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推 薦

医学部医学科小論文問題2

注 意 事 項

1. 試験開始の合図があるまで問題冊子を開いてはいけません。
2. この問題冊子のページ数は 10 ページです。問題冊子、解答用紙（２枚）及び下書き用紙（３枚）に落丁、乱丁、印刷不鮮明などがある場合には申し出てください。
3. 解答は指定の解答用紙に記入してください。
   (1) 文字はわかりやすく、横書きで、はっきりと記入してください。
   (2) 解答の字数に制限がある場合には、それを守ってください。
   (3) 訂正、挿入の語句は余白に記入してください。
   (4) ローマ字、数字を使用するときは、ます目にとらわれなくてもかまいません。
4. 試験時間は 90 分です。
5. 解答用紙は持ち帰ってはいけません。
6. 問題冊子と下書き用紙は持ち帰ってください。

次の文章を読んで、設問 A ～ E に答えなさい。星印 (*)のついた単語には、文末に訳注があります。

One of the lesser-known atrocities* committed during World War II occurred during its waning* months. In September 1944, (A) the Germans were in retreat throughout most of the Europe. They retained, however, a stronghold* in the populous* northwestern portion of the Netherlands, which was of both strategic and symbolic importance to the fading Nazi cause*. But German control of this area was threatened by Allied Forces* approaching from the south, in support of which the exiled* Dutch government ordered a railway strike. Though the Allied Forces were stopped at Arnhem*, the Germans retaliated* for the railway strike and other hostile actions by Dutch partisans* with a food embargo*. Unfortunately, the embargo coincided with the onset of a particularly severe winter during which the canals froze over, disrupting barge* transport. Things further deteriorated* when, in response to the advance of Allied troops from the south, the retreating Germans destroyed what remained of the transportation infrastructure and flooded much of western Holland's agricultural lands.

By the end of November, the diet for most inhabitants of the major cities in western Holland, including Amsterdam, was reduced to only 1,000 calories per day, a huge drop from the 2,300 calories normally consumed by an active woman and the 2,900 calories normally consumed by active man. At the end of February 1945, rations* had dropped to 580 calories in some parts of western Holland. To augment* this meager* fare — consisting largely of bread, potatoes, and a cube of sugar — city dwellers were forced to walk many miles to the nearest farms, where they traded whatever they owned for food. Those without the means to trade were forced to eat tulip bulbs and sugar beets* as a last resort. The worst effects of the famine were largely confined to the major cities of western Holland, particularly the poor and middle class. In the rural areas of the west, farmers were self-sustaining. Eastern Holland — roughly half of the Dutch population — largely escaped the famine.

By the time the Netherlands was liberated by the Allies in May 1945, 22,000 people had died in western Holland. Death by starvation is the traditional measure of a famine's effects. But that measure, it turns out, is inadequate, for many who survived the famine were also severely affected, not least those who experienced the famine in their mothers' wombs*. This group became part of the Dutch Famine Birth Cohort* Study, a pioneering* investigation of malnutrition* that continues to this day.

The Dutch famine was unique in that its onset and end could be precisely dated. Moreover, the Dutch maintained and stored meticulous* health records for all citizens

after this period. (B) These two circumstances comprised what scientists refer to as a *natural experiment.* Clement Smith was the first person to recognize it as such. Smith, of the Harvard Medical School, was among a group of doctors from the United Kingdom and the United States who were flown into the Netherlands in May 1945, immediately after the German surrender. He saw in this tragedy an opportunity to advance our understanding of the effect of maternal* nutrition on fetal* development.

Smith obtained obstetric* records from The Hague and Rotterdam. He found that babies born during the famine weighed considerably less than those born prior to the famine. That this does not seem surprising to us now is due in no small part to Smith's groundbreaking* research efforts. Moreover, as Smith suspected, subsequent research established a strong link between low birth weight and poor neonatal* health.

Others wondered about the longer-term effects of the famine. The first long-term effect was identified, retrospectively*, in eighteen-year-old military conscripts*. Those who were in their mother's womb during the famine came of age for military service — which was compulsory for males — in the early 1960s. At induction they were given a thorough physical examination. These records were subsequently inspected by a group of scientists in the 1970s. They found that (C-1) those exposed to the famine during the second and third trimester* evidenced significantly elevated levels of obesity, roughly double the levels of those born before or after the famine.

A subsequent study, which included both males and females, focused on psychiatric* outcomes. Here again the Dutch penchant* for detailed medical records made the study possible. The investigators who mined* these data found a significant increase in the risk for schizophrenia* in those prenatally* exposed to the Dutch famine. There was also evidence of an increase in affective disorders, such as depression. Among males, there was an increase in antisocial personality disorder.

