# INFLUENCE OF RESPIRATORY AIR SPACE DIMENSIONS ON AEROSOL DEPOSITION*

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*Abstract*—Models used to estimate both total and regional deposition of aerosols in the human respiratory tract have been proposed by a number of individuals and groups. Although the values chosen by different investigators for dimensions of airways or other air spaces may differ significantly from each other, there is the common assumption that the normal human respiratory tract is structurally uniform and that dimensions and branching patterns may be considered as constants in the deposition equations. There has been, therefore, considerable emphasis on estimating the effects of particle size, size dispersion, tidal volume and respiratory frequency. Much less attention has been paid to the normal intersubject variability of the size of air spaces in spite of the obvious influence this would have on aerosol deposition. Work on deposition from our own laboratories, as well as published results of others on pulmonary anatomy, has lead to the conclusion that there is considerable anatomic variability among normal subjects. Aerosol deposition in individuals examined under nearly identical conditions has also shown considerable variability. This paper will discuss the similarity in range of anatomical differences and differences in deposition and the probable relationship between the two.

## INTRODUCTION

The major considerations in predicting aerosol deposition in the human respiratory tract are the anatomy of the tract itself and the dynamics of the particles. The latter area is much more susceptible to investigation than is the former; a much larger, and possibly disproportionate, amount of effort has been devoted to particle dynamics than to airway anatomy. A number of deposition models have been proposed for the human respiratory tract, the earliest being that of FINDEISEN (1935) which was modified by LANDAHL (1950, 1963) and by the I.C.R.P. (1966). Possibly the most widely used model on the details of lung morphometry is that of WEIBEL (1963); this model has been used for predicting deposition by BEECKMANS (1965). More complex models which recognize the asymmetry of bronchial branching have been developed by HORSFIELD *et al.* (1971) and PHALEN *et al.* (unpublished).

Use of an anatomical model makes it possible to predict deposition by sedimentation, diffusion and impaction, and to relate these to certain parameters, most

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frequently the mass median (aerodynamic) diameter (MMAD). Interestingly, the heterogeneity of the aerosol cloud is generally recognized, and in the real-life situation allowance is made for the dispersion by giving the size in terms of the MMAD and a geometric standard deviation. It should be noted, however, that no allowance is made for any dispersion in the size of the air spaces in the various anatomical models. Each treatment uses a fixed morphometry and makes the calculations with the tacit assumption that there is no dispersion. This is clearly an oversimplification and could have serious consequences if standards are set on the basis of this assumption.

## AEROSOL DEPOSITION IN HUMAN POPULATIONS

### *Total Deposition*

The differences in the deposition of aerosol under identical conditions at a series of particle sizes was noted in the first aerosol deposition study at this Institute (ALTSHULER *et al.*, 1957). It was seen that in three subjects breathing a series of graded sizes of triphenylphosphate aerosol from 0.14 to 3.2 $\mu$m in diameter there were distinct differences in the fraction of aerosol deposited. This difference was most marked at 0.4 $\mu$m (MMAD about 0.5 $\mu$m; $\sigma_g$ less than 1.2) where the three subjects showed 17, 19 and 33% deposition, respectively, during steady-state breathing at 15 respirations per minute. Obviously this sample was too small to give any meaningful estimate of dispersion within the population.

At the third BOHS symposium in 1970, LOVE *et al.* (1971) reported on deposition in 48 coal miners, 15 with pneumoconiosis and 33 without pneumoconiosis, breathing a 1.0-$\mu$m monodisperse aerosol under standard conditions of ventilation. Their data showed coefficients of variation ($\sigma$/mean) of 21 and 18% for normal and pneumoconiotic miners, respectively. Later PALMES *et al.* (1973) measured deposition during breath-holding on six subjects breathing 25 ml boluses of a monodisperse triphenylphosphate aerosol of 0.55 $\mu$m diameter to depths from 200 to 800 ml; very large differences were noted in deposition rate, particularly when the aerosol bolus was inhaled to depths of 200 to 400 ml. GIACOMELLI-MALTONI *et al.* (1972) ran the largest group of subjects reported to date at a number of particle sizes and at a fixed breathing regimen. Here again the coefficients of variation at the various particle sizes ranged from 17 to 27%. LAPP *et al.* (1975) ran a series of 46 normal adult subjects of both sexes by a single breath-deposition technique for estimating air-space size by aerosol deposition during breath-holding as previously reported (PALMES and WANG, 1971). It was found that while the intrasubject variability was relatively low over extended periods, the intersubject variability was much higher and the estimated average air-space dimensions for the group ranged from 0.30 to 0.79 mm with a mean of 0.54 and a coefficient of variation of 21%.

