THE YEAR BOOK *of* MEDICINE

1969

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Kidney, Water and Electrolytes

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There are twenty YEAR BOOKS in various fields of medicine and one in dentistry. Publication of these annual volumes has been continuous since 1900. The YEAR BOOKS make available in detailed abstract form the working essence of the cream of recent international medicoscientific literature. Selection of the material is made by distinguished editors who critically review each year more than 500,000 articles published in the world's foremost journals.

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INFECTIONS

DAVID E. ROGERS, M.D.

INTRODUCTION

Some of you may recall that last year I wrote some brave words about my plans, in moving to the Dean's office, to remain a "viable" member of the professional community. While I am happy to report continuing viability of sorts, I must confess that I am hanging on to my professional competence only by my fingernails! Thus, this year I have asked my long-time colleague and friend, Dr. M. Glenn Koenig, Associate Professor of Medicine and Director of the George Hunter Laboratory, Vanderbilt University, to aid me in the selection and critique of this year's literature. His help has been invaluable—and the hours spent together in assembling the material have served to continue my education in fine fashion.

DAVID E. ROGERS

PART I

INFECTIONS

SUGGESTIVE NEW ETIOLOGIC RELATIONSHIPS

► During the past year, further evidence was accumulated pointing to the viral causation of certain diseases of unknown etiology. The following 4 articles were of particular interest. – Ed.

Isolation of Cytomegalovirus from Blood Leukocytes of a Patient with Posttransfusion Mononucleosis. Posttransfusion mononucleosis is a syndrome of fever, circulating atypical lymphocytes and splenomegaly seen in patients given a large volume of fresh blood. Its cause is unknown and the clinical course is always benign and self-limited. Keay M. Foster and Ian Jack[1] (Melbourne) attempted to isolate cytomegalovirus from a patient with posttransfusion mononucleosis.

Woman, 22, was seen at 37 weeks' gestation with a 9-day history of nausea, anorexia and occasional vomiting and a 2-day history of icterus, sore throat and fever. A stillborn child was delivered shortly after admission. Jaundice increased during labor, the patient became hypotensive and oliguric and she was deeply comatose 48 hours after delivery. Peritoneal dialysis was carried out and antibiotics and hydrocortisone were given. She did not improve despite biochemical correction of the renal failure, and a blood ammonia level of 256 μg/100 ml. was found. Pig liver perfusion resulted in slight clinical improvement and a 5-L. exchange transfusion of fresh blood produced slight further improvement. Another pig liver perfusion was helpful. A further 4 L. blood was given in the next 3 days to replace hemorrhage from the bowel. Peritoneal dialysis was continued for 2 weeks. Fever developed 5 weeks after admission and lasted 2 weeks. Eleven days after its onset, atypical lymphocytes appeared in the blood in a count of 3,200/cu. mm., with a total leukocyte count of 16,000/cu. mm. Small tender nodes were felt in the axillae and groins, and the spleen was palpable and tender. A blood film showed fragmented red cells. A direct Coombs test was positive, but it was negative a week later, when hemolysis had subsided. A Paul Bunnell test was negative, and the neutrophil alkaline phosphatase content was normal. The spleen was not palpable 3 weeks after discharge, although atypical cells were still present.

This patient received 29 units of donor blood, each of about

(1) Australasian Ann. Med. 17:135-140, May, 1968.

400 ml., and 19 of them were less than 24 hours old. When washed blood leukocytes, obtained 10 days after the onset of fever, were inoculated onto human fibroblast cells, characteristic changes of cytomegalovirus infection were seen in 6 days. No such effect was seen in an isolation attempt made 16 days after onset of fever. Attempts to isolate virus from plasma were unsuccessful. Serum taken on the first day of detection of viremia had a CF antibody titer against cytomegalovirus of 1:256; earlier specimens contained no CF antibody.

Eight of 25 donors examined had cytomegalovirus CF antibody. All but 1 of 9 additional patients with posttransfusion mononucleosis had positive CF tests, and 4 showed a significant rise in titer. The present patient is considered to have had primary cytomegalovirus infection, contracted from a blood donor or representing a reactivation of a latent infection.

