Tumor Markers in the Blood

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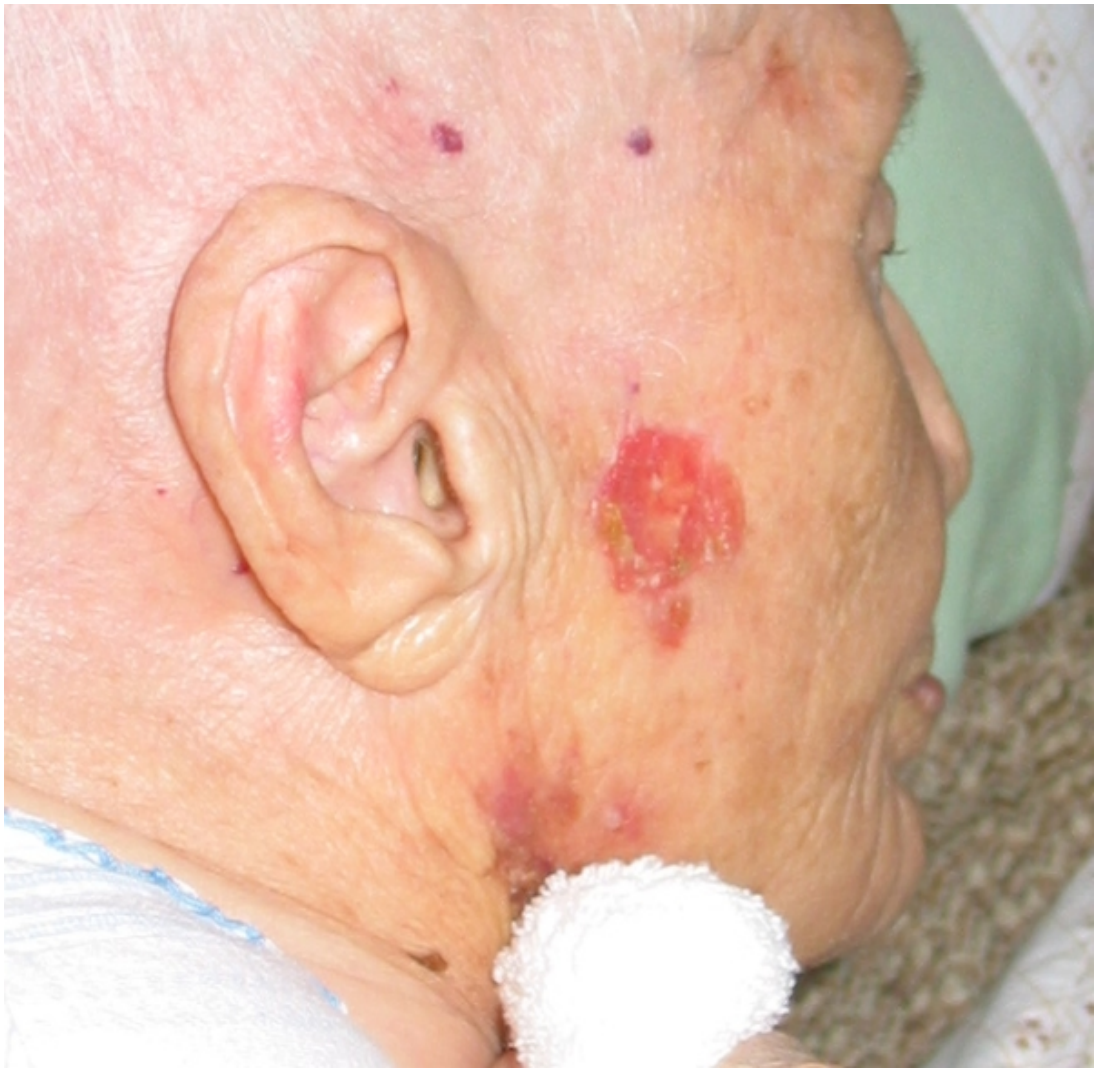
Cancer is one of the most widespread and most feared diseases in the world. Its onset is often insidious and initially proceeds without any noticeable symptoms. For treatment to be successful, an early detection is necessary. However, every year about 225,000 people worldwide lose this race against the clock. Tumor markers in the blood—are they an alarm signal of the organism? Are regular blood tests the best prophylaxis against cancer? Read more about this topic in the following article.



