Anesthetic gases: nitrous oxide. The unique peak for nitrous oxide is at mass number 30, which corresponds to  $(NO^+)^{30}$ . Comparing with Figs. 5, 6, 7 and 8 shows that mass number 30 is relatively constant with air, expired gas and "pure"  $CO_2$ ; therefore, this peak could be used to follow  $N_2O$  concentration changes during anesthesia in the presence of expired gas and of  $CO_2$  added to inspired gas. Other peaks in this record can be derived from Tables 2 and 4. Range of inspired volumes per cent of this gas is 80–100% with  $O_2$ . The expired values can be between 0 and 90%.

problem situation. Three detectors in this instrument allow  $(N_2^+)^{28}$ ,  $(CO_2^+)^{44}$  and  $(O_2^+)^{32}$  to be recorded concurrently with 3 separate amplifiers and mirror oscillograph galvanometers (Fig. 13) (Hunter *et al.*<sup>45</sup>). A

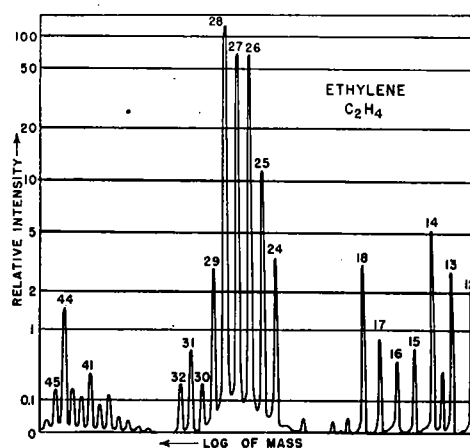


FIG. 10.—Anesthetic gases: ethylene. Mass numbers correspond to the molecule  $H_2C=CH_2$ , to isotope variants and to ionic fragments. The primary peak for  $(C_2H_4^+)^{28}$  is at 28; presumably peaks at the higher mass numbers, such as at 41, are due to higher-molecular-weight impurities in the ethylene; 29 may be due to an isotopic variant. The degraded-ion series  $C_2H_3^+$ ,  $C_2H_2^+$ ,  $C_2H_1^+$  and  $C_2^+$  can be seen at mass numbers 27, 26, 25 and 24. The anesthetic range is 0–90 volumes %.

rapid, continuous gas-transport system, similar to that used with the nitrogen meter, and feedback amplifier design allow response intervals of the order of 0.15 sec (Fig. 14) and reproducible latency intervals of about 0.2 sec. Presumably, further development will shorten

these intervals. A record made with this instrument of  $\text{CO}_2$  and  $\text{O}_2$  entering and leaving a human subject is shown in Fig. 15.

Siri<sup>43</sup> devised a portable mass spectroscope with novel features for analysis of respiratory gases and biologic substances occurring in liquid and solid phases. The mass numbers are displayed on a cathode-ray tube

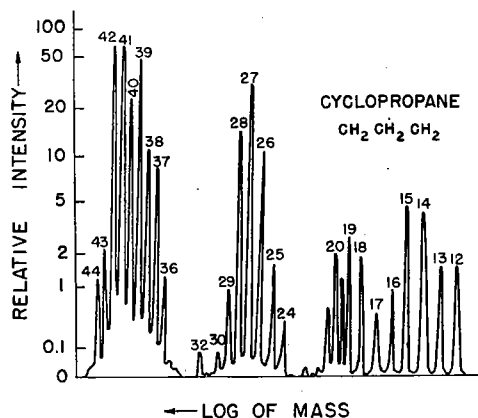


FIG. 11.—Anesthetic gases: cyclopropane. Primary peak ( $\text{C}_3\text{H}_6^+$ ) is at mass number 42; degraded-ion fragments ( $\text{C}_3\text{H}_5^+$ ) have a primary series at 41, 40, 39, 38, 37 and 36; a secondary series ( $\text{C}_2\text{H}_4^+$  degraded) from 28 to 24; a tertiary series ( $\text{CH}_2^+$  degraded) from 14 to 12. Other peaks correspond to doubly charged ions and isotope variants. The anesthetic range is 8–45 volumes %.

at a sweep rate of about 200 cps; the mass range covered is from 4 to 50; an accuracy of 2–5% is achieved in measuring ratios between spikes over a range of 300–1. Larger mass numbers, up to that of uranium, can be covered with a sacrifice in resolution and accuracy. The response time is of the order of 1 sec for a change of concentration of  $\text{N}_2$  of about 5 times; the speed of