A panel of donors free from cytomegalovirus would be useful for patients at high risk who require fresh blood. Donors who had neutralizing antibody several months previously could be accepted as nonviremic.

► [The possible association between cytomegalovirus infection and posttransfusion mononucleosis was reported in the 1967–1968 YEAR BOOK, p. 18. This article, as well as studies reported by Lang *et al* (New England J. Med. 278: 1147, 1968), appears to support this etiologic relationship. Possibly we should begin to screen blood donors for cytomegalovirus.–Ed.]

Interferon Production in Cell Lines Derived from Patients with Infectious Mononucleosis. Peripheral leukocytes from patients with heterophil-positive, acute infectious mononucleosis become established in continuous suspension culture. The cell lines consist of a heterogeneous population of immature lymphoid cells that synthesize immunoglobulins and display phagocytic activity. Cell-free cultures were found to contain an antiviral inhibitor which was studied by J. A. Kasel, A. T. Haase, P. R. Glade and L. N. Chessin[2] (Nat'l Inst. of Health). Cell lines cultivated in RPMI 1640 medium for at least 2 months were examined. Vesicular stomatitis virus was assayed in WI-38 cells by the plaque method and inhibitor activity was determined in chick embryo fibroblasts.

Inhibitor activity was demonstrated in each of eight cell lines derived from 5 patients with mononucleosis. Viral-inhibiting activity was detected as early as 4 weeks after the

(2) Proc. Soc. Exper. Biol. & Med. 128:351-353, June, 1968.

start of culture and it appeared about the time that cell proliferation became evident. The preparations were free from viruses, fungi, bacteria, mycoplasma and endotoxin.

The inhibitor present in the established cell suspensions is interferon. The inducer of interferon synthesis has not been identified but preliminary electron microscopic study indicates the presence of unusual 22-mμ particles in all the cell lines studied for antiviral activity.

► [This provides further evidence for the thought that heterophil-positive mononucleosis is a viral illness. As discussed in the 1968 YEAR BOOK, pp. 11-12, the relationship between EB virus and mononucleosis appears quite convincing. Other recent studies worth reviewing are:

1. Evans, A. S., *et al.*: Sero epidemiologic studies of infectious mononucleosis with EB virus, New England J. Med. 279:1122, 1968.

2. Moses, H. L., *et al.*: Infectious mononucleosis: Detection of herpes-like virus and reticular aggregates of small cytoplasmic particles in continuous lymphoid cell lines derived from peripheral blood. Proc. Nat. Acad. Sc. 60:489, 1968.—Ed.]

↓ The following 2 articles strongly suggest that subacute sclerosing panencephalitis is associated with the measles virus. During the past year, the disease has been transferred from the brain tissue of affected humans to ferrets (Katz *et al.*, New England J. Med. 279:793, 1968), and a second report of the isolation of measles virus from the brain of a patient has been made (Horta-Barbosa *et al.*, Nature, London 221:974, 1969).—Ed.

Subacute Sclerosing Panencephalitis: Spontaneous Improvement in Patient with Elevated Measles Antibody in Blood and Spinal Fluid. Jerome S. Resnick, W. King Engel and John L. Sever[3] (Nat'l Inst. of Health) describe a patient with clinically typical subacute sclerosing panencephalitis and high measles-antibody titers in serum and cerebrospinal fluid. Spontaneous improvement occurred without antiviral or immunosuppressive therapy after almost 20 months of progressive deterioration.