Definition of Tumor Markers

In medicine, the term tumor markers refers to substances or cellular changes which can provide information about the presence, development, and prognosis of malign tumors, using qualitative and quantitative analysis methods. These substances can be proteins

with carbohydrate or lipid portion, enzymes, antigens, or hormones.

Classification of tumor markers

A distinction can be made between **cellular** and **humoral tumor markers**. Cellular tumor markers are, for instance, **tumor antigens** located in the membranes, receptors for growth-promoting substances, and cell markers that indicate an increased expression of oncogenes and monoclonal cell growth. They are detected histologically from tumorous tissue that is obtained in a biopsy.

Humoral tumor markers are produced in the organism as an reaction to a tumor. These kind of substances will be detected in bodily fluids such as blood or urine in higher concentrations than would be normal under physiological conditions. Humoral tumor markers are synthesized and secreted by the tumorous tissue itself or will be released when the tumor disintegrates. To serve as a laboratory diagnostic instrument for tumor detection, there are certain criteria the ideal humoral or cellular tumor marker has to meet:

1. 100 % specificity in distinguishing healthy persons from persons who have a tumor;
2. Identifying all tumor patients; if possible, in an early stage;
3. Organ specificity, providing information about the localization of the tumor;
4. Correlation with tumor stages;
5. Indicating all changes in the patient under treatment; and
6. Prognostic conclusiveness.

Epidemiology of Malign Diseases

According to a report of German Cancer Aid, in Germany, around 500,000 people per year develop cancer, and around 224,000 people each year do not survive this disease. 1,800 children and adolescents under the age of 15 are diagnosed with cancer each year. In men, **prostate cancer** is the most common type of cancer and third most frequent cause of death. The number of new cases in Germany has been rising continually over the past years and is now estimated at 70,000.

Breast cancer is with approximately 75,000 new cases each year the most common type of cancer in women. In children under the age of 15, **leukemia** accounts for 60 % of all cancerous conditions. After cardiovascular diseases, tumors are the second most common cause of death in industrialized countries. Statistically speaking, one in three persons in the Western world suffers from a tumorous condition at least once in his or her life. For one in four persons, this type of condition becomes the cause of death.

