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The Sudden Infant Death Syndrome: A Possible Hypersensitivity Reaction Determined by Distribution of IgG in Lungs

Specimens used in the experimental section of this paper were obtained primarily from Wayne County, Michigan. This population has been under study since 1959 by one of the authors (C. R.) [*1-3*]. Some characteristics compiled from 1000 sudden infant death syndrome (SIDS) deaths in this population are summarized as they relate to the experimental findings. An additional complementary study [*4*] presents an in-depth epidemiologic survey.

Epidemiology

The epidemiology of the syndrome indicates the highest number of deaths occurred between two and four months of age, with a peak at two months (Fig. 1). A second rise, beginning at four months with a peak at six, may be related to premature births [*3*]. A seasonal periodicity of SIDS is shown in Fig. 2. The annual seasonal increase occurs between October and April with a peak in February [*4*], coinciding with the increase of acute respiratory syncytial virus infection in children [*5*].

In at least 60% of SIDS autopsies in Wayne County there was a history of a "cold" for several days prior to death, sometimes coughing and difficulty in breathing or, occasionally, apneic episodes. Usually the infant was put to sleep and found lifeless an hour or more later. Three quarters of all SIDS deaths were attributed to diseases of the respiratory system, with the majority evidencing interstitial pneumonitis.

The incidence in nonwhite infants was almost three times higher than in white infants, with a predominance in males in the original 1000 cases. High-risk factors to the infant during pregnancy included environmental influences, socioeconomic factors, illegitimacy, inadequate nutrition, ill health and complications of pregnancy, poor medical care, smoking, drugs, and noxious agents. These high-risk factors were more frequent in the nonwhite socially deprived community. One third of the nonwhite and one fifth of the white children were premature. The maternal ages were lower than expected, and risk of SIDS decreased with increasing maternal age. The distribution of the birth weights was lower than expected, even when the premature births were eliminated. The number of SIDS victims dying during the weekend was excessive. The distribution of the

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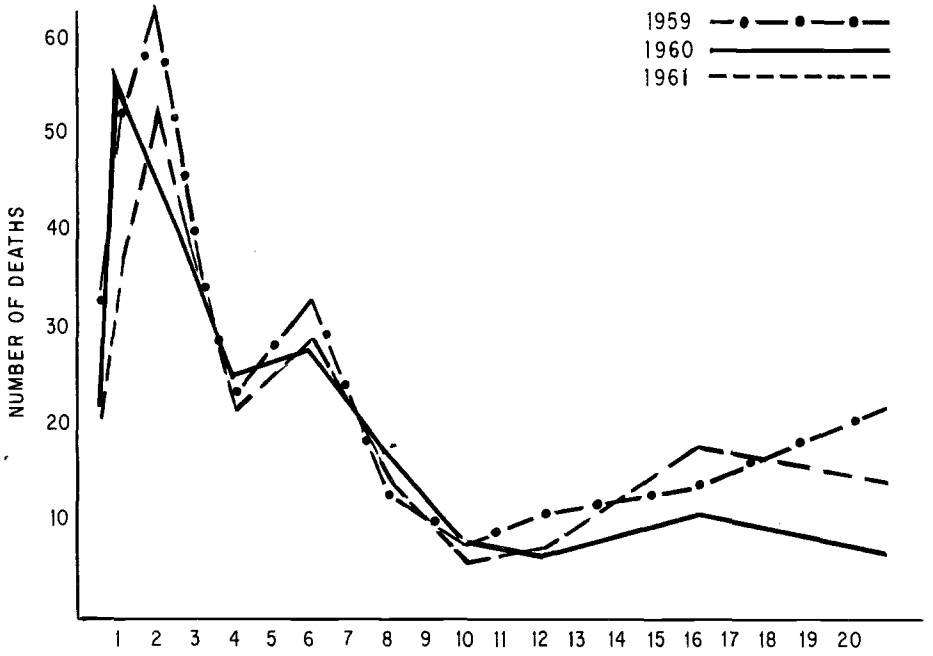

FIG. 1—*Distribution of yearly SIDS deaths by age at death for 1959 through 1961 in Wayne County.*