### *Tracheobronchial Deposition*

It has been previously reported from this Institute that T-B deposition is highly variable among normal humans, and that it is increased and even more variable among

cigarette smokers (LIPPMANN *et al.*, 1971; ALBERT *et al.*, 1973; LIPPMANN, in press). The observed deposition differences among normal individuals were consistent with reported variations in the size of the human trachea and major bronchi, assuming that other bronchial airways were proportional in size (LIPPMANN and ALBERT, 1969). However, the effect of anatomical variations on T-B deposition could not be expressed in quantitative terms because there was no way to measure the critical dimensions of the human airways *in vivo*.

Recently BOHNING *et al.* (1975) proposed an anatomic parameter related to bronchial particle deposition which could be defined on the basis of experimental deposition measurements, and applied this airway morphometry parameter to a determination of the effect of constitutional factors on the variability of bronchial deposition and mucociliary clearance.

The rationale for Bohning's approach is that the bronchial airways function as a series of particle collectors. He assumed that each of sixteen airway generations has a relatively low and constant collection efficiency during inspiration and a negligible collection during expiration. The basic formulation, which is patterned after Landahl's equation for impaction deposition in bronchial airways is:

$$TB = 1 - P = 1 - \left(\frac{1}{1 + yd^2}\right)^{16} \tag{1}$$

where $TB$ = fraction deposited on ciliated tracheobronchial airways,
$P$ = fraction penetrating the ciliated tracheobronchial airways,
$d$ = aerodynamic particle diameter, $\mu$m,
$y$ = deposition parameter reflecting morphometry dependent factors.

The exponent of 16 is arbitrary, and was selected on the basis that WEIBEL's (1963) symmetric lung model has 16 generations of bifurcating conductive airways. This assumption is not a critical one. Results obtained using other arbitrary values for the exponent yield essentially the same result. For an exponent of 5, the rate of increase in tracheobronchial deposition with particle size is about 5% lower than for an exponent of 16.

The usefulness of $y$ as a characteristic deposition parameter was investigated using the accumulated *in vivo* regional deposition data in our laboratory. These data are based on measurements of the *in vivo* retention of $\gamma$-tagged monodisperse $Fe_2O_3$ microspheres in the human thorax following a 1- to 2-min inhalation period. A measurement made within 2 min after the end of the particle inhalation indicates total lung deposition, while one made 1 day later indicates deposition in non-ciliated regions of the lung. The difference between the two represents deposition on the ciliated tracheobronchial tree. Penetration of the tracheobronchial airways was taken as the sum of the alveolar deposition and the exhaled aerosol. Data were available for 104 tests on 26 normal non-smokers, for 132 tests on 46 cigarette smokers without clinical disease, and 14 tests on 6 patients with severe bronchitis. Most of the subjects had more than one test, i.e. 20 non-smokers, 42 smokers, and the 6 patients, permitting evaluation of both intrasubject and intersubject variability.

In order for $y$ to be an effective morphometry-dependent deposition parameter, it should be independent of particle size and respiratory flow. The effect of flowrate

cannot be tested with the available *in vivo* deposition data, since almost all of the tests were conducted within a narrow range of flow. The tests did, however, cover a wide range of aerodynamic diameters, i.e. from 2.5 to 12.5 $\mu$m, and were used to test the hypothesis that $y$ was independent of size.