Tumor Pathology

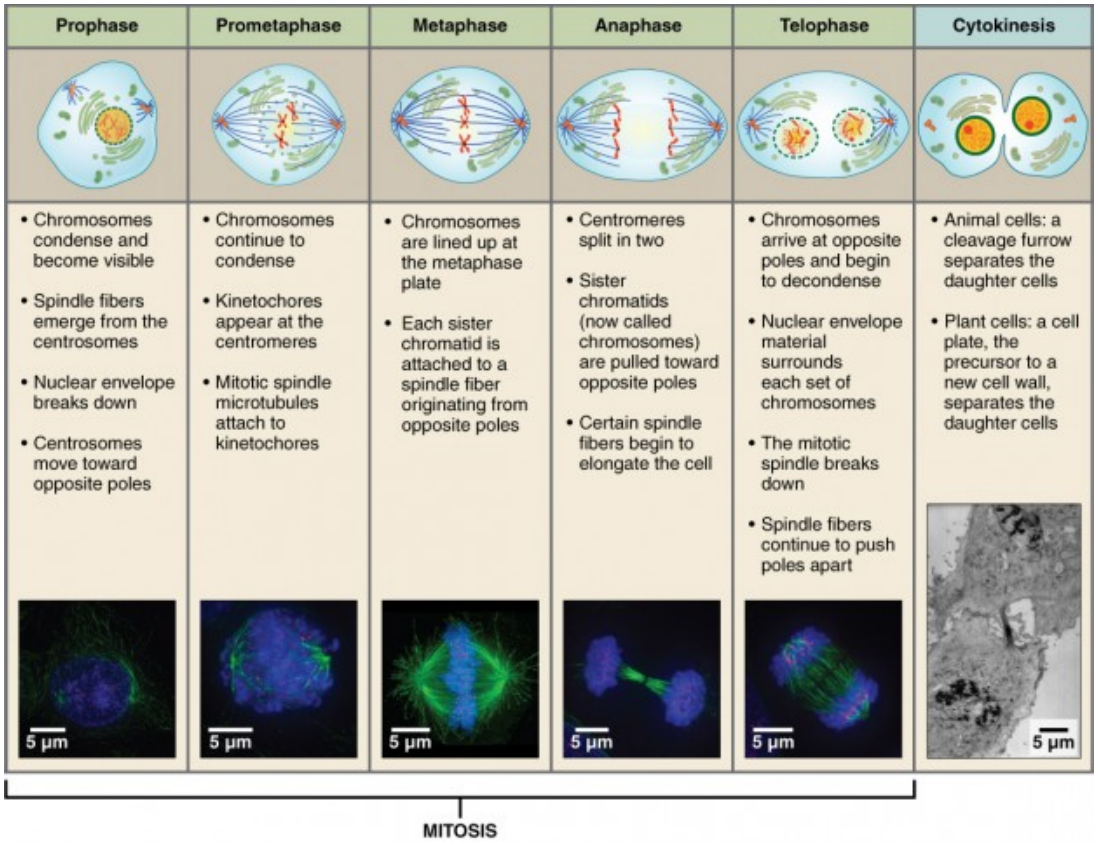


Image: “Stages of Mitosis and Cytokinesis” by philschatz. License: CC BY 4.0

Every tumor begins as a localized lesion in one single cell (**monoclonality**). Chemical, viral, and physical noxae can have **mutagenic effects** in humans and animals as well. Normal cells stop to proliferate as soon as they touch each other (**contact inhibition**). With the help of cell adhesion molecules, they attach to each other, communicate, and form a healthy tissue.

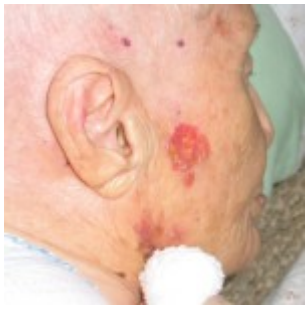


Image: “Basal Cell Carcinoma” by philschatz. License: CC BY 4.0

Tumorous cells, on the other hand, possess a mutated genome, due to the influence of the noxae. Their differentiating characteristics have changed so that the communication between the cells becomes disrupted and, among other things, their growth can no longer be controlled. They are no longer held together, thereby limiting their proliferation, and so they no longer need to remain in a cell group.

Tumor cells are characterized by their lack of a fixed location. The original cell group “grows wild”, changes its morphology, and spreads like weed.

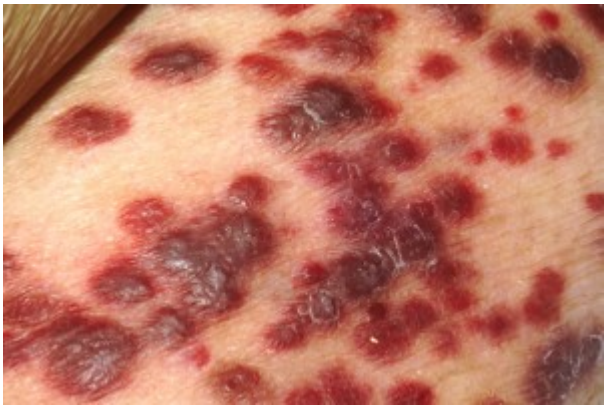
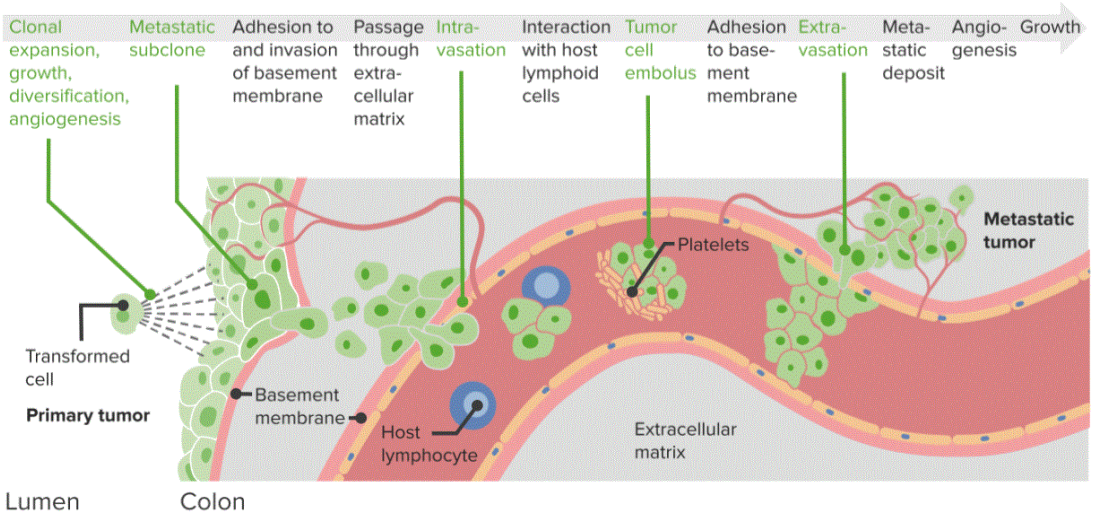