Boy, 15, experienced drop attacks 2-5 times daily, followed by a major motor seizure with tonic-clonic movements. Examination showed impaired mental function and frequent minor and major motor seizures. The EEG showed periodic bursts of bilateral symmetrical slow wave complexes. An air study was normal. Dilantin, Mysoline and Celontin gave little improvement in the seizures. He could not walk or feed himself and was disoriented, with sparse, slurred speech. There were frequent twitches of the mouth and jerks of the left limbs, usually in synchrony. When the seizures occurred the head and eyes turned to the right and the left arm was elevated. There was a left visual field defect and mild weakness of the left face. Tone was increased in all limbs and there was generalized hyperreflexia. The colloid gold curve was 5543321000. Viral isolation was not possible from the cerebrospinal fluid. Cerebral biopsy showed collections of mononuclear cells, patchy myelin loss, a prom-

(3) New England J. Med. 279:126-129, July 18, 1968.

inent as rocytic reaction and decreased cort al neurons. Prednisone in a daily dose of 60 mg. gave no apparent improvement.

Remarkable improvement was noted abo t 2 months after discharge, when the patient could run and feed himself, as well as read and speak clearly. Seizures were less frequent and later stopped, as did he myoclonic jerks. For 5 months he r mained free from seizures off medication and increased alertness was evident. Examination 4 years after the initial admission show d definite intellectual impairment and language difficulty, as well s residual partial left hemiparesis. The visual field defect was still present. No seizures or myoclon c phenomena were noted. Attempts at virus isolation by inoculating cerebrospinal fluid into human fibroblast and human embryo kidney cultures were negative. The EEG was markedly improved, with no periodic discharges.

Serum taken initially and tested 4 years late showed an elevated complement-fixing antibody titer against measles. High titers were found at the later time in serum and cerebrospinal fluid. Monkeys and ferrets inoculated with brain biopsy material from the patient remained well, and on autopsy they had no evidence of an abnormality rese mbling subacute sclerosing panencephal tis.

The findings in this case suggest a poss ble etiologic relationship between measles virus and the patient's illness. The prolonged elevation of measles antibody titers is of interest with respect o the occurrence of slow-virus infections in the nervous systems of animals and possibly of man.

Subacute Sclerosing Panencephalitis: Propagation of Measles Virus from Brain Biopsy in Tissue Culture is reported by Tsu Teh Chen, Itaru Watanabe, Wolfgang Zeman and John Mealey, Jr.[4] (Indiana Univ.). Subacute sclerosing panencephalitis is a disease of children and adolescents. The usual presenting signs are intellectual deterioration or convulsive disorders, followed by extrapyramidal-type motor disturbances and myoclonic jerks. The EEG shows synchronous, slow frequency, high-voltage waves. The serum and cerebrospinal fluid contain increased amounts of immunoglobulin G, often associated with M-gradients and abnormalities in the precipitation arc of γ-globulin. The electron microscopic implication of measles virus in this condition has been supported by the finding of high levels of measles antibodies in serum cerebrospinal fluid and brain tissue extracts and demonstration of intracellular measles antigen with fluorescein-labeled measles antibody. Recently, measles virus has been propagated in tissue culture The present study extends these observations.

(4) Science 163:1193-1194, Mar. 14, 1969.

Boy, 8, showed the characteristic course of subacute sclerosing panencephalitis except that he had allegedly not been exposed to measles or vaccinated against the virus. He had serum hemagglutination inhibition and complement fixation titers for measles antibodies of 1:512 and 1:64, respectively. No delayed response was seen after the intradermal injection of live or killed measles virus.

Brain tissue was obtained at right frontal craniotomy. Histologic examination revealed subacute sclerosing panencephalitis, including Cowdry type A intranuclear inclusion bodies, lymphoplasmocytic perivascular and interstitial infiltration and microglial proliferation. Rabbit antiserum to human γ-globulin produced fluorescent staining of perivascular and interstitial mononuclear cells. Electron microscopy showed intranuclear and intracytoplasmic aggregates of microtubules having a diameter of 20-22 nanometers. Minced brain tissue was incubated in 0.25% trypsin and then in medium NCTC 109 with 20% fetal calf serum. Monolayers were formed after a week of incubation, and multiple areas of lysis developed a week later in all 20 cultures, lined by multinucleated syncytial giant cells. Their nuclei contained from one to five eosinophilic inclusion bodies. Secondary cultures showed the same cytopathic effect, as did subsequent cultures, usually by the 4th day of incubation. Electron microscopy showed microtubules similar to those seen in the biopsy specimen. The inclusion bodies showed selective fluorescence when incubated with the patient's serum and with monkey antiserum to measles, as well as with the serum of another patient with subacute sclerosing panencephalitis having measles hemagglutination inhibition and complement fixation antibody titers of 1:128 and 1:1024, respectively. Isolated VERO and human embryonic kidney cells displayed a cytopathic effect after about 10 days of incubation with infected brain cells, but neither infectivity nor hemagglutination was shown in secondary cultures by transmission of the supernatant of brain cell and VERO or human kidney cell cultures. The supernatant of infected cultures produced hemagglutination of green monkey red blood cells. Subcutaneous or intraperitoneal injection of disrupted cultured VERO cells produced hindleg paralysis and hair loss in 3 of 18 gnotobiotic mice.