Since $y$ varies from subject to subject, as well as from test to test for a given subject, the effect of particle size was investigated by comparing the deviation of $y$ in a given test from $\bar{y}$, i.e. the average values of $y$ determined for all tests on a given subject. Figure 1 shows a plot of $(y - \bar{y})/\bar{y}$ vs. particle size. If $y$ were dependent on particle

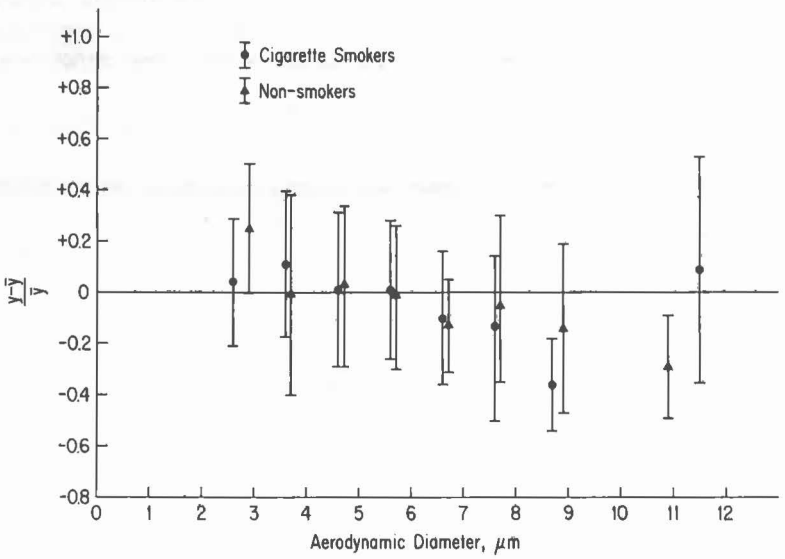


FIG. 1. Deviation of $y$ values determined in individual tests from the average $y$ for a given subject, *versus* aerodynamic particle diameter. The data are grouped by size intervals and shown as averages and standard deviations for both non-smokers and cigarette smokers.

size, there would be a systematic deviation from the zero line. Since there is little systematic variation, it may be concluded that $y$ is substantially independent of particle size for aerodynamic sizes $>2.5$ $\mu$m.

It can be seen from Fig. 2 that there is considerable variability in $y$ values for individual tests among cigarette smokers. Previous reviews of these data indicated that some of this appeared to be due to intrasubject variability, but that a larger portion was due to intersubject differences. Use of the $y$ parameter permits a more quantitative separation of the sources of variability. Analyses were done separately for non-smokers and cigarette smokers since smoking has previously been reported to affect regional deposition. The results are summarized in Table 1. It can be seen that cigarette smoking increases the average $y$ value, i.e. causes on the average a proximal shift in deposition. It also increases the intersubject variability of $y$. The increase in average $y$ value due to smoking was evaluated using the $t$-test and is significant at the 0.005 level. The increase in the variance of $y$ was evaluated using the $F$-test and was also significant at the 0.005 level.