Image: “Kaposis Sacroma Lesions” by philschatz. License: CC BY 4.0

Thereby, the tumor cells practically suffocate adjacent healthy cells and sometimes even themselves. This is why cancer cells are considered to be **destructive and antisocial**. This tissue neoformation is due to an autonomous, progressive, and excessive cell proliferation, which in turn is caused by activated growth-inducing genes (**oncogenes**) and ineffective growth-inhibiting genes (**tumor suppressor genes**).

In addition, the apoptosis program shows a genetic defect. Because of the damages in the genome, the expression of regulatory genes that regulate growth has been eliminated. These uncontrolled cell divisions are also referred to as the **immortalization** of cells. Among the participating genes are the master control genes (**Hox genes**), **growth factor genes** (continuous proliferation), and the above mentioned oncogenes and suppressor genes.

In most cases, the changed tissue patterns and mutated tumor cells are not recognized by the immune system as being “strange” and will therefore not be attacked and eliminated. Defective differentiating genes have caused the tumor cells to develop false identifying marks that mislead the immune system so that it simply does not notice the mutated cells (immune evasion).



“Maligant Neoplasms” Image created by Lecturio

If the tumor cells find other tissue areas that are suitable for them outside their area of origin, they will spread into other organs. This process, called **metastasis**, is probably the most feared aspect of any tumor disease as it makes it impossible to confine the

disease to one cell area, building tumorous foci everywhere in the organism that all have to be treated at once. Cells metastasize by using the circulatory systems of the lymph or the blood. The activation of mobility factors facilitates the process of metastasis.

Note: A tumor disease is characterized by the following processes: uncontrolled growth, immortalization, no fixed localization, immune evasion, and metastasis.

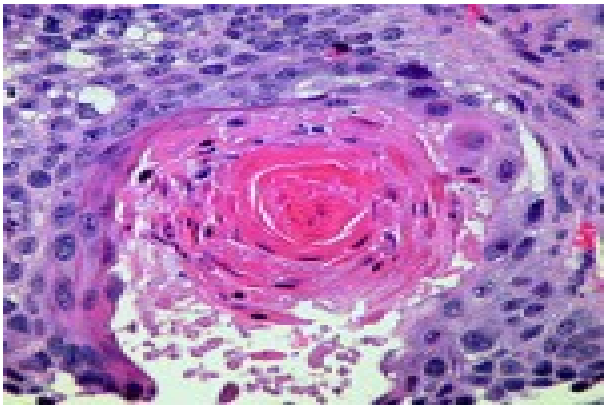


Image: " Squamous Cell Carcinoma" by philschatz. License: CC BY 4.0

Note: The term "tumor" refers to any new, uncontrolled growth of tissue. Depending on their behavior, they are classified as benign or malignant. The morphology of a tumor can histologically be examined and admits conclusions on its origin and its biological behavior.

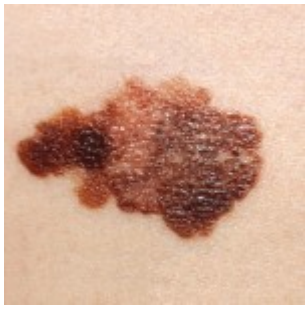


Image: "Melanoma" by philschatz. License: CC BY 4.0

Clinical Significance

Tumor markers are, however, not an appropriate method for screening for malign diseases. The following example may serve as an explanation: When cycling or palpating the prostate gland, this gland becomes activated. As a consequence, the prostate gland and the periurethral glands increase their production and secretion of the protein **PSA (prostate-specific antigen)**. An increase of PSA-levels in the blood can therefore be caused by many different processes happening in the prostate:

- An increase of size of the prostate (**hyperplasia**);
- An inflammatory change (**prostatitis**);
- Or a neoplastic change.

