Toshiaki Shimizu, M.D.
Yukiko Yarita, M.D.
Kazunari Kaneko, M.D.
Yuichiro Yamashiro, M.D.
Osamu Segawa, M.D.
Ryuichi Ohkura, M.D.
Ikue Taneike, M.D.
Tatsuo Yamamoto, M.D.

Departments of Pediatrics (TS, YY, KK, YY), Pediatric Surgery (OS) and Gastroenterology (RO)
Juntendo University School of Medicine
Tokyo

Department of Microbiology
Niigata University School of Medicine (IT, TY)
Niigata

Japan

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Address for reprints: Dr. Toshiaki Shimizu, Department of Pediatrics, Juntendo University School of Medicine, 2-1-1, Hongo, Bunkyo-ku, Tokyo, 113-0033 Japan. Fax -81-3-5800-0216; E-mail tshimizu@med.juntendo.ac.jp.

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Letter

OLDEST DESCRIPTION OF ROSEOLA AND IMPLICATIONS FOR THE ANTIQUITY OF HUMAN HERPESVIRUS 6

To The Editors:

I here note the oldest known description of roseola (exanthem subitum, "sixth disease"), predating by more than 100 years Zahorsky's definitive description of roseola in *JAMA* in 1913.[1] I also point out that antiquity of human herpesvirus 6 (HHV6)[2] can be tracked via roseola.[3] Thus I also push back the antiquity of HHV6 by 100 years.

Roseola is characterized by a few days of high fever, followed by a maculopapular nondesquamating rash on the face and trunk which tends to appear quite suddenly after the fever breaks (*subitum* is Latin for *suddenly*).[4] The best known and definitive description of roseola is that of pediatrician John Zahorsky in his classic 1913 paper.[1] However, Zahorsky cites a paper of his own from 1910[5] and as well gives a description from *A Practical Treatise on the Diseases of Children* by JF Meigs and W Pepper which he believes to be an earlier description of roseola. Zahorsky did not indicate to which of the seven editions of this book (from 1848 to 1882) he was referring. I have obtained Editions 1 through 6. I find this description as early as the 1853 second edition[6] (by Meigs alone).

Given the authoritative nature of this description, I thought there was a possibility of an even earlier one. Indeed I found a nearly identical description in the 1809 book *On Cutaneous Diseases*[7] by British dermatologist Robert Willan: "The roseola aestiva is sometimes preceded by chilliness, alternating with flushes of heat, by slight pains in the head and limbs, faintness, lassitude, restlessness, and incapacity of close attention. The rash appears on the third, four, fifth, sixth, or seventh day after the commencement of these symptoms. It is distributed first on the face and neck and afterwards, in the course of a day or two, over the whole body." There are likely even earlier descriptions of roseola than Willan's. His 1809 account shows that a keen observer could distinguish roseola even in the preantibiotic and vaccine (except for smallpox) era.

Recently HHV6[2] was shown to be the cause of roseola.[3] Therefore the antiquity of HHV6 is also increased by more than 100 years.

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Eric Lewin Altschuler, M.D., Ph.D.
Brain and Perception Laboratory
University of California, San Diego
La Jolla, CA

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DENOUEMENT—*CONTINUED FROM P. 888*

An ultrasound examination of the neck showed a heterogeneous mass lesion in the left lobe of the thyroid gland measuring 20 by 14 by 36.5 mm with enlargement of the regional lymph nodes. A computed tomography (CT) scan confirmed the presence of pathologic changes in the left thyroid lobe consistent with acute suppurative thyroiditis (AST). The inflammation extended into the surrounding tissues, causing displacement of the trachea. Thyroid function

tests were normal, but the thyroglobulin level was raised to 98 μg/l (normal, 0 to 25).

The diagnosis of acute suppurative thyroiditis was made, and the patient was treated with 100 mg/kg/day cefotaxime intravenously for 4 days, followed by oral amoxicillin/clavulanate for 7 days. A barium swallow examination performed 3 weeks after discharge demonstrated a small fistula extending from the left pyriform sinus downward and anteriorly (Fig. 1). Surgical excision of the fistula was considered. Because of the small size of the fistula, we opted to refrain from surgery and consider surgical intervention with the first recurrence. The patient has been well and without recurrence for 2 years.