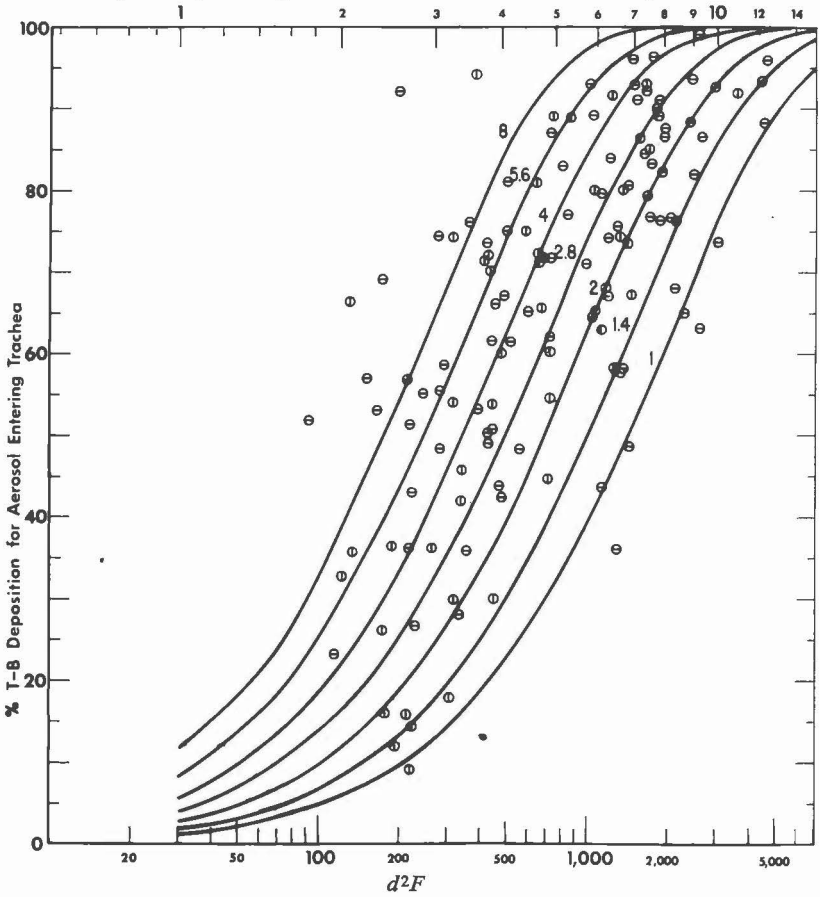


FIG. 2. The points represent the percentage of the aerosol entering the trachea which deposited on the ciliated tracheobronchial tree in individual tests on a population of cigarette smokers without clinical symptoms. The lines labeled 1 through 8 indicate the depositions predicted by equation (1) for the corresponding $y$ values ($y$ equals the number on the curve times $10^{-3}$). The data points were plotted according to $d^2F$, the product of the aerodynamic diameter squared in $\mu$m, and the average inspiratory flowrate in litres/min. The scale at the top gives the equivalent aerodynamic size in $\mu$m, assuming a constant flowrate of 30 litres/min.

TABLE 1. VARIABILITY IN TRACHEOBRONCHIAL PARTICLE DEPOSITION PARAMETER, $y$, IN HUMANS

| Population | No. of subjects | No. of inhalation Tests | $\bar{y}$ ($\times 10^3$) | Coeff. of variation—all tests | No. of subjects with multiple tests | Av. intra-subject coeff. of variation |
|---|---|---|---|---|---|---|
| Non-smokers | 26 | 104 | 2.28 | 0.57 | 20 | 0.28 |
| Cigarette smokers | 46 | 132 | 3.28 | 0.71 | 42 | 0.29 |
| Bronchitic patients | 6 | 14 | 17.15 | 0.66 | 6 | 0.55 |

The extent of intrasubject variation was evaluated on the subjects with multiple tests. The average coefficient of variation among 42 smokers was 0.29, while among 20 non-smokers it was 0.28. For the non-smokers about half of the variability was due to variability between subjects. For smokers, the intrasubject variability was 41% of the total, indicating that intersubject variability played a greater role.

## DISPERSION IN ANATOMIC MEASUREMENTS

There are very few measurements of air space dimensions at normal states of inflation. While the original deposition estimates of FINDEISEN (1935) were based on very little morphometric data, reasonably good predictions have been made using this model and, in fact, the widely employed ICRP TASK GROUP (1966) model used the Findeisen anatomic estimates as its basis. Techniques for measuring the size of lung air spaces are very involved and the measurements themselves are extremely tedious. While the studies of WEIBEL (1963), HORSFIELD *et al.* (1971), and PHALEN *et al.* (unpublished) were remarkably detailed and thorough, the very small number of lungs studied precluded their giving any insight into intersubject variability.

MATSUBA and THURLBECK (1971) after carefully controlled inflation and sectioning, measured the size of the small airways, i.e. less than 2 mm in diameter and not alveolated, of 20 normal cadavers. They found that there was a considerable variability between the different subjects and, plotted in a similar manner, Fig. 3, their results have a striking similarity to those of LAPP *et al.* (1975) cited above in that the coefficients of variation for the two studies were 0.24 and 0.21 respectively.

THURLBECK and HAINES (1975) measured cross-sectional areas of bronchi in 75 consecutive adult necropsies. Of these, 24 were considered non-emphysematous, and the

