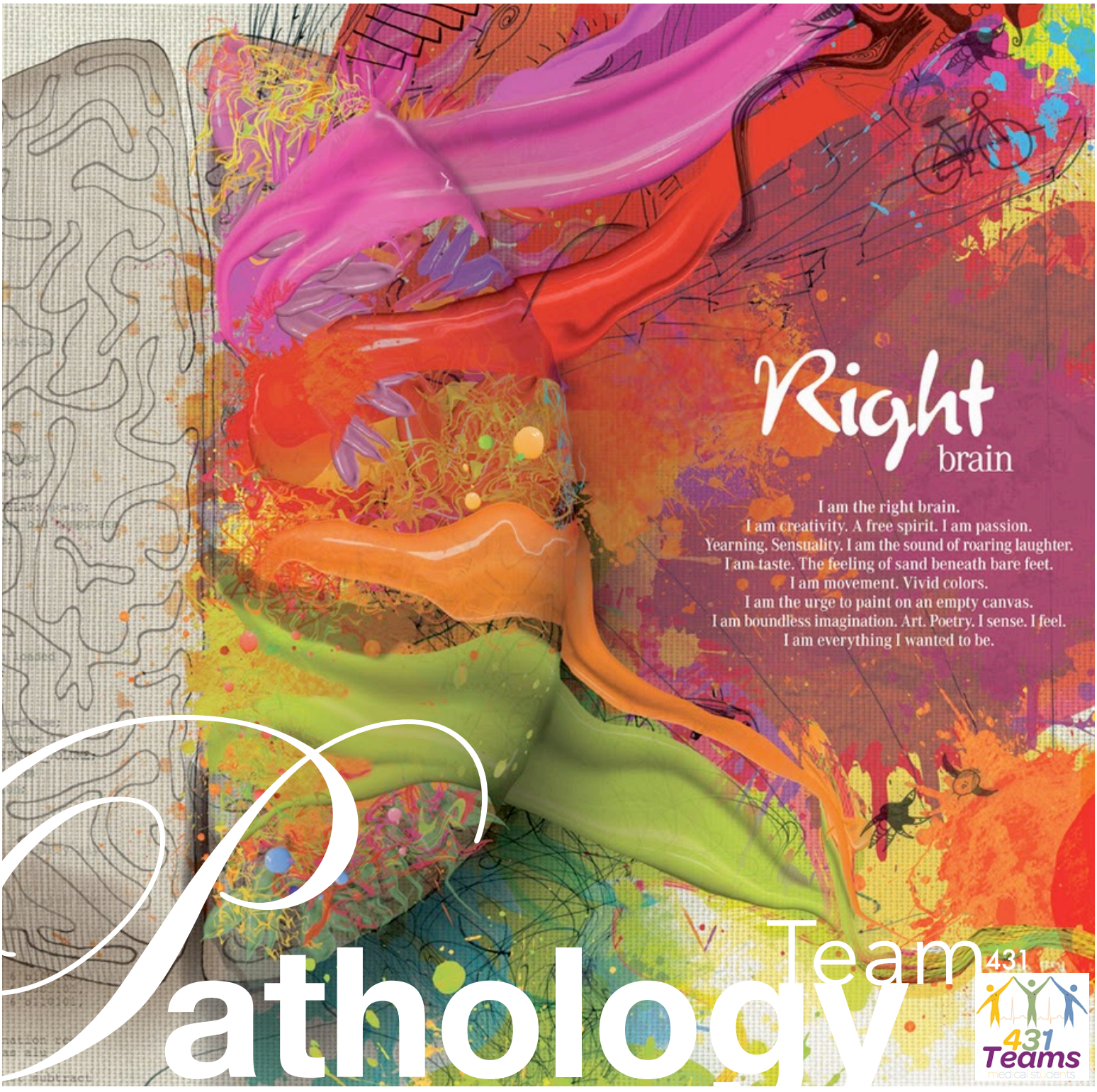

Pathology Team 431

8 / 9

CNS Block

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Objectives

Know the common types of congenital malformations of the CNS and have a basic knowledge of their pathological features.

- Correlate CNS normal development with the classification of congenital CNS malformations.

- Appreciate the role of folate deficiency as an etiological factor in neural tube defects and understand the role of Alpha feto-protein measurement and ultrasound in antenatal diagnosis of neural tube defects.

- Understand the various mechanisms that lead to the development of hydrocephalus.

- List and classify the main causes of hydrocephalus.