Acute suppurative thyroiditis is a rare infection. The resistance of the thyroid gland to infection has been attributed to its rich vascular supply, lymphatic drainage, fibrous capsule and high iodide content.[1] Most cases of AST are associated with an underlying pyriform sinus fistula.[2] AST usually occurs in infancy or childhood, but neonatal cases have been reported.[3] There is a left-sided predominance, but bilateral and right-sided lesions have also been described.[4, 5] Onset of symptoms may be abrupt, usually after an upper respiratory tract infection. Symptoms include fever, dysphagia, hoarseness and a sore throat. There may be pain on swallowing or extension of the neck. On examination a tender swelling can be felt in the area of the thyroid. The overlying skin is usually erythematous, with edema of the subcutaneous tissue that may obscure the margins of the mass. Fluctuance may be difficult to detect. Airway compression is unusual.[2, 6] When associated with a fistula, recurrences are frequent without surgical excision.[1] It is now accepted that a pyriform sinus fistula plays a role in the majority of cases of AST. The exact origin of pyriform sinus fistulae remains controversial, but most authors believe they are remnants of either the third or fourth pharyngeal pouches.[6] Other pathogenic mechanisms for AST include hematogenous and lymphogenous spread of organisms, direct trauma, complications of diagnostic puncture, invasion from adjacent structures and infection of a remnant of the thyroglossal duct.[2, 4, 6] The clinical presentation in conjunction with raised inflammatory parameters should suggest the diagnosis of acute suppurative thyroiditis, which is confirmed by imaging studies. Although several modalities are mentioned in the literature, it seems that only ultrasound and barium swallow are indicated in most cases.[6] Ultrasound adequately demonstrates intra- or extrathyroid abscesses and solid or mixed lesions of the thyroid as well as adjacent inflammatory lymph nodes.[6, 7] Barium swallow usually shows an internal fistula originating from the apex of the left pyriform sinus. This fistula may be visible only after the acute inflammation has subsided.[7] Radionuclide scans may reveal no or diminished activity in the affected area.[4] CT and magnetic resonance imaging have also been recommended.[8, 9] Needle aspiration under ultrasound guidance may confirm the presence of pus.[4] The internal opening at the apex of the pyriform fossa may be visualized by hypopharyngoscopy. Sometimes pus springs from this opening when the neck is pressed. Cannulation for localization of the fistula during dissection may be done.[8] A wide spectrum of organisms, including normal oropharyngeal flora, have been implicated in the development of AST thus emphasizing the need for culture and sensitivity testing of aspirated material and surgical specimens. Prevalent organisms include *Staphylococcus*, *Pneumococcus*, *Streptococcus* spp. and anaerobes such as *Bacteroides* and *Peptococcus*. Gram-negative organisms such as *Pseudomonas*, Enterobacteriaceae and *Haemophilus* as well as mixed bacterial cultures are also not unusual.[2, 9]

Thyroid function tests are not affected by the disease process, but the thyroglobulin level is elevated.[2] It may be difficult to differentiate AST from several other conditions such as cervical lymphadenitis, tuberculous adenitis, cellulitis, subacute thyroiditis, lipoma, acute haemorrhage in an adenoma, thyroid malignancies, Ludwig's angina, perichondritis of the laryngeal cartilage, inflamed thyroglossal duct cyst remnants, inflamed branchial cleft cyst, ectopic thyroid, cystic hygroma, lymphoma, haemangioma, metastatic malignant neoplasms and carotid body tumors.[2, 10]

Treatment consists of appropriate antibiotic therapy and surgical drainage when abscess formation occurs. Complete fistulectomy should be performed once the acute inflammation has abated.[10] Left untreated, complications such as rupture into the esophagus and trachea may arise. Infection may spread to other fascial spaces of the neck and mediastinum. Thrombosis of the internal jugular vein and external airway compression may occur.[4] Recurrence of the abscesses is likely if the fistula is not removed surgically.

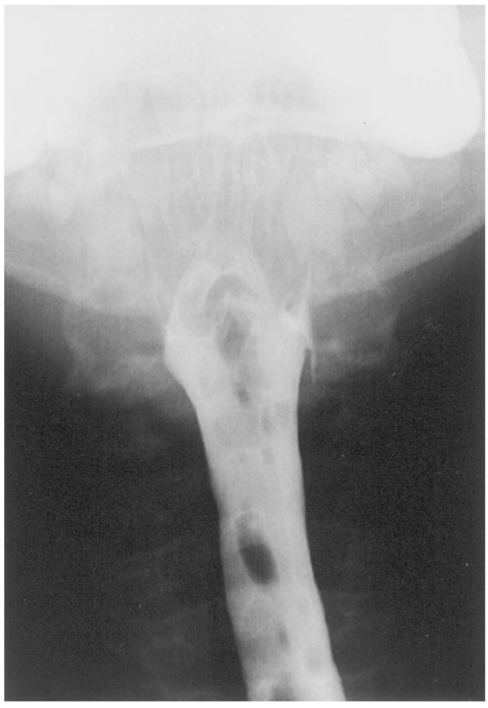

FIG. 1. During barium swallow, a small fistula extending from the left pyriform sinus downward and anteriourly is demonstrated.

Key words: Pyriform sinus, fistula, thyroiditis.

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Current Abstracts

EDITED BY ROBERT J. LEGGIADRO, M.D.

SCHOOL-BASED HEPATITIS B VACCINATIONS PROGRAMME AND ADOLESCENT MULTIPLE SCLEROSIS. A. Sadovnick and D. Scheifele. *Lancet 2000;355:549–50.*

This study from British Columbia compares the incidence of multiple sclerosis before and after a hepatitis B vaccination program was initiated in the province for children ages 11 to 12 years. From 1992 to 1998, 267 412 students completed the 3-dose vaccination series (92.3% program participation), providing a follow-up of about 966 000 person-years. This was compared with same-age children from 1986 to 1992, preceding the hepatitis B vaccinations, with 41 237 children providing a follow-up of 1.14 million person years. To identify cases of multiple sclerosis, investigators examined the medical records of British Columbia's Children's Hospital and the database of the provincial multiple sclerosis clinic and contacted all pediatric neurologists in the province. There were 9 cases of adolescent onset multiple sclerosis during the prevaccination period and 5 cases during the postvaccination period. These numbers were not statistically different. The authors also found no statistical difference between the cases of postinfectious encephalomyelitis before (29 cases) or after (31 cases) initiation of the hepatitis B vaccinations program.