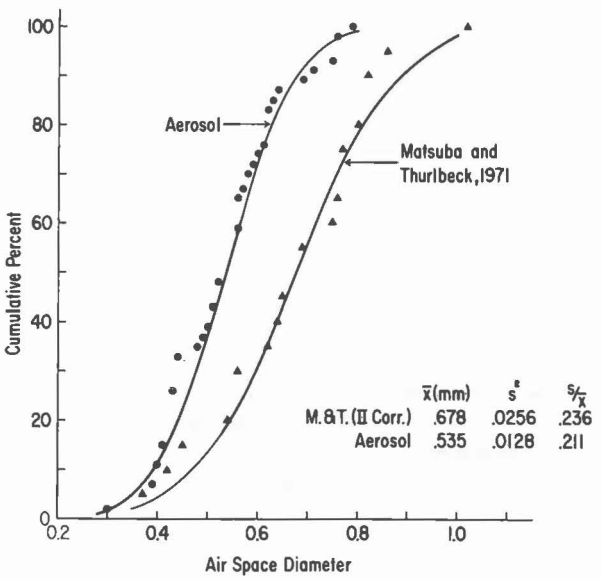


FIG. 3. Comparison of air space diameters, as estimated by MATSUBA and THURLBECK (1971) and LAPP *et al.* (1975) (Reproduced from LAPP *et al.*, 1975, by permission of the authors and the Editor of *Thorax*)

coefficient of variation of their summed main bronchial cross-sections was 0.21. The cross-sections varied with the square of body length, and if normalized by subject height have a coefficient of variation of 0.16. In 22 of the 75 cases, both the lobar and main bronchial areas could be determined, and were highly correlated ($r = 0.93$). JESSEPH and MERENDINO (1957) measured tracheal and main bronchial diameters of 36 female and 21 male cadavers, and found coefficients of variation in both groups of 0.11 to 0.13. Since airway cross-sections vary as the square of their diameters, these variations are similar to those of THURLBECK and HAINES (1975). Jesseph and Merendino also found that the lengths of the left major bronchi of males and females showed approximately the same variability as their diameters, but the lengths of the right major bronchi had coefficients of variation of 0.29 and 0.24 for males and females respectively. It should be pointed out that the length of a segment can be a major determinant of deposition in that segment.

Another factor of importance as an indirect measure of air space size is the number of alveoli. WEIBEL (1963) found a remarkable consistency in the estimated total number of alveoli on 5 cadavers, the coefficient of variation being about 0.04. ANGUS and THURLBECK (1972), however, made measurements on 32 cadavers and found a coefficient of variation of 0.27. They concluded that the number of alveoli is not random, but is significantly related to body length. However, the scatter of the data on bronchial cross-sections and numbers of alveoli is so great that at present there is no satisfactory basis for predicting either size or number of air spaces for individual subjects from body size or the lung volume.

## DISCUSSION

The purpose of this presentation is to draw attention to a neglected area in the study of aerosol deposition. If variability in lung anatomy is as large as these examples of both anatomic measurement and of deposition indicate, this is a matter of serious concern in standard setting. If, for example, the results of GIACOMELLI-MALTONI *et al.* (1972) on particles of $<2\ \mu m$ are used for prediction of deposition in individuals rather than average deposition as they reported, the results look quite different. This is shown in Fig. 4 where their data are plotted for deposition as a function of aerosol particle size. The average is, of course, the 50% line, but if account is taken of the dispersion in their population of 25, it is seen, for example, that the values are higher by a factor of 34 to 54%, corresponding to coefficients of variation of 17 to 27%, for the top approximately 2% (+2 standard deviation) than they are for the average subject. The implications for estimating dose for an individual exposed to a given aerosol are clear.

The data presented here on deposition vs. particle size in the tracheobronchial region show a substantially larger degree of intersubject dispersion than shown for total deposition. If equation (1) is a reliable empirical equation for tracheobronchial deposition, then it can be used to generate families of curves which will predict median and population behaviour. Such a family of deposition curves is shown on Fig. 2, for $y$ values extending from 0.001 to 0.008. As shown in Table 1, the $\bar{y}$ and $\sigma$ for cigarette smokers were 0.00328 and 0.00234. The fit of the bulk of the data points within curves which are $1\sigma$ from the mean, i.e., within the curves labelled 1 and 5.6, appears to

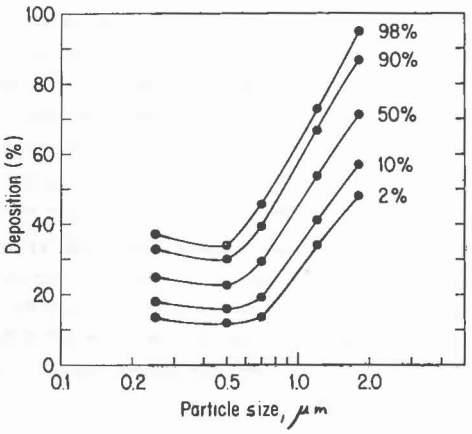


FIG. 4. Range of expected total respiratory tract deposition values based on experimental data of GIACOMELLI-MALTONI *et al.* (1972). Each curve represents the indicated percentile of the overall population.

indicate that equation (1) can provide predictions of human tracheobronchial deposition within the 2.5–12.5-$\mu$m size range.

