

# Immunoglobulin E Pattern in Cigarette Smokers

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Serum IgE levels in healthy blood donors who had no history of atopy were measured by a paper-disc RIA and analyzed according to the donors' smoking habits. The IgE geometric mean for regular smokers was 41.7 IU/ml, which was significantly higher than that for nonsmokers (19.3 IU/ml) or rare smokers (22.7 IU/ml). Whereas 28% of smokers had IgE levels greater than 200 IU/ml, none of the rare smokers or nonsmokers did. IgE levels in smokers showed a moderate inverse correlation with the degree of smoking. The mean IgE level was 189.8 IU/ml in those who smoked 1-9 cigarettes/day but only 32.8 IU/ml in those who smoked 10-19 cigarettes per day and 11.1 IU/ml in those who smoked 20 or more cigarettes/day. The number of years a person smoked did not seem to significantly influence the IgE level. The mean IgE level in ex-smokers (50.5 IU/ml) was much lower than in current light smokers but was still higher than in nonsmokers. There was a moderate inverse correlation between IgE levels and duration of cessation of smoking. Our data suggest a characteristic pattern for the influence of cigarette smoking on serum IgE level, namely, a striking rise associated with light smoking and a remarkable drop in heavy smokers, and such changes seemed reversible after the habit was stopped. Smoking status, therefore, appears to be an important consideration in interpreting serum IgE levels and in revising the "norms" of IgE levels.

*Key words:* cigarette; immunoglobulin E; smoking; tobacco.

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Since the discovery of IgE and its association with atopic diseases, the determination of serum IgE level has been a commonly used procedure in both clinical practice and research. During the past decade, in addition to atopy, many clinical conditions have been reported to be associated with elevated IgE levels (20). Certain viral infections were noted to be associated with an enhanced IgE production in the acute phase, followed by suppression during convalescence (2, 3).

In a preliminary report in February 1980, we presented the first evidence of modulation of serum IgE levels in man by varying degrees of cigarette smoking (4). Later the same year, a preliminary communication of Gerrard et al.

(13) suggested a stimulation of the IgE system by smoking, but the effect was significant only in grain handlers and not in teachers. In a study by Burrows et al. (9) the effect of smoking in IgE was significant only in older age groups and was striking in subjects with positive allergy skin tests, whereas in another study the effect was noted regardless of both such factors (44). Zetterström et al. (48) noted a bimodal distribution of IgE concentration in smokers but not in nonsmokers, and that such a pattern was more evident in nonatopic smokers.

We designed our study with the sole objective of investigating the relationship between tobacco smoking and serum IgE level. Variables studied included the smoking status, degree of smoking, inhalation of smoke, years of smoking experience, and cessation of the smoking habit.

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## MATERIAL AND METHODS

### *Subjects*

Volunteer blood donors, mostly middle-class healthy subjects, were informed that only those who had no present or past history of symptoms suggestive of allergic rhinitis, asthma, urticaria, atopic dermatitis, food intolerance, or adverse reactions to drugs, may enroll in the study. Skin testing was not included in the protocol of this study. Initially, 89 volunteers enrolled, but after detailed history and physical examination by one of the investigators (S.L.B.), four subjects were excluded for possibly being atopic. Data of two other volunteers (one was smoking a pipe and the other was chewing tobacco) were excluded to maintain the homogeneity of cigarette smokers. The study group was thus limited to 83 apparently nonatopic subjects (58 men and 25 women) ranging in age from 17 to 58 years (mean: 30.1 years). Each individual completed a questionnaire on the smoking habit.

### *Smoking status*

The subjects were classified according to the smoking status into four main groups: 1. "smokers," those who smoked regularly at least one cigarette per day for at least 1 month before the study; 2. "ex-smokers," those who had smoked at least one cigarette per day for at least 1 year in the past but had quit smoking more than 1 month before the study; 3. "rare smokers," those who smoked only occasionally and did not exceed six cigarettes per week during the year preceding the study; 4. "nonsmokers," those who never smoked or had smoked in the past for less than 1 year and did not smoke for a year or more before the study. According to these definitions, the 83 subjects comprised 36 (43.4%) smokers, 15 (18.1%) ex-smokers, 8 (9.6%) rare smokers, and 24 (28.9%) nonsmokers.

The degree of smoking was arbitrarily classified according to the average number of cigarettes smoked per day during the month preceding the study into: "light," 1–9 cigarettes per day; "moderate," 10–19 cigarettes per day; and

"heavy," 20 or more cigarettes per day. Accordingly, the 36 smokers comprised 12 (33.3%) light smokers, 8 (22.2%) moderate smokers, and 16 (44.4%) heavy smokers).