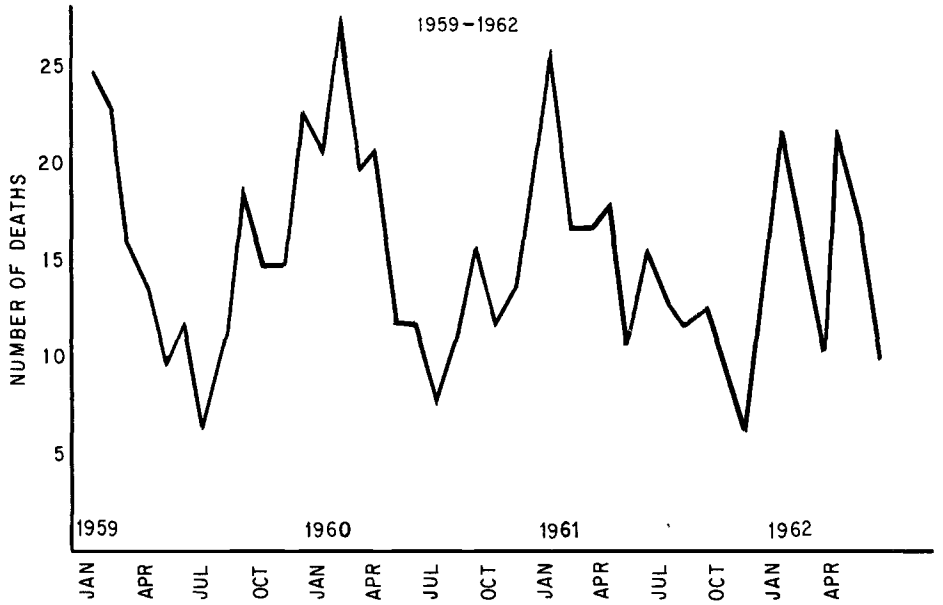

FIG. 2—*Seasonal incidence of all SIDS deaths in Wayne County, 1959 through 1962; distribution by month.*

age of the children who died between two and eight months closely followed the distribution of all infant deaths. Over 30% of the infants were premature, had low birth weights at term, were illegitimate, or were born to young or high-risk mothers. The incidence of SIDS deaths was higher in the central portion of Detroit and decreased peripherally.

The epidemiologic characteristics of SIDS deaths in the Wayne County population are essentially the same as those reported for other communities [*6-8*].

Pathology

More than 1000 SIDS deaths were studied in the Office of the Medical Examiner of Wayne County. In several instances, full-mount lung sections on 82.5 by 107.9-mm (3¼ by 4¼-in.) slides provided a good perspective of the geographic lung pathology (Fig. 3).

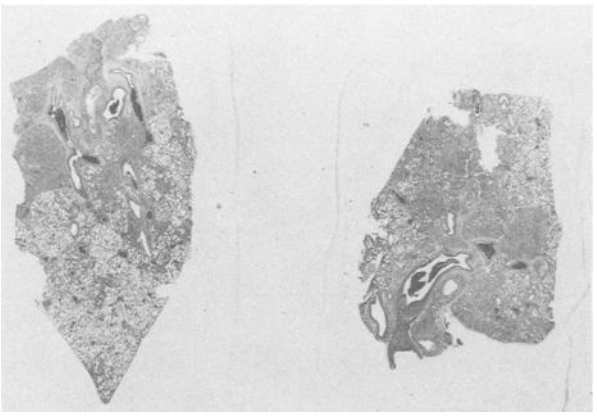

FIG. 3—*Whole mount sections of lung on 82.5 by 107.9-mm (3¼ by 4¼-in.) slides to show the geographic morphological lesions in interstitial pneumonitis. The lesions are segmental and hilar in location, radiating to periphery.*

Although some of the cases responded to the SIDS autopsy criteria, most of the infants demonstrated more severe pulmonary pathology [*1-3*] (see Figs. 4*a-f* and 5). In agreement with Coe and Hartman [*9*], severity of the pulmonary lesions seemed to be age-dependent as well as season-dependent. Consistent with an acute respiratory tract infection, acute interstitial pneumonitis, bronchiolitis, or segmental pneumonia was most common. However, there was overlapping of morphological lesions that spanned the entire length of the respiratory tract, including rhinitis, laryngopharyngitis, tracheobronchitis, bronchiolitis, interstitial pneumonia, or some combination of these, and occasionally early bronchopneumonia. In the younger infant, under two months of age, there was moderate congestion and edema, capillary engorgement, sometimes intravascular clotting or hemagglutination, minimal mononuclear infiltration of the interstitium, frequent moderate desquamation of alveolar and bronchiolar epithelium, and proliferative obstructive bronchiolitis. In older infants, between two to five months of age, the lesions were more severe, with more marked segmental interstitial pneumonia, more marked mononuclear infiltration, and proliferative and desquamative tracheobronchitis, bronchiolitis and alveolitis. In infants older than five months, the lesions were yet more exaggerated, with necrotizing bronchiolitis and diffuse interstitial pneumonitis. The desquamation of bronchial and bronchiolar epithelium was down to the basement membrane. Proteinaceous cellular debris and desquamated epithelium often filled bronchi, bronchioles, and alveolar lumena. Hyaline membrane was not infrequent. Alveolar damage was associated