Knowing the mean value and standard deviation of $y$ for a given population, equation (1) can be used to compute population estimates of tracheobronchial deposition. For example, for the top approximately 2% ($+ 2\sigma$) of a population of cigarette smokers who do not exhibit clinical symptoms, the tracheobronchial deposition of 5, 3.5 and 2.5 $\mu$m particles will be 94, 78 and 54% respectively, as compared to 59, 36 and 20%, respectively, for an average non-smoker. These results further emphasize the limitations of using a single value for a normal population.

The chief question raised is the importance of this observed variability in setting standards for inhalation exposure. The question is "what fraction of the exposed population must be protected?" The obverse, however, is that if these differences are real, reproducible and measurable, then a procedure for measuring the population prior to exposure could give indications of which members are the most susceptible. This would, of course, provide the basis for pre-screening and avoiding heavy aerosol exposures for this group.

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## DISCUSSION

D. C. F. MUIR: We have related total deposition to other measures of lung function. There was a close relationship to measurements of airways obstruction. This may be a more practical approach, because of its simplicity, to the detection of individuals with high deposition values. The presence of obstructive airways disease accounts for the high deposition values found in smokers.

Dr LIPPMANN: The only reply I would have is that the variability is still rather large in our non-smoking normal population. Pulmonary function tests do not account for the variability in deposition efficiency among the non-smoking normals.

R. WOLFF: I am happy to see these results because our group has noted very similar results in that deposition in smokers has tended to vary in this manner from non-smokers. One thing I was wondering about, is that the other aspect of the toxicity problem is how long the particles remain in the lungs. Was there any correlation between faster clearance and higher deposition, or any correlation at all with clearance of the particles?

Dr LIPPMANN: I will discuss the results of our measurements of mucociliary clearance in another paper (p. 305). Deposition patterns certainly do affect the time required for clearance, but I do not think that clearance times are relevant to the present discussion. These data on regional deposition are based on the difference between initial deposition and retention at 24 h, which is well after the end of the mucociliary clearance.

J. FERIN: Did you attempt to correlate anatomical features of the individuals with deposition and in this way explain part of the interindividual variability? A close correlation between lung or body weight and deposition has been found in some animal experiments.

Dr LIPPMANN: We have tried to correlate deposition with physical and physiological parameters, but we have not found any parameter that has a statistically significant relation to deposition. The trend is in the right direction, that is for taller people, whose airways presumably are larger, to have less bronchial deposition.

V. PRODI: I am glad that Dr Lippmann has raised the issue of subject variability. In our deposition studies (GIACOMELLI-MALTONI, G. *et al.*, 1972, *Am. ind. Hyg. Ass. J.* 33, 603) we tried to answer a simple question, i.e. Is the individual variability among subjects significant to the industrial hygienist? We used relatively unsophisticated equipment and did not provide very much control of our breathing patterns. If we find an intersubject variability of a factor of 2, is this important? If we cannot neglect variability, what is the easiest way to measure it? Should we run tests on any worker who is exposed to the risk of inhalation?

Dr LIPPMANN: The questions you pose are very difficult. Your group's data on total deposition served as a basis for part of our discussion. I also presented data on the variability in bronchial deposition. I think the issue must be faced for each specific disease associated with inhaled particles. In many cases, we must consider regional deposition as well as total deposition. If our concern is pneumoconiosis, then efficient bronchial deposition would be advantageous, i.e. it would protect the sensitive region. If our concern is bronchial cancer, efficient bronchial deposition may be undesirable. since particles deposited in the alveoli are spread over a much larger surface area than those depositing in the bronchi. I don't have any good answers to your questions, but I think it is important for us to begin to face them.

# INHALED PARTICLES

# IV

(IN TWO PARTS)

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