### *IgE assay*

Serum IgE concentration was determined by a paper-disc RIA similar to that originally described by Céska & Lundkvist (10). The assay had a sensitivity of 0.5 IU/ml and has been described in detail in a previous report (2). Serum aliquots were obtained from the donated blood, and the specimens were stored at  $-20^{\circ}\text{C}$  until all samples were included in one assay. Each standard and sample were tested in duplicate, and the mean count of the pair was used in determining the IgE values; in no case did either of the counts deviate by more than 10% from the mean of the pair.

### *Statistical analysis*

Data analysis followed standard procedures (1). In all computations, IgE values were transformed into natural logarithms. Mean IgE values were always calculated as geometric means ( $G\bar{x}$ ), whereas means of other variables were calculated as arithmetic means ( $\bar{x}$ ). Pearson's correlation coefficient ( $r$ ) was used to assess the correlation between two quantitative variables. Appropriate forms of Student's  $t$  test were applied in evaluating the difference between two means or in testing the significance of the correlation coefficient. In evaluating the variation between more than two means, analysis of variance (ANOVA) was applied. Whenever the  $P$  value exceeded 0.05, the observation tested was considered statistically nonsignificant.

## RESULTS

### *Smoking status* (Fig. 1)

The smokers' group had a geometric mean of serum IgE level of 41.7 IU/ml, which did not differ significantly from that in ex-smokers (50.5 IU/ml), but each of these means was

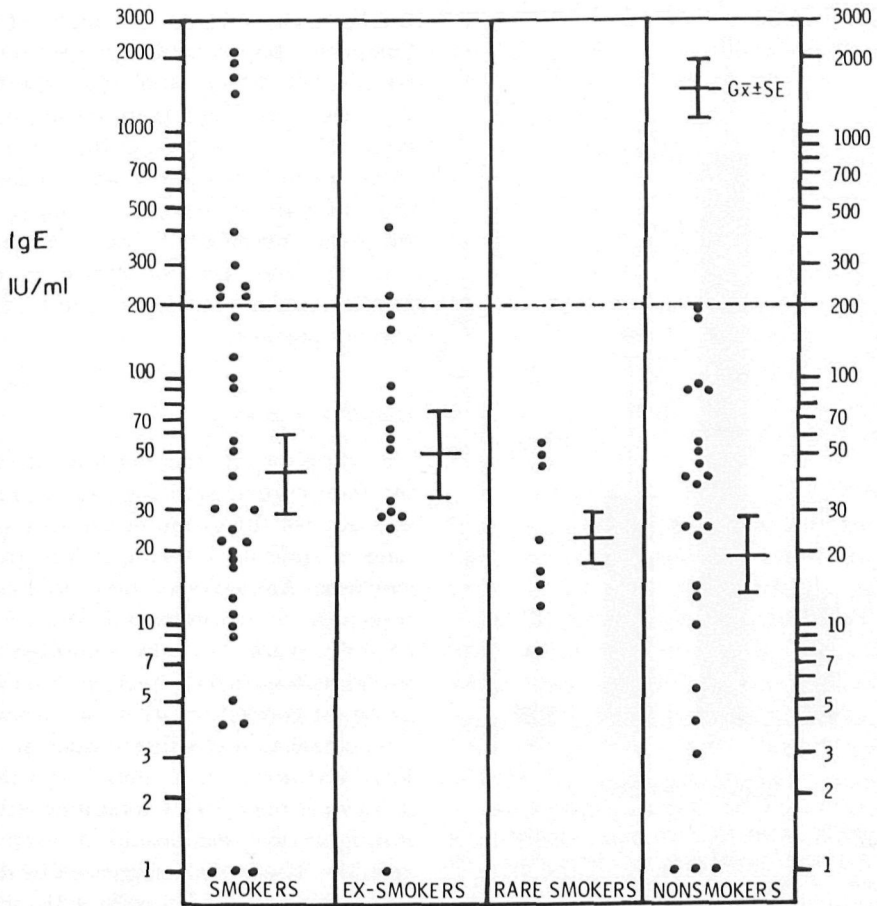


Fig. 1. Distribution and geometric mean ( $G\bar{x}$ ) of serum IgE levels according to the smoking status in blood donors who had no history of atopy.

significantly higher ( $P < 0.05$ ) than that of rare smokers (22.7 IU/ml) or of nonsmokers (19.3 IU/ml). Levels higher than 200 IU/ml were noted in 28% (10/36) of smokers and in 13% (2/15) of ex-smokers, but in none of rare smokers or nonsmokers. In our laboratory, serum IgE values greater than 200 IU/ml are above the geometric mean by more than 2 SD for our healthy, nonatopic adult population.