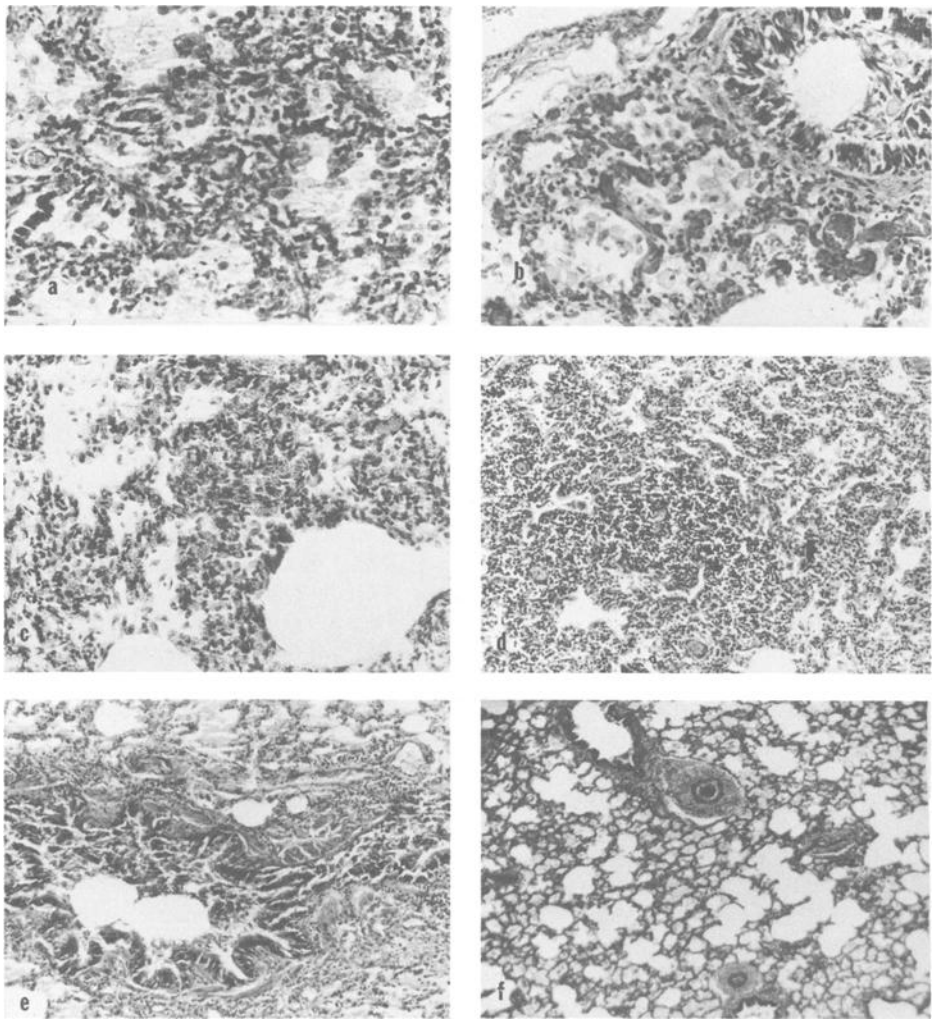

FIG. 4—*Photographs of lungs stained with hematoxylin-eosin.* (a) *Section shows marked proliferation and desquamation of alveolar lining cells and cellular necrosis and pseudometaplasia of bronchial and alveolar cells. Alveoli contain proteinaceous debris (Specimen 13; see Fig.* 6c). (b) *Section shows marked hyperplasia and proliferation of bronchiolar epithelium. Alveoli contain many septal cells. Capillaries are engorged with agglutinated red cells (Specimen 8, see Fig.* 6b). (c) *Section shows marked capillary engorgement and interstitial hemorrhage. The bronchial lining is denuded of epithelium to basement membrane (Specimen 15, see Fig.* 6a). (d) *Section shows severe mononuclear interstitial pneumonitis with alveolar collapse and partial atelectasis with occasional alveolar cell metaplasia (Specimen 6, see Fig.* 6d). (e) *Section shows marked hyperplasia of bronchiolar and acinar duct epithelium with partial occlusion of bronchiole and alveolar duct. There is also adjacent edema of interstitium and alveoli (Specimen 19).* (f) *Section shows moderate edema. Septa are moderately thickened. Capillaries are engorged with blood; alveoli are distended with air; and the bronchiolar epithelium is hyperchromatic. The periarterial muscle is hypertrophied (Specimen 7, see Fig.* 6f).