This shows that any signal to the cells to increase the production of PSA can lead to elevated PSA-levels, which, however, is not necessarily caused by a tumor or a malignant disease.

The above example should have shown that tumor markers cannot—with only a few exceptions—be used as a primary diagnostic tool for detecting a malign tumor. Benign tumors whose cells are multiplying may as well produce these markers without posing a dangerous health risk. On the other hand, measurements may show normal marker concentrations despite the presence of a possibly serious condition.

In sum, tumor markers are not able to give specific information on whether and in which organ there is a malign tumor growing or starting to grow. The diagnosis of tumor localization remains imprecise. Elevated concentrations in the blood may as well be the result of other processes occurring in the body and do not qualify as a primary diagnostic tool.

Note: Test results within the **reference range** do not rule out a tumor since the blood concentration of a tumor marker does not necessarily have to rise despite the presence of a tumorous growth, especially in the early stages (**lack of sensitivity**). Benign tumors also elevate the marker concentration in the blood, without being dangerous (**lack of specificity**).

Tumor diseases with their corresponding tumor markers and reference ranges

CEA	Carcino-embryonic antigen	Liver, colon, rectum, mamma, stomach, bronchial tract	3.4 µg/l
AFP	Alpha-fetoprotein	Gravidity, liver, germ cell tumor	9 IU/ml
CA 19-9	Carboanhydrate antigen 19/9 or cancer antigen 19/9	Gall bladder, pancreas, stomach, liver	≤ 37 IU/ml
CA 72-4	Cancer antigen 72-4	Stomach	≤ 4 IU/ml
CA 125	Cancer antigen 125	Ovaries	≤ 35 IU/ml
CA 15-3	Cancer antigen 15-3	Mamma, pancreas	≤ 25 IU/ml
NSE	Neurone-specific enolase	Small-celled bronchial tumor, neuroblastoma, cerebral diseases	serum: ≤ 18.3 g/l; liquor: 3 – 20 g/l
SCC	Squamous cell carcinoma antigen	Cervix, esophagus, lungs, head, mouth, throat	≤ 1.5 µg/l
CYFRA 21-1	Cytokeratin 19 fragment	Non-small-celled bronchial tumor	2 µg/l
hCG	Human chorionic gonadotropin	Gravidity, germ cell tumor, chorionic carcinoma, testis carcinoma with chorionic parts	men under the age of 45: ≤ 2 U/l; women under the age of 45: ≤ 3 U/l; both from the age of 45: ≤ 7 U/l
PSA	Prostate-specific antigen	Prostatic hyperplasia, prostate tumor, inflammatory diseases, after rectal palpatation	men under the age of 40: 1.4 µg/l; 40 – 60 years: 3.1 µg/l; 60 – 70 years: 4.1 µg/l; 70 – 120 years: 4.4 µg/l
HTG	Thyroglobulin	Thyroid, follicular and papillary	

HCT	Human calcitonin	Thyroid, medullary	
Calcitonin		C-cell tumor, medullary thyroid carcinoma	men: ≤ 18.2 ng/l; women: ≤ 11.5 ng/l
Beta-2 microglobulin		Multiple myeloma, lymphoma, leukemia	0.6 – 2.45 mg/l; elevated level in cases of limited renal functions

Evaluation of changes over time

Tumor markers provide good indications of the activity of a tumor. As a **prognostic parameter for the progression** of the disease while being treated, tumor marker levels can serve only as benchmarks and are not 100% accurate; still, they offer solid prognoses about the success of the treatment. If one of the examined marker concentrations falls below 50% of the biological halftime of the marker, this is considered a sign of **remission** (i.e., the temporary or permanent subsidence of the symptoms of the disease). This situation would occur in the post-operative phase.

A constant **tumor persistence** or further increase by more than 25% point to a stable disease. An increase of the marker concentrations after treatment and after a previous normalization of those levels points to a **relapse**, indicating further diagnostic measures.