In the early 1990s, a new series of studies commenced, based on individuals identified at birth from hospital records, most notably, Wilhelmina Gasthuis Hospital in Amsterdam. The first of these studies was restricted to females and focused primarily on birth weight. The investigators again found that those exposed to the famine during the third trimester were abnormally small at birth. But they also found that (C-2) those exposed during the first trimester were larger than average, suggesting some compensatory* response, perhaps in the placenta*, to food stress early in pregnancy.

In the second study of this series, which commenced when the cohort had reached 50 years of age, both males and females were included. For the first time, investigators turned their attention to cardiovascular* and other physiological

functions. At this age, those prenatally exposed to the famine were more prone to obesity than those not exposed. Moreover, they showed a higher incidence of high blood pressure, coronary heart disease*, and type II diabetes*. When the cohort was resurveyed at the age of fifty-eight years, these health measures continued to trend adversely.

But the nature of the adverse effects of the famine on the fetus* depended largely on the timing of exposure. For instance, coronary heart disease and obesity were associated with early exposure during the first trimester. Women exposed during the first trimester also had an increased risk of breast cancer. Those exposed during the second trimester had more lung and kidney* problems. Altered glucose intolerance was most evident in those exposed during late gestation*.

By the late 1990s, several research groups were independently studying the Dutch famine cohort, studies which continue to this day. Together they provide some of the most compelling evidence for the long-term effects of the fetal environment on our health. Having documented these effects of the famine, some of the scientists involved have turned their attention to the mechanism underlying them. That is, they now seek to understand how mothers' malnutrition during pregnancy* can cause obesity or schizophrenia in their offspring when those offspring are adults.

It will come as a surprise to many that our external environment affects us through our genes, by modulating their activity. Our environment does not affect our genes directly. Rather environmental influences on our genes are mediated by changes in the cells in which our genes reside*. Different kinds of cells respond differently to the same environmental factor, whether it is social stress or food deprivation* in the womb. As such, and despite the fact that all of the cells in our body have the same genes, any environmental effect in you is cell type-specific. Your liver cells will react one way to poor nutrition, your neurons* will react in a different way, and many cell types won't react at all. Therefore, in determining any environmental influence on gene action, scientists look at specific cell populations, such as neurons in a particular part of the brain, liver cells, pancreatic* cells, and such.

The Dutch famine clearly affected many different kinds of cells in the exposed individuals, some in the brain, some in the heart, some in the liver, some in the pancreas*, and so forth. If we were to compare, say, the liver cells of those in the Dutch famine cohort with those unaffected by the famine, we are likely to find different patterns of gene activity. Some genes in the liver cells of affected individuals will be more active and some less active than in unaffected individuals. The initial goal is to identify the particular genes in these liver cells that are altered activity-wise by food deprivation in the womb. Then comes the hard work of establishing a causal* link

between these altered gene activities in the liver cells and diabetes or whatever condition we seek to explain.

The control of gene activity by a cell is called *gene regulation.* Before the advent* of epigenetics, biologists already knew a great deal about short-term gene regulation, that is, gene regulation that occurs over time spans ranging from minutes to weeks. I will refer to this short-term gene regulation as "garden-variety" gene regulation, because this is the form of gene regulation long taught in introductory biology courses. Epigenetic gene regulation is not garden-variety gene regulation. For reasons we will explore later, epigenetic gene regulation occurs over much longer intervals, sometimes spanning an entire lifetime. Epigenetic gene regulation is long-term gene regulation. It is the kind of gene regulation that is most relevant to the Dutch famine cohort.

Epigenetically regulated genes can be identified by characteristic marks in the form of particular chemical attachments. The most common sort of chemical attachment involves the methyl group*, which consists of one carbon atom bonded to three hydrogen atoms. A gene with methyl attachments is said to be *methylated**. Methylation is not an all-or-none affair; genes can be methylated to varying degrees. Generally, the more methylated a gene is, the less active it is. It is with these facts in mind that scientists have begun to look for epigenetic alterations induced by the Dutch famine. Though these are still the early days, this research has already borne fruit.

In one recent study of the Dutch famine cohort, a number of epigenetically altered genes were identified in blood cells. That is, the degree of methylation in these genes differed in those exposed to the famine compared with those who were not exposed. Of particular note were the epigenetic differences in a gene that codes for the hormone *insulin*-like growth factor 2* (IGF2), so called because it closely resembles insulin and because it promotes growth, through cell division, in a variety of cell types. (The "2" reflects the fact that it was the second of three IGF molecules to be discovered.) IGF2 is essentially a growth hormone, one that is particularly important for the growth of the fetus.