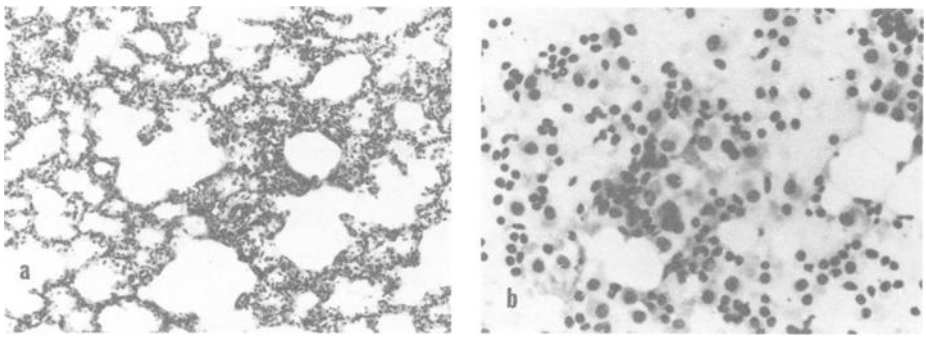

FIG. 5—*Photographs of lung tissue section stained with hematoxylin-eosin and an impression smear stained with Grünwald-Giema stain from the same case as in Fig. 7 (Specimen 7, see Fig. 4f).* (a) *Note markedly thickened septa; capillary engorgement; bronchiolar ecstasia; alveolar emphysema; alveolar desquamation and metaplasia.* (b) *Smear shows numerous lymphocytes and plasma cells; note hyperchromatic and hyperplastic clumps of bronchial epithelium.*

with atypical epithelial hyperchromatism, pseudometaplasia of bronchial and alveolar epithelium, and large bizarre giant cells. Desquamated epithelium, when examined by Papanicolaou technique, revealed "ciliocytophthoria" [*10*]. This pulmonary pathology for SIDS has been described for influenza by Askanazy in 1919 [*11*], Winternitz in 1920 [*12*], and Walsh and co-workers in 1961 [*13*]. Liebow in 1967 [*14*] described similar morphologic lesions when he classified interstitial pneumonitis using histological criteria. Obstructive interstitial pneumonitis and bronchiolitis, compensatory emphysema, and alveolar collapse, alternating with air entrapment in distended alveolar sacs and dilated bronchioles, suggest oxygen diffusion defects. Bronchiolitis obliterans is the reparative, proliferative stage of acute bronchiolitis and interstitial pneumonitis. Systemic involvement in older infants (six to nine months of age) and during the summer months also included focal hepatitis, interstitial myocarditis, focal encephalitis, serous meningitis, and adrenalitis.

Beckwith [*15*], in a thorough review of SIDS in 1975, stated that his study of 500 consecutive cases of SIDS since 1965 still convinced him that the narrow spectrum of minor pathological findings does not reveal a "cause." The accepted minimal findings include intrathoracic petechiae on the epicardial, pleural, cerebromeningeal, and thymic surfaces; mild inflammation of the upper respiratory tract; pulmonary congestion and edema associated with the presence of alveolar macrophages; and minor interstitial lymphocytic infiltrates.

Causation in SIDS is currently an area of speculation. In young SIDS victims lung lesions may be minimal. Those who claim the lesion insufficient to explain death propose multiple causation, each essential but neither sufficient alone. For example, prolonged apneic spells occurring during sleep may be lethal for those with respiratory inflammation but not for others [*16*]. An essential defect may be distal to the lung lesion involving respiratory autonomic control and affecting laryngeal reflexes [*15*]. Likewise, apparently minimal lesions may initiate a variety of possible immunopathologic responses involving autoimmune disease, immune-complex disease, or allergic responses [*17*]. The antibody may be maternal or newborn; the antigen may be endogenous altered lung tissue, organic or inorganic agent, or exogenous (viral, toxin, or bacterial) protein presented pre- or post-natally. Efforts to isolate viable microorganisms have been unrewarding.

The present study concerns a consistent finding of bound immunogammaglobulin (IgG) in the lungs from SIDS deaths and limited evidence for respiratory syncytial viral antigen.

Material and Methods

Tissue Sections

Thinly cut sections (under 3 μm) of paraffin-embedded, formalin-fixed lung tissue from infants who had died suddenly were supplied from two sources: (1) 18 specimens from the collection of cases examined by Dr. Clara Raven while serving as deputy chief medical examiner for Wayne County, Detroit, Mich.; these cases included suspected SIDS deaths and controls from infants who had died of mechanical injuries (inhalation of a marble and fall from a crib) and (2) four specimens from the files of Dr. Alfred Golden of Toledo, Ohio; these cases were also classified as SIDS deaths.

Impression Smears

Impression smears were made on clean glass slides (under 1 mm thick) from freshly cut lung tissue taken at autopsy from two cases of SIDS death in Pontiac, Michigan. The slides containing the impression smears were fixed in acetone at room temperature for 10 min, air dried, and stored in the freezer until tested.