It is crucial that tumor marker levels should not be treated as an isolated phenomenon; rather, the patient's entire condition, including all diagnostic measures, have to be taken into account. In 50 % of all tumor cases, the increase of tumor marker levels precedes diagnostic imaging. This means, a tumor can be detected first in the blood and then in, for instance, radiological images.

Note: The diagnostic accuracy of tumor marker lab tests is low. Still, they offer the opportunity of controlling the disease progression and the success of treatment without imposing any strain on the patient.

Westergren's erythrocyte sedimentation rate as a non-specific diagnostic tool

The erythrocyte sedimentation rate (ESR) is defined as the rate at which red blood cells settle out of the plasma under the conditions of gravity in blood that has been treated to be unable to coagulate. The standard method is Westergren's method, in which the height of the plasma layer above the settled red blood cells is measured in millimeters. The normal value for men is 3 – 8 mm within one hour; for women, it is 6 – 11 mm per hour.

The rate of sedimentation depends on the number of **erythrocytes (hematocrit)** and the form and aggregation of the erythrocytes. The more erythrocytes, the greater is the friction and interference between them and the slower they sink to the bottom.

Since women generally have a lower hematocrit than men (42 % vs. 47%), their ESR is accordingly higher. The erythrocytes sink at a faster pace. Furthermore, changes in the composition of the plasma protein, the temperature, or contaminations influence the ESR values, but this will not be further discussed at this point.

It is, however, of vital importance that an increase of the ESR is to be expected in the event of inflammations, immune responses, and tumors. Yet like the tumor marker

concentrations, the ESR can only serve as a non-specific exploratory test for inflammatory and malign diseases.

Note: When a tumor is present in the organism, the erythrocyte sedimentation rate in the **non-coagulating blood** will be increased.

Tumor prophylaxis and diagnostic imaging

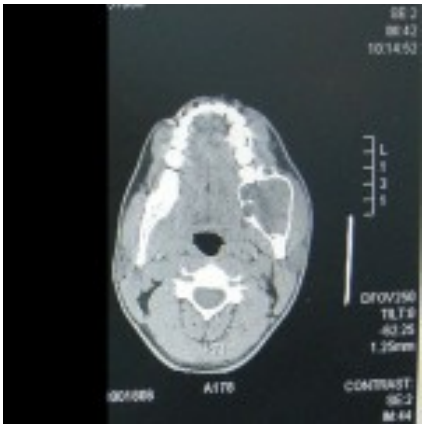


Image: “CT-Scan” by Berto1286. License: Public Domain.

In oncology, the field of cancer prevention is categorized into three stages: **primary prevention** (preventing development of the disease), **secondary prevention** (early detection or screening), and **tertiary prevention** (preventing recurrence). Imaging diagnostics can be useful in all three stages. Still, they can and should not replace the histological confirmation of a malign tumor.

In any case, the best approach is a holistic treatment that takes into account changes of tumor marker levels, diagnostic images, and biopsy results.

The diagnostic imaging starts with non-invasive procedures. Only when there is a reasonable and grounded suspicion, computed tomography (**CT**), magnetic resonance imaging (**MRI**), digital subtraction angiographies (**DSA**), and positron emission tomography (**PET**) will be taken as further steps

Popular Exam Questions on Tumor Markers

The answers are below the references.

1. Which statement is correct? Tumor markers…

A. …are, biochemically speaking, carbohydrates.
B. …only appear in malign diseases.
C. …are synthetized by cancer cells.
D. …are only detectable at the beginning of the tumor disease.
E. …are organ-specific.

2. Which statement is not correct?

A. Chemical noxae are potentially mutagenic.
B. Humoral tumor markers are tumor antigens that are located in membranes.
C. Tumor markers mostly do not qualify as a primary diagnostic tool.
D. Test results within the reference range do not rule out a tumor.

E. An increase in marker concentrations after previous therapy points to a relapse.

3. Which statement is correct?

A. In 50 % of all cases, the tumor marker increase precedes a radiological diagnosis.
B. In 25 % of all cases, the tumor marker increase precedes a radiological diagnosis.
C. In 70 % of all cases, the tumor marker increase precedes a radiological diagnosis.
D. Diagnostic imaging is only used for mamma carcinomas.
E. For tumor diagnosis, only magnetic resonance imaging is suitable.

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Correct answers: 1C, 2B, 3E

Notes