The observed differences in IgE according to the smoking status were unlikely to be due to age differences. The average age for the groups were: smokers,  $29.7 \pm 1.60$  years; ex-smokers,  $36.2 \pm 2.79$  years; rare smokers,  $30.5 \pm 4.16$  years; and nonsmokers,  $26.5 \pm 1.63$  years. Although ex-smokers had a mean age higher than

that for each of the other three groups, comparing the four groups by analysis of variance showed no statistically significant intergroup variation in age. The groups of smokers and nonsmokers, in particular, had the closest mean and the lowest standard errors in age distribution.

#### *Degree of smoking (Fig. 2)*

Analysis of serum IgE levels in the group of smokers according to number of cigarettes smoked per day revealed a significant, moderate inverse relationship ( $r = -0.32$ ;  $P < 0.05$ ). The geometric mean IgE level was 19.3 IU/ml in nonsmokers and 189.8 IU/ml in light smokers

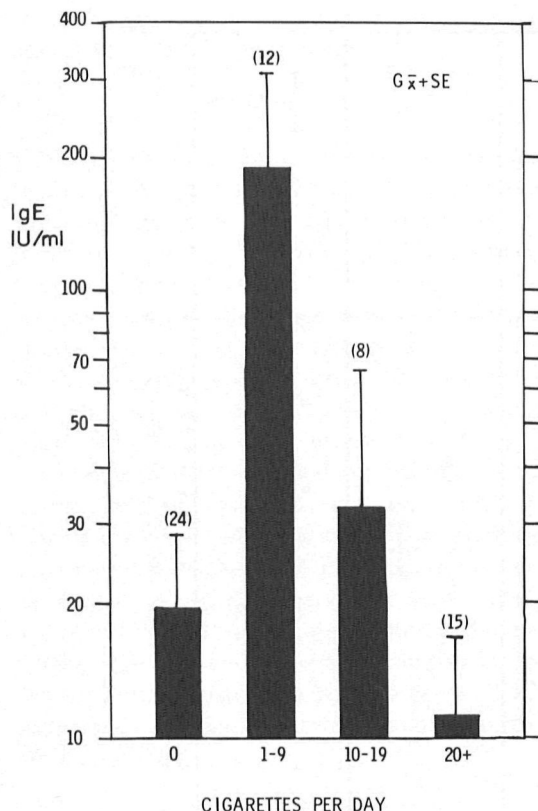


Fig. 2. Serum IgE geometric mean ( $G\bar{x}$ ) according to the number of cigarettes smoked per day in blood donors who had no history of atopy. (In parenthesis is the number of subjects. An outlying IgE value was excluded from the group smoked 20+ cig/d, although its inclusion would not change the trend).

(883% increase above nonsmokers), but only 32.8 IU/ml in moderate smokers (70% increase above nonsmokers) and 11.1 IU/ml in heavy smokers (42% decrease below nonsmokers). Sequential comparisons by *t* test showed that each of these geometric means was significantly different from the preceding one.

#### *Inhalation of smoke* (Table 1)

Smokers who reported that they immediately expell the smoke without actively inhaling it, had a mean serum IgE level of 201.3 IU/ml, which is more than sixfold that in smokers who actively inhaled the smoke (32.4 IU/ml). The level was lowest of all in the group of heavy

smokers who inhaled the smoke (13.3 IU/ml). Smokers who inhaled, however, consumed a significantly larger number of cigarettes ( $\bar{x}$  = 15.5 cigarettes/day) than those who did not inhale ( $\bar{x}$  = 10.8 cigarettes/day). Therefore, the lower mean IgE in those who inhaled could be due, in part at least, to a higher degree of smoking. Because of the small number of smokers who did not inhale in this series, further evaluation of the effect of inhalation was not possible.