Deparaffinization of Tissue Sections

Paraffin tissue sections for fluorescent antibody staining were processed prior to staining by first dipping the slides containing the paraffin tissue sections in xylene (analytical grade) and then placing them in the following reagents for the prescribed time and sequence: xylene (5 min), absolute ethyl alcohol (5 min), 95% ethyl alcohol (5 min), and 70% ethyl alcohol (5 min). After the 70% ethyl alcohol treatment, the slides were washed in two changes of phosphate-buffered saline (PBS), pH 7.8, for 10 min each.

Antisera

Unlabeled sheep anti-human IgG antiserum was supplied by Dr. Max Moody of Burroughs-Wellcome Co., Research Triangle Park, N.C., and unlabeled goat anti-human IgM, IgA, and IgE antisera were purchased from Antibodies Inc., Davis, Calif. All unlabeled antisera were fractionated with a concentration of ammonium sulfate to obtain the IgG fraction of the sera [*18*]. The number of precipitations and the concentration of ammonium sulfate were dependent on the animal serum (sheep or goat). Labeling of the sera with fluorescein isothiocyanate was by the dialysis method and performed under labeling conditions that would result in a fluorescein/protein molar ratio *F/P* of 2 or 3. After conjugation, unattached fluorescein isothiocyanate was removed by dialysis and the *F/P* molar ratio of each serum was determined [*17,18*]. The specificity of each antiserum was checked by immunoelectrophoresis with purified IgG, IgA, and IgM purchased from Cappel Laboratories, Inc. and against pooled normal human serum. All sera were used at a 1:2 dilution in the direct fluorescent antibody test.

Bovine anti-respiratory syncytial virus serum, bovine negative serum control, and anti-bovine immunoglobulin (rabbit), fluorescein labeled, were supplied by Dr. Moody for the virus studies.

Staining and Examination of Specimens

Staining of the specimens, including both the rehydrated tissue sections and the acetone-fixed impression smears, was accomplished by the addition of antiserum to the specimen, allowing it to react for 45 min in a moist chamber at room temperature, washing for 10 min in PBS, and mounting under No. 0 coverslips with buffered glycerine. Both negative and suspected SIDS tissue sections were stained during each time in parallel.

Examination of the slides was made in a Zeiss fluorescent microscope using a BG-12 exciter filter and OG-4 and BG-4 barrier filters. Pictures were taken with a Polaroid® ASA 3000-speed film and a KP-490 exciter filter.

Results

All specimens stained with anti-human immunoglobulins IgA, IgM, and IgE (AME) were negative, that is, no fluorescence was noted in any area of the slide. In all specimens, except control specimens (1 and 2) and Specimen 12, IgG was clearly demonstrated (Table 1) when conjugated anti-human IgG was used in the direct fluorescent antibody test. Twenty-one specimens (1–11, 13–22) were negative when reacted against anti-AME conjugates. Although a large number of negative cases was not available, the use of anti-AME conjugates on serial cut tissue sections of the 21 cases provided additional negative controls on the specificity of the immunofluorescent staining, since each antiserum was fractionated, conjugated, and contained an equivalent *F/P* molar ratio and an equivalent concentration of protein. In the examination of specimens for immunofluorescence, the extent of fluorescence occurring at the edges of tissue was not assayed. Many of the specimens showed folding at the edges and increased thickness, providing a possible tissue area for the entrapment of conjugated antiserum that may result in nonspecific fluorescence. Only the internal areas of the cut tissue sections were taken into consideration. With the above criteria for evaluating immunofluorescent staining, there was an increase in the number of fields showing immunofluorescent staining per number of fields examined as the age at death increased. Tissue sections from children 4.5 months or less at the time of death showed one positive immunofluorescent field out of ten fields examined, whereas tissue sections from children seven to nine months of age at the time of death showed immunofluorescent staining in every field examined.

Typical immunofluorescent staining with conjugated anti-IgG is shown in Fig. 6. Areas of fluorescence were in the basilar membrane of a bronchus (*a*), desquamated bronchial epithelium (*b*), alveolar wall and capillaries (*c* and *d*), capillary wall (*e*), and alveolar epithelial cells (*f*). With the use of a BG-12 excitation filter only the specific fluorescent areas could be photographed. To provide better topography of nonfluorescent areas a KP-490 interference blue excitation filter and an HBG-200 mercury vapor lamp were used to provide the light intensity necessary for photographing the nonfluorescent areas.