Free infective virus, transmissible to HeLa cells, has been obtained from the brain biopsy of the second patient with subacute sclerosing panencephalitis by mixing brain cells, cultured in the same way and fused with HeLa cells.

BASIC STUDIES ON LEUKOCYTE FUNCTION

► In recent years there has been a resurgence of interest in the phagocytic cells responsible for ingesting, containing and destroying microorganisms. We now know much more about the morphologic changes which accompany polymorphonuclear leukocyte phagocytosis. It has been shown that the cytoplasmic granules disappear, their membranes fusing with the phagocytic vacuole. The granular contents composed of hydrolytic enzymes and cationic proteins

which have specific antibacterial properties are discharged into the phagocytic vacuole during this process, and phagocytosis is associated with a dramatic burst in respiratory activity. The next 4 articles further explore some other parameters of leukocyte function under various clinical or experimental conditions.—Ed.

Infection and Nitroblue-Tetrazolium Reduction by Neutrophils: Diagnostic Aid. During natural infection an organism is phagocytosed by neutrophils. It was proposed that such challenge might induce metabolic changes in the cell sufficient to cause spontaneous in vitro reduction of nitroblue-tetrazolium (NBT) dye by an increased proportion of neutrophils. B. H. Park, S. M. Fikrig and E. M. Smithwick[5] (State Univ. of New York) tested this hypothesis using blood from healthy persons and patients with and without infection. Heparinized venous blood on a microslide was mixed with an equal part of NBT solution (0.2% NBT in physiologic saline with 0.15M phosphate-buffered saline at pH 7.2). The slide was incubated at 37 C. for 15 minutes and then kept at room temperature for another 15 minutes. The white blood cells were air-dried and counterstained with Wright's stain.

The addition of NBT dye to heparinized whole blood was sufficient for formazan formation as a large, black precipitate in the cytoplasm. Precipitates were seen in mature and juvenile neutrophils and occasionally in monocytes and

ABSOLUTE NUMBER AND PERCENTAGE OF NBT-POSITIVE NEUTROPHILS

Group	No.	Age	Mean (and range) N.B.T.-positive neutrophils per c.mm.	
			%	Absolute
Healthy controls	30	3 mo.–33 yr.	8·5 (3–10)	411 (145–720)
Rheumatoid arthritis ..	5	2–8 yr.	6·2 (4–11)	521 (325–725)
Systemic lupus erythematosus	4	7–13 yr.	5·8 (3–9)	350 (250–620)
Viral infections	37	3 mo.–17 yr.	9·5 (3–13)	265 (36–566)
Mumps encephalitis ..	8	4–12 yr.	7·8 (4–12)	382 (120–750)
Primary tuberculosis ..	11	9 mo.–10 yr.	7·2 (5–11)	285 (124–660)
Bacterial meningitis ..	19	2 mo.–4 yr.	46·6 (18–70)	5825 (2069–13,166)
C. albicans septicæmia ..	4	2–7 yr.	43·2 (25–56)	4560 (3250–6850)
Other acute bacterial infections	6	4 mo.–11 yr.	28·7 (12–35)	3890 (1115–7917)

(5) Lancet 2:532-534, Sept. 7, 1968.