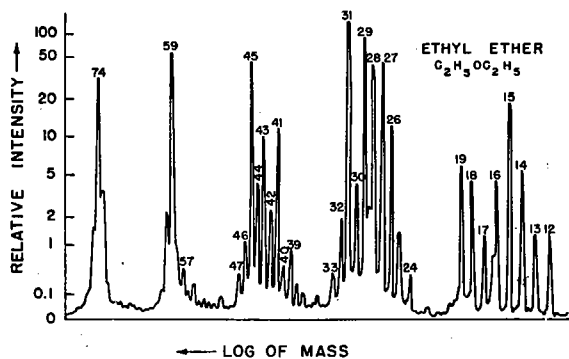


FIG. 12.—Anesthetic vapor: ethyl ether. Primary peak ( $\text{C}_4\text{H}_{10}\text{O}^+$ ) is at 74; secondary ones at 59 ( $\text{C}_2\text{H}_5\text{OCH}_2^+$ ), at 45 ( $\text{C}_2\text{H}_5\text{O}^+$ ), at 31 ( $\text{C}_2\text{H}_5^+$ ), etc., with degraded series of each at lower mass numbers. Anesthetic concentration range, in air, is 4–7%.

analysis for  $\text{CO}_2$ ,  $\text{O}_2$  and  $\text{H}_2\text{O}$  are not given. Presumably this response interval could be reduced to at least that obtained in the instrument of Hunter. Some of the desirable features of Siri's instrument are use of an oscillating accelerating voltage, a-c amplifiers for output measurement, permanent magnets for the deflecting field and a relatively simple type of construction with all electric leads into the vacuum through a single, flat, metal face-plate.

In mass spectrometers, some trouble is experienced with water vapor and  $\text{CO}_2$ . Both tend to be slowly discharged from the walls inside the vacuum (Symposium<sup>16</sup>).

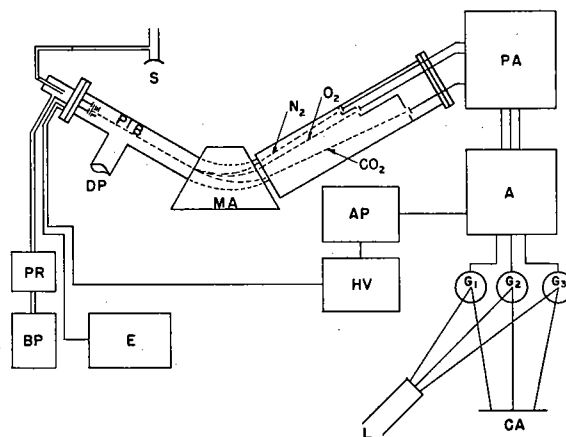


FIG. 13.—Three-detector mass spectrometer. *S*, subject; *PR*, pressure regulator; *BP*, bleeder pump; *E*, emission regulator; *DP*, diffusion pump; *PIB*, positive-ion beam; *MA*, magnet; *PA*, preamplifier; *A*, amplifier; *AP*, amplifier power supply; *HV*, high-voltage supply; *L*, light; *CA*, recording camera. Principles of operation are those given by Nier,<sup>42</sup> but unique variation in design is the use of 3 detectors, each with its own amplifier and recording galvanometer ( $G_1$ ,  $G_2$ ,  $G_3$ ). One detector is at mass number 44, one at 32 and one at 28. The resulting ion currents are measures of the concentrations of  $\text{CO}_2$ ,  $\text{O}_2$  and  $\text{N}_2$ , subject to limitations given in Tables 2 and 4 and by factors in Figs. 5–9. Latency interval of this instrument is about 0.2 sec; response to a step-change of composition is shown in Fig. 14; a respiration record in Fig. 15. (Courtesy of R. Stacey and F. A. Hitchcock, Columbus, O.)