Key principles to be discussed:

1] CNS congenital malformation incidence and introduction to the basic concepts behind the pathogenesis. These include genetic and environmental factors and the role of the stage of gestation development.

- Definition and pathological changes in forebrain anomalies:

    - Megalencephaly, microencephaly and lissencephaly.

    - Microencphaly causes.

- Definition and pathological changes in neural tube defects:

    - Meningomyelocele, spina bifida, anencephaly and encephalocele.

    - Pathogenesis with special emphasis on the role of folate and alpha fetoproteins and their clinical significance.

- Definition and pathological changes in posterior fossa anomalies:

    - Arnold Chiari malformation.

2] Hydrocephalus:

    - Definitions of normal pressure hydrocephalus, noncommunicating hydrocephalus and communicating hydrocephalus - Pathophysiology and etiology.

Background

- The incidence of CNS malformations, giving rise to mental retardation, cerebral palsy, or neural tube defects, is estimated at 1% to 2%.

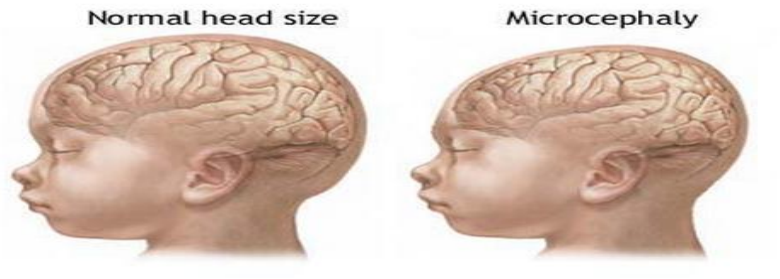
- Malformations of the brain are more common in the setting of multiple birth defects.

- Because different parts of the brain develop at different times during gestation (and afterwards), the timing of an injury will be reflected in the pattern of malformation.

- Prenatal or perinatal insults may either cause:
  - failure of normal CNS development.
  - tissue destruction.
- Although the pathogenesis and etiology of many malformations remain unknown, both **genetic** and **environmental** factors are clearly at play.
- **CNS malformation can be caused by Mutations** affecting molecules in pathways of neuronal and glial:
  - Development
  - Migration
  - connection

- Additionally, some **toxic compounds** and **infectious agents** are known to have teratogenic effects.

Forebrain Malformations



- The volume of brain may be abnormally large (*megalencephaly*) or small (*microencephaly*). Microencephaly, by far the more common of the two, is usually associated with a small head as well.

- It can occur in a wide range of clinical settings, **including**:
  1. chromosome abnormalities
  2. fetal alcohol syndrome
  3. human immunodeficiency virus 1 (HIV-1) infection acquired in utero

Microcephaly : is small skull

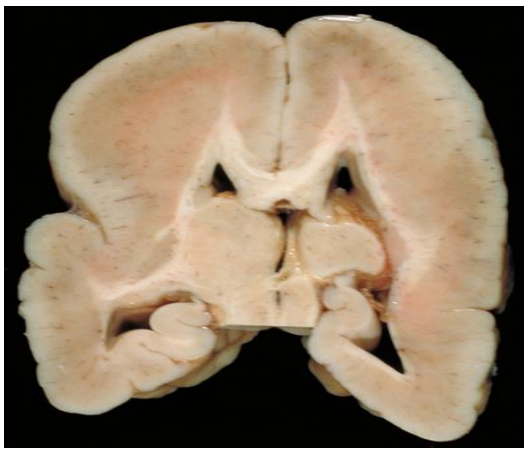
Microencephaly : is small brain

Megalencephaly : is large brain

- All causes are associated with: a decreased number of neurons destined for the cerebral cortex. Disruption of normal neuronal migration and differentiation during development can lead to a disruption of the normal gyration and six-layered neocortical architecture

Lissencephaly (agyria) or, in case of more patchy involvement, *pachygyria* is characterized by Absence of normal gyration and a smooth-surfaced brain.