#### *Duration of smoking*

The duration of smoking was calculated from the date regular smoking began until the date of study for the group of smokers, or until the date of quitting smoking in the group of ex-smokers. Among the smokers, that duration ranged from 5 months to 37 years, with a mean of 13.5 years. In only two subjects was the duration less than 1 year, indicating that the group in general consisted of chronic smokers. The correlation coefficient between serum IgE level and duration of smoking in the smokers group was only  $-0.09$ , indicating either a weak, nonsignificant relationship or a nonlinear correlation. The latter is suggested by the fact that the mean IgE level was 31.8 IU/ml when the duration of smoking was less than 5 years (7 subjects), rose to 75.0 IU/ml (136% increase) when the duration was 5–14 years (14 subjects), and then declined to 20.1 IU/ml (37% decrease) when the duration was 15 years or more (15 subjects). Such a pattern, however, was not statistically significant. The low mean IgE level in those who smoked for 15 years or more was probably due to their higher degree of smoking ( $\bar{x}$  = 21.6 cig/d) than those who smoked for less than 5 years ( $\bar{x}$  = 9.1 cig/d) or for 5–14 years ( $\bar{x}$  = 11.7 cig/d). Therefore, the duration of smoking seemed to have little influence compared with that for the number of cigarettes per day. In support of this point are the data from four smokers who had highly elevated IgE levels ranging from 1450 to 2100 IU/ml ( $G\bar{x}$  = 1770.8 IU/ml); they smoked an average of eight cigarettes per day, whereas their duration of smoking averaged 14.8 years.

Table 1

Relationship between active inhalation of smoke and serum IgE level in smokers who had no history of atopy

| Inhalation of smoke           | n  | Serum IgE IU/ml |                                       | P value  |
|-------------------------------|----|-----------------|---------------------------------------|----------|
|                               |    | Range           | Geometric mean (G $\bar{x}$ $\pm$ SE) |          |
| Do not inhale                 | 5  | 30-1700         | 201.3<br>(103.3-392.2)                | P < 0.05 |
| Inhale                        | 31 | < 1-2100        | 32.4<br>(21.8-47.9)                   |          |
| Inhale and smoke<br>20+ cig/d | 15 | < 1-1450        | 13.3<br>(7.8-22.7)                    | P < 0.05 |

*Rare smokers*

The group of rare smokers had IgE levels between 8 and 55 IU/ml, with a geometric mean of 22.7 IU/ml, which is similar to that of non-smokers (19.3 IU/ml). Subjects in this group smoked only occasionally, and none of them smoked more than five cigarettes per week.

*Ex-smokers*

The group of ex-smokers had smoked in the past for durations ranging from 1 to 20 years, with a mean of 10.5 years. The duration between date of quitting smoking and the date of the study ranged from 1 to 18 years, with a mean of 7.1 years.

Analysis of data of ex-smokers disclosed two main findings. First, the mean serum IgE level in ex-smokers was much lower than that of current light smokers (50.5 vs 189.8 IU/ml;  $P < 0.01$ ), but was still higher than that of non-smokers (50.5 vs 19.3 IU/ml;  $P < 0.05$ ). Second, there was a moderate inverse correlation between serum IgE level and duration of cessation of smoking ( $r = -0.39$ ;  $0.05 < P < 0.1$ ), i.e., serum IgE levels seemed to decline as the duration of cessation of smoking increased.

## DISCUSSION

The ill effect of exposure to tobacco smoke in patients with respiratory allergies, particularly

bronchial asthma, is thought to be irritative rather than immunologic, mainly because no evidence has been found that reaginic antibodies to tobacco smoke components exist in such patients (26, 35). Today, the evidence for allergenicity of tobacco smoke in humans derives mostly from cutaneous reactivity (7, 30), a criterion that has several limitations, especially because the tobacco combustion product is a heterogeneous mixture of an estimated 2000 particulate, gaseous, and semivolatile components, mostly irritants (29, 36).

In experimental animals, several components of tobacco smoke have proved to be immunogenic and could influence both the humoral and cell-mediated immunity (14, 25, 39, 42). In man, inhalation of tobacco smoke suppresses the local defense mechanisms of the respiratory tract (16, 18, 22, 27). Studies on the humoral immunity revealed some degree of suppression in serum immunoglobulins, particularly IgG (11, 13, 17, 24, 43, 47) and a decreased persistence of hemagglutination inhibition antibody titer to influenza virus after natural infection or vaccination (12). The effects on the cellular immune responses, however, have been inconsistent (33, 34, 37, 46).

Our findings agree in general with those of other studies (9, 13, 44, 48) in that serum IgE levels are higher in smokers than in non-smokers. Our data, however, suggest a characteristic pattern of remarkable enhancement in IgE production by light smoking and of

significant suppression by heavy smoking. Such a relationship was not noted by Warren et al. (44) or Zetterström et al. (48), but these authors neither reported their data on this point nor their method of analysis, particularly since the relationship appears from our work to be non-linear. Interestingly, however, Zetterström et al. noted that IgE level in smokers had a bimodal distribution that the authors could not explain and it possibly might be attributed to the intensity of smoking. The mean IgE level was highest in smokers who did not actively inhale the smoke (201.3 IU/ml) or who smoked fewer than 10 cigarettes per day (189.8 IU/ml), and was lowest in those who smoked 20 cigarettes or more per day, especially if they actively inhaled the smoke. The stimulant effect on IgE by low degrees of exposure to tobacco smoke seems to be evident even in young children from smoking families (23). Because the mean serum IgE level in rare smokers was found to be normal, exposure to smoke apparently needs to be rather persistent.