Scientists are far from being able to causally connect the epigenetic alteration in *IGF2*, the gene for IGF2, to any of the Dutch famine's diverse health impacts, such as birth weight, diabetes, and schizophrenia. For starters, they will need to determine whether similar epigenetic changes in *IGF2* can be found in other types of cells. They will then need to establish a causal link between the cell type-specific epigenetic alterations in *IGF2* and these conditions. This result is nonetheless quite significant in demonstrating that the epigenetic effects of the fetal environment can extend over six decades.

Most epigenetic attachments are removed during the production of sperm* cells and egg cells. Hence, the fertilized egg* commences development with an epigenetically clean slate*. Sometimes, though, epigenetic attachments can be passed on, along with the genes to which they are attached, to the next generation. It is noteworthy, in this regard, that the adverse effects of the famine were not confined to those who lived through it. The children of those who experienced the famine through their mother's womb are more prone to ill health later in their lives than children of mothers not exposed to the famine.

This is really quite an astounding* discovery, a nongenetic* mode of inheritance that influences our health. Scientists are increasingly aware of nongenetic inheritance of various sorts, some of which we can call true epigenetic inheritance. (D) It is far from clear, however, that this (E) grandmother effect of the Dutch famine represents true epigenetic inheritance, that is, the inheritance of methylated genes. As we will see, there are other possible explanations. To better understand whether this grandmother effect is or isn't true epigenetic inheritance, we need some background. I begin with the stuff to which epigenetic marks are attached: What, exactly, are these things we call genes? And what do they actually do?

出展: Richard C. Francis 著, Epigenetics, W. W. Norton & Company, 2012 より、一部改変

訳注

atrocities	凶悪性、極悪さ
wane	衰える、弱くなる、(月が) 欠ける
stronghold	砦、要塞、拠点
populous	人口の密集した
Nazi cause	ナチ主義
Allied Forces	連合軍
exile	国外に追放する
Arnhem	アーネム、アルンヘム (オランダのヘルダーラント州の州都)
retaliate	報復する、仕返しする
partisans	遊撃兵、パルチザン
embargo	通商禁止、禁輸
barge	はしけ、平底荷船
deteriorate	悪化させる
ration	配給量
augment	増大させる
meager	貧弱な、乏しい
sugar beet	砂糖ダイコン
womb	子宮
cohort	年齢層、コホート
pioneering	先駆的な
malnutrition	栄養不良
meticulous	細心の、注意の行き届いた
maternal	母の
fetal	胎児の
obstetric	妊娠と出産に関係ある、産科の
groundbreaking	革新的な、画期的な

neonatal	新生児の
retrospectively	遡及的に、後ろ向きに
conscripts	徴収兵
trimester	3か月間、全妊娠期間の3分の1
psychiatric	精神医学的な
penchant	強い傾向、趣味
mine	発掘する
schizophrenia	統合失調症
prenatally	出生前に、胎児期に
compensatory	代償的な（一定方向への変化傾向が、他の変化により妨害され、元の変化がわからなくなる過程を表す）
placenta	胎盤
cardiovascular	心臓血管の
coronary heart disease	冠血管（心臓に血液を送る血管）の疾患
diabetes	糖尿病
fetus	胎児
kidney	腎臓
gestation	妊娠期間
pregnancy	妊娠
reside	居住する、住む
deprivation	はく奪
neuron	神経単位、ニューロン
pancreatic	膵臓の
pancreas	膵臓
causal	原因の
advent	出現
methyl group	メチル基
methylated	メチル化された
insulin	インスリン（膵臓でできるタンパク質ホルモン）
sperm	精子

fertilized egg	受精卵
clean slate	白紙の状態で
astounding	驚異的な、びっくり仰天させるような
nongenetic	遺伝子を介さない

設問

A. 下線部(A)について、ドイツは他の2国と条約を締結し軍事的な同盟関係にあった。他の2国の名前を解答用紙 2-1 の A-(1) 欄に書きなさい。また、この戦争が行われた当時のドイツおよび他の2国の政治体制について、解答用紙 2-1 の A-(2) 欄に日本語 160 文字以内（句読点も含めて）で説明しなさい。

B. 下線部(B)について、この二つの条件を満たすデータが研究に利用できる理由を、解答用紙 2-1 の B 欄に日本語 140 文字以内（句読点も含めて）で説明しなさい。

C. 下線部(C-1)、(C-2)について、そのような現象が起こる理由として考えられることを、解答用紙 2-2 の C 欄に日本語 240 文字以内（句読点も含めて）で説明しなさい。

D. 下線部(D)について、どのようなことを明らかにするために何が不足しているか、解答用紙 2-2 の D 欄に日本語 140 文字以内（句読点も含めて）で説明しなさい。

E. 下線部(E)について、どのような場合にこの効果が現れるのか、解答用紙 2-2 の E 欄に日本語 80 文字以内（句読点も含めて）で説明しなさい。