1. The cortex is abnormally thickened and is usually only four-layered.
2. Single-gene defects have been identified in some cases of lissencephaly.
3. Cortical sulci are absent except, usually, for the Sylvian fissure
4. The cortex is thick and consists of the molecular and three neuronal layers
5. The deepest of these layers is also the thickest and most cellular, presumably comprised of neurons that migrated a certain distance from the ventricles but failed to reach their normal destinations
6. There is a small amount of myelinated white matter between the abnormal cortex and the ventricles



Neural tube defect

(Spina bifida)

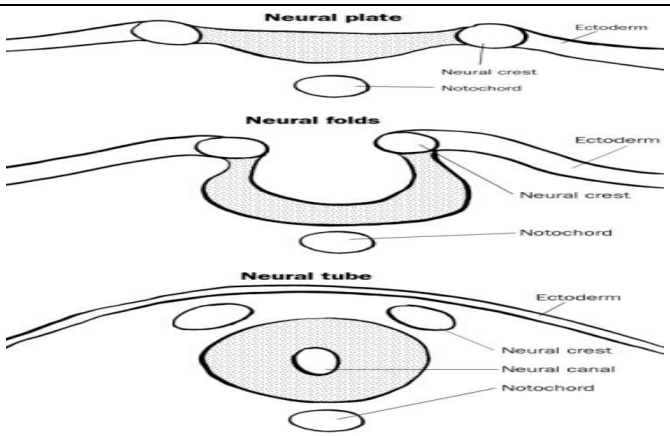
- **Normally** among the earliest stages in brain development is the formation of the neural tube:
  - the inside of it will become: the ventricular system
  - the wall of it will become: the brain and spinal cord

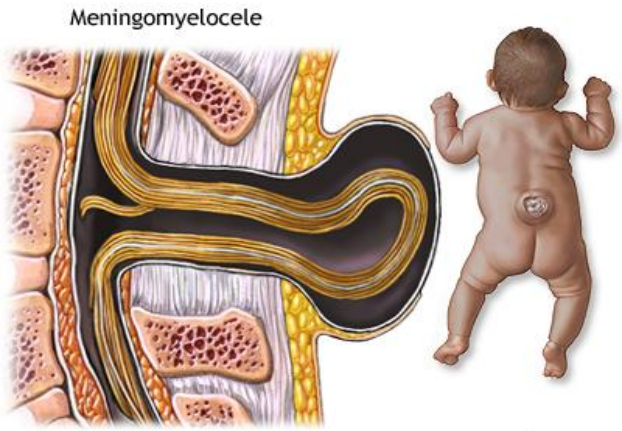
- **Mechanism:** Failure of a portion of the neural tube to close, or reopening after successful closure, may lead to one of several malformations. All are characterized by abnormalities involving some combination of:
  - neural tissue
  - menginges
  - overlying bone or soft tissues

- Collectively, neural tube defects are the most frequent CNS malformations.
- **Risk factor:** Folate deficiency during the initial weeks of gestation.
- **Reducing the risk:** prenatal vitamins are aimed.
- **Early detection:** using the combination of ultrasound and maternal screening for elevated α-fetoprotein.
- The overall recurrence risk in subsequent pregnancies is: 4% to 5%
- **Examples:**

If there is increasing of α-fetoprotein level, the baby has more risk to develop neural tube defect.

Myelomeningocele	Anencephaly	Encephalocele
- Extension of CNS tissue through a defect in the vertebral column. - Site of occurance : most commonly in the lumbosacral region. - Manifestations: patients have motor and sensory deficits in the lower extremities and problems with bowel and bladder control. - The symptoms: derive from the abnormal spinal cord in this region, and are often compounded by infections extending from thin or ulcerated overlying skin.	- A malformation of the anterior end of the neural tube, with absence of the brain and top of skull	- A diverticulum of malformed CNS tissue extending through a defect in the cranium - It most often involves the occipital region or the posterior fossa (when it occurs anteriorly, brain tissue can extend into the sinuses)



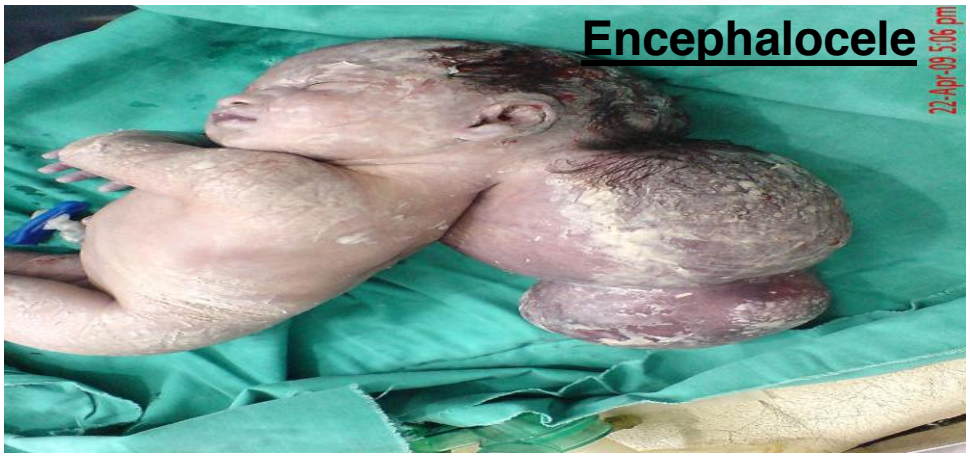


Myelo : bone(spinal cord)