Specimen 7 provided a comparison of the use of formalin-fixed paraffin imbedded tissue and impression smears of unfixed fresh lung tissue. By direct and indirect immunofluorescence staining, IgG and respiratory syncytial virus were identified in alveolar and bronchial epithelium in sections cut from paraffin blocks, and also in impression smears of fresh tissue (Fig. 6*f* and Fig. 7*b*). Interstitial pneumonitis, mononuclear infiltration, evidence of prior desquamation and regeneration and proliferation of alveolar and bronchial epithelium have been described (Fig. 4*f* and Fig. 5*a*). Increased periarteriolar muscle mass is indicative of prior hypoxia and pulmonary deficit. In Fig. 5*b* the slide-impression-smear of lung stained with Grünwald-Giemsa identifies a predominance of plasma cells and lymphocytes, suggestive of an immune response. Scattered alveolar and bronchiolar epithelial cells in various stages of degeneration, regeneration, and metaplasia are consistent with tissue injury.

In Fig. 7 immunofluorescent staining of respiratory syncytial virus is shown. Of 22 specimens tested by the direct fluorescent antibody method for IgG, 15 specimens (1–4, 6–15, and 18, Table 1) were selected to be tested for respiratory syncytial virus by the indirect fluorescent antibody test. As an additional control on specific staining for respiratory syncytial virus, all sera (negative bovine serum and positive bovine anti-respiratory syncytial virus serum as well as conjugated anti-bovine serum) were tested against human epidermoid-2 cells (uninfected and infected with virus) and diluted and used according to the directions

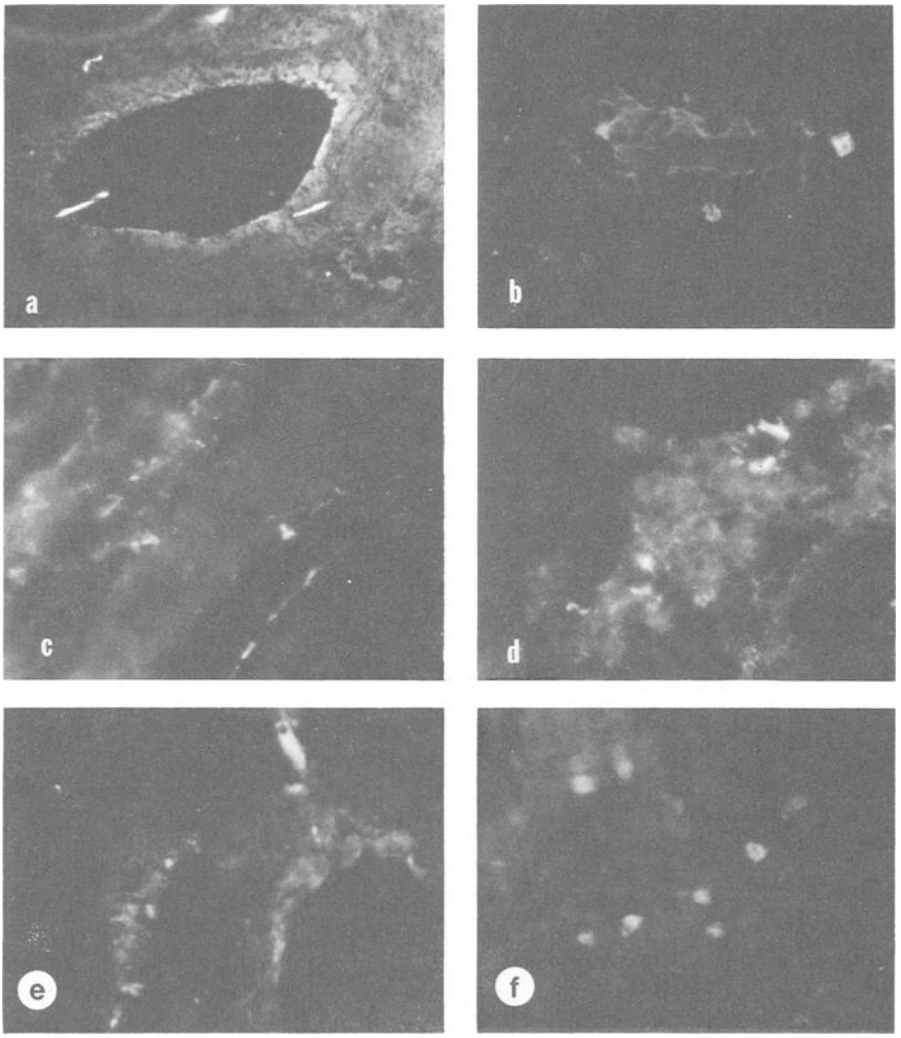

FIG. 6—*Direct immunofluorescent staining of tissue sections with a 1:2 dilution of fluorescein isothiocyanate-labeled anti-IgG.* (a) *Specific fluorescent staining of the basal membrane of a bronchus. The desquamated epithelium in the cavity of the bronchus is not visible* (*Specimen 15, see Fig. 4*c). (b) *Light specific staining of desquamated epithelium within a bronchus* (*Specimen 8, see Fig. 4*b). (c) *Specific staining of interstitial tissue and a venule in an area of atelectasis* (*Specimen 13, Fig. 4*a). (d) *Specific staining of lumpy deposits in the alveolar wall and interstitial tissue* (*Specimen 6, see Fig. 4*d). (e) *Specific staining in the wall of alveolar capillaries* (*Specimen 3*). (f) *Specific staining of alveolar cells* (*Specimen 7, see Fig. 4*f).