Comment by Jaime E. Fergie, M.D., Corpus Christi, TX: This study confirms the absence of an association between hepatitis B vaccination and the development of adolescent onset multiple sclerosis, or the development of postinfectious encephalomyelitis. These data also support the findings of an international multidisciplinary expert panel convened by the World Health Organization after the October 1998 decision by the French government to temporarily suspend the school-based administration of hepatitis B vaccine while continuing universal infant immunization. Whenever theoretical concerns arise about the safety of the hepatitis B vaccine, the large global impact of this infection must be considered. There are more than 350 million chronic carriers of the hepatitis B virus who are at high risk for the development of cirrhosis and liver cancer (Halsey NA, et al. Pediatr Infect Dis J 1999;18:23–4). The success of the hepatitis B immunization programs in the United States is reflected in a decrease of more than 50% of acute hepatitis B cases during the past decade, from 21 102 cases reported to CDC in 1990 to 10 258 cases in 1998.

INFLUENZA VIRUS NEURAMINIDASE INHIBITORS. L. Gubareva et al. *Lancet 2000;355:827–35.*

A novel class of antiviral agents that targets influenza virus, the neuraminidase (NA) inhibitors, is reviewed. NA is a surface glycoprotein of influenza viruses that destroys receptors recognized by hemagglutinin, the surface glycoprotein that promotes attachment and fusion of the virus to cells. This action of NA allows the virus to penetrate through mucin-containing secretions and allows it to escape aggregation after budding from the cell. NA inhibitors act by binding to the active site of NA, preventing its enzymatic action such that budding viruses stay bound to receptors on the cell and viral spread is inhibited. These compounds are effective against both influenza A and B viruses, unlike amantidine and rimatidine which target the M2 protein of influenza A virus and thus are ineffective against influenza B viruses.

Two drugs have received Food and Drug Administration approval and are available for treatment of influenza. Zanamivir is a poorly bioavailable compound administered as an aerosol of the dry powder, and oseltamivir is an orally available compound marketed as a tablet. Both drugs have been proved safe, tolerable and clinically effective in the treatment or prophylaxis (not approved yet for this indication) of influenza. Side effects are minimal and resistance is slow to emerge, in stark contrast to amantidine and rimantidine.

Comment by Jon McCullers, M.D., Memphis, TN: This review is a comprehensive look at a new class of antiviral drugs, of which two are currently available and others are under study. It provides a great deal of detail but remains readable by nonspecialists. The neuraminidase inhibitors are a significant advance in the treatment of influenza virus infections. Prescribing physicians should be cautioned that efficacy depends on administration early in the course of the disease, and use of these drugs should not be allowed to delay recognition and treatment of potentially deadly late complications of influenza such as bacterial pneumonia.

Q FEVER 1985–1998: CLINICAL AND EPIDEMIOLOGIC FEATURES OF 1383 INFECTIONS. D. Raoult et al. *Medicine 2000;79:109–23.*

A retrospective analysis of 74 202 sera tested for Q fever from 1985 to 1998 at the authors' French diagnostic center, National Reference Center and World Health Organization Collaborative Center for Rickettsial Diseases, is reported. One thousand seventy cases of acute Q fever and 313 of the chronic form were recorded, respectively. Monthly distribution of cases peaked in April, May and June. Mean age was 45 years (range, 6 to 87 years) and the male:female ratio was 2.45.

Clinical forms of acute Q fever included hepatitis (40%), pneumonia and hepatitis (20%), pneumonia (17%), isolated fever (17%), meningoencephalitis (1%), myocarditis (1%), pericarditis (1%) and meningitis (0.7%). Immunosuppression was more frequently associated with pulmonary involvement and less frequently with hepatitis. Mean age was significantly lower for patients with isolated hepatitis and significantly higher for patients with isolated pulmonary involvement. The 13 patients with fatal acute Q fever were significantly older (mean age, 65 years) than other patients with Q fever. Endocarditis was diagnosed in 229 (73%) of the 313 patients with chronic Q fever. Immunodeficiency was found in 23 (11.8%) chronic Q fever patients compared with 20 (4.7%) of 427 patients with acute infection ($P = 0.001$).

Comment: This is a very nice review of "Q" for "query" fever, a zoonosis caused by the rickettsia Coxiella burnetii. *As a rickettsial infection it is somewhat unusual because mode of transmission is generally by inhalation and rash is an infrequent feature. A single serum sample enables the clinician to differentiate acute and chronic infection. Tetracycline continues to be the drug of choice, although the fluoroquinolones are highly effective in vitro.*