Meningo: meninges

Cele : cyst

myelomeningocele



Posterior Fossa Anomalies

- The most common malformations in this region of the brain result in either misplaced or absent cerebellum
- Typically, these are associated with hydrocephalus.
- The *Arnold-Chiari malformation* (Chiari type II malformation) consists of:
    1. a small posterior fossa.
    2. a misshapen midline cerebellum.
    3. downward extension of *vermis* through the foramen magnum.
    4. Hydrocephalus.
    5. a lumbar myelomeningocele .

In the *Chiari I malformation,* low-lying cerebellar tonsils extend through the foramen magnum at the base of the skull. This can lead to obstruction of CSF flow and compression of the medulla, resulting in symptoms of headache or cranial nerve deficits. Increasing the space for the tissue through neurosurgery can alleviate the symptoms.

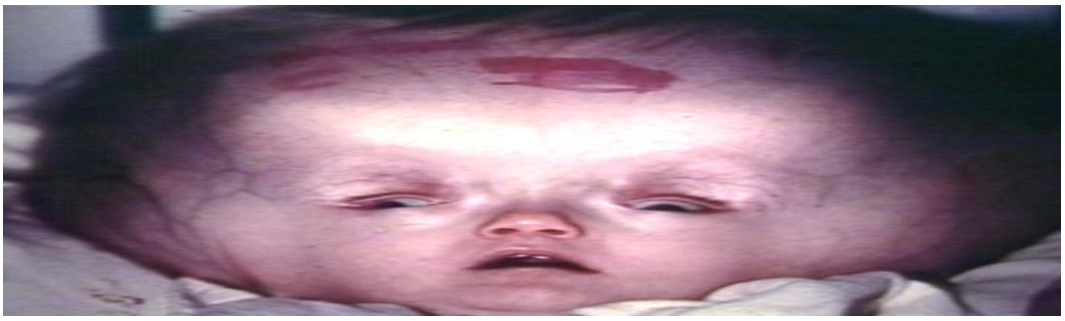
1. After the CSF being produced by the choroid plexus within the ventricles, cerebrospinal fluid (CSF) circulates through the ventricular system and exits through the foramina of Luschka and Magendie.
2. CSF fills the subarachnoid space around the brain and spinal cord, contributing to the cushioning of the nervous system within its bony confines.
3. The arachnoid granulations are responsible for the resorption of CSF.
4. The balance between CSF generation and resorption keeps the volume of this fluid stable.

Hydrocephalus

- *Hydrocephalus* refers to: the accumulation of excessive CSF within the ventricular system
- Most cases occur as: a consequence of impaired flow or impaired resorption of CSF
- in rare instances (e.g., tumors of the choroid plexus), overproduction of CSF may be responsible.

Types of hydrocephalus according to time of developing:

Before closure of the cranial sutures	After fusion of the sutures
- In infants - There is enlargement of the head	- Expansion of the ventricles and increased intracranial pressure - No change in head circumference



Types of hydrocephalus according to amount of enlargement of the ventricular system:

When there is an obstacle to the flow of CSF within the ventricular system, one of these types could develop**:**

Noncommunicating hydrocephalus	Communicating hydrocephalus
- A portion of the ventricles enlarges while the remainder does not - Most commonly seen with masses at the formamen of Monro or aqueduct of Sylvius**(cerebral aqueduct)**	- All of the ventricular system is enlarged - The cause is most often reduced resorption of CSF

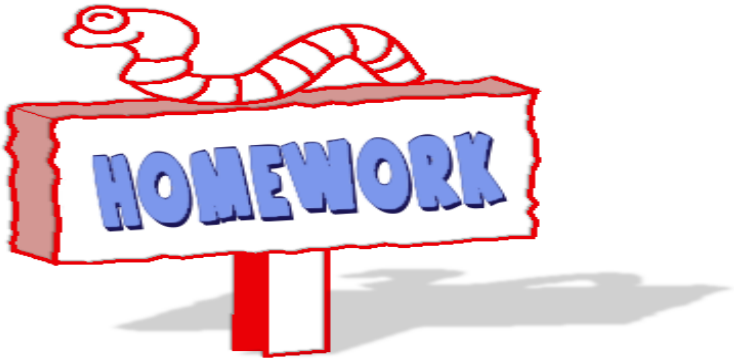
What can cause hydrocephalus?