The duration of smoking did not seem to have a significant role on IgE level, an observation similar to that of Warren et al. (44). Our subjects were chronic smokers, however, and therefore we cannot postulate on the acute effect of smoking. Of interest would be a study of the kinetic relationship of serum IgE and acute smoking, particularly to determine the duration of smoking at which changes in the IgE level begin and then reach maximum. The appropriate approach, however, might be unethical in man.

Although tobacco smoking and changes in IgE level have not been proved to interrelate in cause-and-effect manner, our data on ex-smokers suggest that they probably do. The geometric mean of IgE in our group of non-smokers (19.3 IU/ml) is within the range for nonatopic subjects reported by other authors (6, 44, 48). The mean IgE level in ex-smokers was between the two means of current light smokers and nonsmokers, suggesting that the effect on IgE is reversible after a person quits smoking. Such reversibility showed a moderate correlation with time, a finding that has been also noted by others (9, 44). A similar relationship

was shown for mice, whose primary immune response was first enhanced, then became remarkably suppressed, by continual exposure to cigarette smoke, and recovered after exposure ceased (40, 41, 42). If this relationship exists with the IgE-producing plasma cell in man, then recovery of such a cell might lend an explanation to the reversibility of IgE suppression. It may also explain the anecdotal observation that some patients with respiratory allergies complain of exacerbation of their symptoms shortly after quitting smoking (5). Interestingly, bronchial sensitivity to mecholyl inhalation in asthmatics increased after cessation of smoking (8).

Because the observed IgE changes appear to result from tobacco smoking, further investigation into such a relationship would be valuable, primarily to answer two main questions. First, what substance(s) stimulate(s) the IgE-producing plasma cell? Second, what is (are) the underlying mechanism(s)? As to the first question, the effector substance could be one or more of the almost 2000 constituents of tobacco smoke. It may also be one or more of the many chemical, enzymatic, or metabolic substances produced in the body secondary to smoking. The answer to the second question is also elusive but perhaps not quite so complex. One hypothesis might invoke a hypersensitivity reaction, since exposure to tobacco smoke is known to frequently aggravate or precipitate respiratory allergy symptoms. All individuals in this series, however, were asymptomatic. Furthermore, no IgE antibodies to tobacco smoke antigens could be detected by RAST, even in sera of atopic patients with respiratory symptoms precipitated by tobacco smoke (26). Also, sera may contain IgE antibodies to tobacco leaf antigens regardless of clinical sensitivity (45). These observations, however, do not invalidate the reports of the occasional occurrence of immediate-type hypersensitivities to tobacco smoke (32) or to tobacco leaves (15, 31).

A second possible mechanism is an increased alveolar permeability in cigarette smokers, which has been reported by Jones et al. (21). In theory, this could facilitate penetration by small aeroallergens that in turn may sensitize the

subject and stimulate IgE production. Our study did not include skin testing or RAST, which perhaps would be of help in detecting subclinical atopy. Studies on the relationship between smoking and allergen skin reactivity reported inconsistent results, including reduced frequency of reactors in smokers (9), increased frequency of reactors (48) or no association (44).

A third possibility is that the absorbed constituents of tobacco smoke may influence B cell function either directly or through modulation of the interaction between B cell and T cell subpopulations. Indeed, cytotoxic substances have been identified in both the gaseous and the particulate constituents of cigarette smoke (19, 38). Such substances in low concentrations may be irritative or stimulative, and in higher concentrations may be toxic or suppressant. Nicotine, for example, in low concentrations enhanced the adenosine triphosphatase activity of sheep alveolar macrophages, whereas in higher concentrations it inhibited such activity (28). The influence of tobacco smoke on T cell helper and suppressor effects on IgE production is worth investigating.

In conclusion, our study supports other reports in that serum IgE level is generally higher in smokers than in nonsmokers. It further suggests the presence of a characteristic pattern for the relationship between IgE and smoking, namely an enhancement by regular light smoking and a suppression by heavy smoking, and such changes appear to be reversible following cessation of smoking. It would be prudent, therefore, that the smoking habit be taken into consideration for appropriate interpretation of serum IgE levels in individual subjects as well as in re-evaluation of current "norms" of IgE levels.

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