furnished by Burroughs Wellcome Co., Wellcome Reagent Division. With the use of the indirect fluorescent antibody method for detection of respiratory syncytial virus, 4 of the 15 specimens showed positive immunofluorescent staining for the virus. Two of the specimens (14 and 15) with positive viral staining were from twins. Specimens 7 and 11 also were positive for respiratory syncytial virus. Impression smears with lung tissue from Case 7 were made. The impression smear was examined for respiratory syncytial virus by the indirect fluorescent antibody method. A large number of adhering cells showed immunofluorescent staining (Fig. 7*b*).

TABLE 1—*Direct immunofluorescent studies on lung tissue stained with conjungated anti-human IgG.*[a]

Specimen[a]	Age, months	Sex/Race	Month of Death	Clinical History[b]	Pathology	Fluorescent Antibody Results
1	3	m/w	Feb.	inhaled a marble	massive pulmonary edema and congestion	–
2	5	m/w	March	fell from crib	subdural hemorrhage; severe pulmonary edema	–
3	0.75	m/w	Feb.	NA	mild bronchiolitis and alveolitis	+
4	1	f/w	Jan.	NA	desquamative bronchiolitis and interstitial pneumonitis	+
5	1	f/w	April	cold	pulmonary congestion, edema; moderate interstitial pneumonitis (patent ductus of Botallo and foramen ovale)	+
6	2	m/b	March	cold	bronchiolitis; mononuclear interstitial pneumonitis (Fig. 4*d*)	+
7	2	m/w	April	cold	bronchiolitis; desquamative alveolitis; interstitial pneumonitis (Fig. 4 *f*)	+
8	2.2	f/b	Feb.	cold	proliferative and desquamative bronchiolitis; intravascular hemagglutination, red blood cell sickling (Fig. 4*b*)	+
9	3	m/w	March	galactosuria	interstitial pneumonitis; focal bronchopneumonia	+
10	3	f/w	March	cold, 3 weeks	interstitial pneumonitis; focal bronchopneumonia	+
11	3	m/b	April	NA	mild interstitial pneumonitis; marked intravascular clotting	+
12	4	f/w	May	premature; diarrhea, 3 days	subacute pneumonitis; desquamative bronchiolitis; gastroenteritis (congenital defects)	–
13	2	m/b	March	premature	desquamative bronchiolitis and alveolitis; interstitial pneumonitis (Fig. 4*a*)	+
14	4	f/b	March	cold	desquamative, proliferative (obstructive) bronchiolitis; intravascular hemagglutination (sickle cell)	+
15	4	m/b	March	cold (twin)	marked desquamative, proliferative (obstructive) bronchiolitis; interstitial pneumonitis; intravascular hemagglutination (sickling) (Fig. 4*c*)	+

16	4	f/b	June	emphysema	necrotizing bronchiolitis; desquamative alveolitis; epithelial pseudometaplasia; focal encephalitis, nephritis, and adrenalitis	+
17	4.5	f/w	May	cold; cyanosis	proliferative and desquamative alveolitis; vascular engorgement (congenital heart disease)	
18	7	m/b	April	NA	mononuclear pneumonitis; proliferative alveolitis; intravascular hemagglutination (sickle cell) (anomalies of coronary arteries)	+
19	8	f/b	June	found collapsed on floor	proliferated and desquamative alveolitis; focal myocarditis, hepatitis, and adrenalitis (Fig. 4*e*)	+
20	8.5	m/w	Jan.	collapsed while playing	moderate bronchiolitis; lymphadenitis; pulmonary congestion, edema; intravascular clotting	+
21	9.0	f/w	May	cold (post-whooping cough)	necrotizing bronchiolitis; early bronchopneumonia	+
22	9.0	NA/NA	June	cold (post-whooping cough)	interstitial pneumonitis; focal hepatitis, myocarditis, encephalitis	+

[a] Positive fluorescence observed in at least one in ten fields examined. Conjugated serum diluted 1:2 used in all tests. Controls are Specimen 1 and 2.
[b] NA = not available.