1. **Hypersecretion of CSF**: e.g. choroid plexus tumor
2. **Obstructive hydrocephalus**
   - ✓ Obstruction of the foramina of Monro e.g. colloid cyst.
   - ✓ Obstruction of the third ventricle e.g. pilocytic astrocytoma.
   - ✓ Obstruction of the aqueduct e.g. aqueductal stenosis or atresia and posterior fossa tumors.
   - ✓ Obstruction of the foramina of Luschka or impairment of flow from the fourth ventricle (Chiari malformation, meningitis, subarachnoid hemorrhage, posterior fossa tumors).
   - ✓ Fibrosis of the subarachnoid space e.g. meningitis, subarachnoid hemorrhage, meningeal dissemination of tumors
3. **Defective filtration of CSF**: postulated for low-pressure hydrocephalus.

END OF THE LECTURE

Take home messages

- ☒ Malformations of the brain can occur because of genetic factors or external insults.
- ☒ The timing of the injury will determine the pattern of the injury, based on the type of developmental processes occurring at the point of injury.
- ☒ Patterns of malformation include alterations in the closure of the neural tube, proper formation of the separate portions of the neural tissue, and migration of neurons to the appropriate locations.
- ☒ Hydrocephalus is an increase in CSF volume within all or part of the ventricular system.



Define: meningocele ?

Meningocele: is a form of spina bifida, where the meninges of the spine protrude out of the vertebrae into a sac that appears on the back.

Define: polymicrogyria ?

Polymicogyria: is characterized by an increased number of irregularly formed gyri that result in an irregular bumpy or cobblestone – like surface these changes can be focal or widespread. The normal cortical architecture can be altered in different ways and adjacent gyri often show fusion of the superficial (molecular) layer.

What is the difference between microcephaly and microencephaly?

Microcephaly: is a rare neurological condition in which an infant's head is significantly smaller than the heads of other children of the same age and sex.

Microencephaly: is a condition when the brain itself is small.

So Microcephaly is small head and Microencephaly is small brain substance.

Define: hydrocephalus ex vacuo ?

The term hydrocephalus ex vacuo refers to dilation of the ventricular system with a compensatory increase in CSF volume secondary to a loss of brain parenchyma, as may occur after infarcts or with a degenerative disease. (It is only a descriptive term)

Summary

- Hydrocephalus is abnormal buildup of cerebrospinal fluid (CSF) in the ventricles of the brain.
- It can result from congenital and acquired etiologies.
- The fluid is often under increased pressure (but not always) and can compress and damage the brain.
- Perinatal brain injury mostly takes one of two forms:

  - Ether hemorrhage, often in the region of the germinal matrix with the risk of extension into the ventricular system,
  - or ischemic lesions, leading to periventricular leukomalacia .

Q1/ What is the most frequent CNS malformations ?

A. Neural tube defect
B. *Megalencephaly*
C. *Microencephaly*
D. *Microcephaly*

Q2/ If we found elevated α-fetoprotein level in the amniotic fluid of a child, what disease most probably the child will present with ?

A. Spina bifida
B. *Megalencephaly*
C. Hydrocephalus
D. Lissencephal

Q3/ On physical examination, a female newborn is found to have a defect in the lumbosacral region through which a segment of the spinal cord protrudes with an overlying meningeal outpouching. The mother did not receive prenatal care or routine prenatal screening. The abnormality seen in this newborn is associated with a maternal deficiency of which of the following substances?

A. Ascorbic acid.
B. Cystathionine.
C. Folic acid.
D. Vitamin A.
E. Vitamin B12.

Q4/ A triple screen for neural tube defects entails examination maternal serum for elevated levels of human chorionic gonadotropin, estriol, and which other substance?

A. Acid phosphatase.
B. Alpha-fetoprotein.
C. Carcinoembryonic antigen.
D. Chromogranin.
E. Methylmalonic acid.

Q1 / A

Q2 / A

Q3 / C

Q4 / B