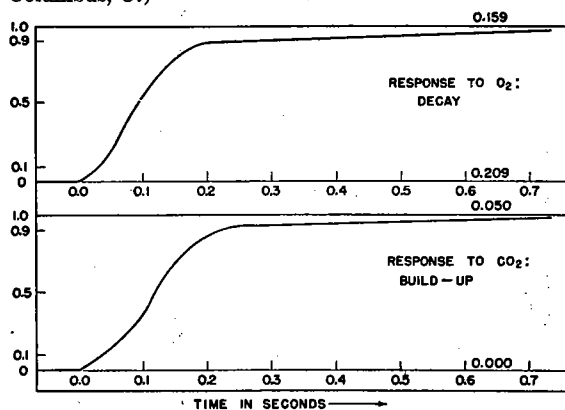


FIG. 14.—Response of 3-detector mass spectrometer. Only 2 channels (44 and 32) were used. The step-change in composition was carried out in reverse fashion to that described for the nitrogen meter (Fig. 3). Relative amplitude of response is given by scale on left. Initial level is a mixture of 0.209 volume fraction of  $\text{O}_2$  plus 0.000  $\text{CO}_2$ ; final level, a mixture of 0.159  $\text{O}_2$  and 0.050  $\text{CO}_2$ ; the residual gas is  $\text{N}_2$ . Response curve is complex (cf. Fig. 1), involving a slow start, a fast change and a slow "tail-off" to the final value. The response interval is 0.15 sec not taking into account the long tail-off (about 1.0 sec to within 1% of the final value). Presumably, further development of this instrument will eliminate this relatively long response tail. (From original record of R. Stacey.)

For respiratory work with  $\text{H}_2\text{O}$ -saturated gases, this difficulty may possibly be overcome by running the analyzing vacuum-system walls at a high temperature;

in this event, the all-metal construction of Siri and others has definite advantages over the use of the glass envelope of earlier instruments.

The vast range of analysis problems handled by the mass spectrometer makes its further development imperative for physiologic and medical research. Specialized instruments with great speed or with great sensi-

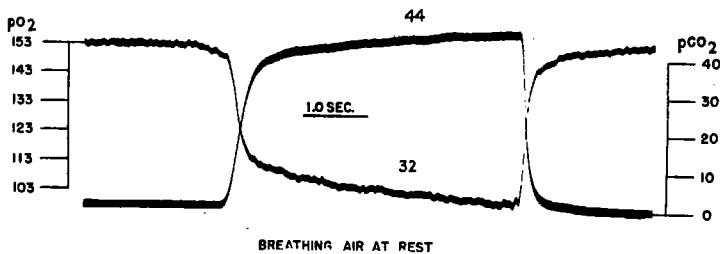


Fig. 15.—Record of respiration with mass spectrometer. Record begins during inspiration, shows 1 expiration and ends during an inspiration. Trace marked 44 is the current from the detector at mass number 44; 32, that at mass number 32 (Fig. 13). Calibration of instrument with known mixtures of  $O_2$  and  $CO_2$  generated the scales of  $pO_2$  and  $pCO_2$  (partial pressures) at each end of the record. For accurate analysis of this record, time factors of Fig. 14 and species factors should be taken into account. In addition, a record of total gas volume (or of flow-volume velocity), of total pressure, of mixture temperature,  $pN_2$  and  $pH_2O$  are needed for a complete analysis. (Courtesy of R. Stacey.)

tivity should be developed for manufacture at moderate prices. The instrument can handle respiratory gas analysis, stable isotope analysis and general chemical analysis in a way that no other apparatus has yet achieved. In medicine a high-sensitivity model could probably be applied to gases other than  $CO_2$  and  $H_2O$  produced by the body or absorbed from contaminated air and given off in the respiratory tract (acetone, carbon monoxide, carbon disulfide, etc.), the feces ( $H_2S$ , methane, etc.), urine ( $NH_3$ , mercaptans, etc.), skin, hair and by bacterial or fungous infections of the feet or other body area. Diagnosis of specific diseases and toxic agents may well develop from this method. Any

substance with an appreciable vapor pressure in sufficient concentration can be determined. With extreme sensitivity, even olfactory problems in physiology may be attacked (Moncrieff<sup>46</sup>).

**Methods Using Nuclear Properties.**—Unstable radioactive elements have been used in respiratory gases as tracers. Use of  $\beta$ - and  $\gamma$ -ray spectrometers (Langer and Cook;<sup>47</sup> Quade and Halliday<sup>48</sup>) may facilitate use of several tracer species concurrently; however, these instruments are yet to be applied to gas analysis.

Non-radioactive, nuclear properties may in the future be used for gas analysis. The field of nuclear physics is being actively investigated, new methods are being devised and results obtained which may give simpler, faster and more economic methods than are at present available. The phenomena of the magnetic resonance of the nucleus causing absorption (Bloemberger *et al.*<sup>49</sup>), though at present best seen in liquids and solids, may furnish a lead for a future analysis method.

The history of gas analysis shows that research to delineate the structure of matter produced the most powerful methods for separating the varieties of matter from one another. All the methods mentioned in this article were first developed in fundamental physical researches; it is only somewhat later, in terms of years, that they began to be applied to chemical, biologic and physiologic problems. The gas-analysis methods of the future are present, potentially, in the experimental and theoretical physics of today (Bethe<sup>17</sup>), including that withheld from publication for reasons of national security. Future releases may be useful in the analysis of respiratory gases, as well as in other fields of public research.

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