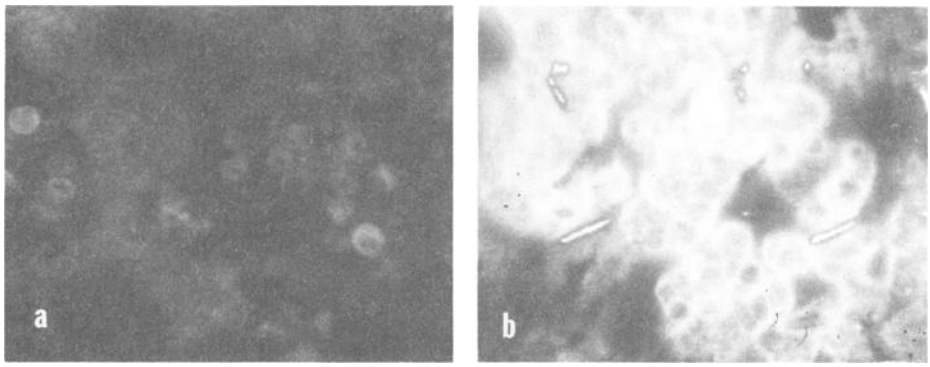

FIG. 7—*Indirect immunofluorescent staining with bovine anti-respiratory syncytial virus serum undiluted and conjugated anti-bovine globulin at 1:40 dilution.* (a) *Specific staining of a tissue section for respiratory syncytial virus in alveolar or bronchial epithelial cells of a fixed tissue section (Specimen 7, see Fig. 4f).* (b) *Impression smear from the same case showing specific respiratory syncytial virus immunofluorescence in same type of cells (Specimen 7, see Fig. 4f).*

Discussion

A consistent finding has been granular deposits of IgG in alveolar capillaries, lung interstitium, bronchioles, and smears from SIDS cases of all ages tested, but IgG was not found in postmortem tissue from traumatic deaths. Tissues with IgG contained no IgM, IgA, or IgE. The absence of other immunoglobulins, particularly IgM, rules out any consideration of the presence of IgG as a nonspecific, superficial residue of serum components.

The findings indicate some consistent and therefore essential pathologic process in the lung that must relate (directly or indirectly) to the lethal malfunction of the lung. One can only speculate as to mechanisms involved; the local immune reaction may even influence or act in conjunction with some remote, distal target (for example, the autonomic nervous system). That target would represent a second essential but not sufficient cause in a complex disease pattern.

Since the immunoglobulin found in lungs of very young SIDS victims is IgG and IgM is absent, it is entirely possible that in those cases the immunoglobulin is maternal antibody. The antigen involved might be endogenous, that is, altered lung proteins bound in an autoimmune complex. Alternatively, the antigen could be exogenous, presented pre- or post-natally. Respiratory syncytial viral antigen was detected in 4 cases but not in 18 others. While antibody directed against this antigen might preclude isolation of viable virus, it is less likely that virus in the tissue would be so completely encumbered by the child's IgG that it is undetectable with specific anti-viral antibody. Further, as yet it has not been established that endogenous IgG in the four positive cases is bound to the respiratory syncytial virus antigen.

Perhaps the principal significance of these preliminary findings is to reveal a new common underlying thread in SIDS [*14,17,21,22*]. Using indirect fluorescent antibody techniques, maternal sera, and postmortem sera from SIDS cases, one should be able to determine whether a common or limited number of specific foreign antigens plays a role in this disease entity, whether human complement functions in the immune reaction, and whether the antibody is maternal.

In 1967, Liebow [*14*] classified interstitial pneumonia as the evolution of a process that may be called "diffuse alveolar damage" of varied causes, including (1) classical usual interstitial pneumonia, (2) bronchiolitis obliterans and diffuse alveolar damage, (3) desquamative interstitial pneumonia, (4) lymphoid interstitial pneumonia, and (5) giant cell interstitial pneumonia.

Although electron microscopy was not available to Liebow, he suggested a sequence of events in the adult lung as compatible with acute viral pneumonia as a hypersensitivity reaction [*21,22*]. He bewailed that "the lung as a stage for study of morphologic expression of immunologic phenomenon has been neglected." The pulmonary pathology for SIDS briefly presented here, together with other preliminary studies, may be the answer to his plea.

Summary

Lung sections and smears from 22 SIDS victims of various ages, exhibiting varying degrees of interstitial pneumonia, gave evidence of bound IgG when examined by the direct fluorescent antibody technique. Appropriate control specimens were negative. All specimens containing IgG failed to exhibit IgM, IgA, or IgE. Four specimens containing IgG also contained respiratory syncytial viral antigen. The deposition of IgG and the relationship to the pulmonary lesions in SIDS suggest an immunologic or some phase of a hypersensitivity reaction to be further explored.

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