E llen Roche was a 24 year old techni-
cian from the Johns Hopkins
Asthma and Allergy Centre who
volunteered to take part in a study
designed to provoke a mild asthma
attack in order to help doctors discover
the reflex that protects the lungs of
healthy people against asthma attacks.
After inhaling hexamethonium, a medica-
tion used for treating high blood pres-
sure in the 1950s and 60s, Ms Roche
became ill. She developed a cough and
her condition worsened over the next
week until she was put on a ventilator.
With her lung tissue breaking down, blood
pressure falling and her kidneys
beginning to fail, nothing could be done
to save her. She died on June 2, about a
month after entering the study.

The Office for Human Research
Protection (OHRP) investigated the cir-
cumstances of Ms Roche’s death and
accused the Hopkins Institutional
Review Board (IRB) of failing to take
proper precautions. It also evaluated
the human subject protection system at
Hopkins. The OHRP found that prior to
approving the study, Hopkins researcher
Dr Alkis Togias and the Institutional
Review Board failed to uncover pub-
lished literature about the toxic effects
of inhaling hexamethonium. According to
the OHRP, this information was “readily
available via routine MEDLINE and
Internet database searches, as well as
recent textbooks on pathology of the
lung”. Togias had performed a standard
PubMed search and consulted standard,
current edition, textbooks which pro-
duced four publications relating to simi-
lar studies. But these publications did
not mention the 1950s era reports of
toxicity and Togias failed to look up the
1950s medical journals. The Hopkins
review board neither requested nor
searched for additional safety data be-
yond what was provided. In a letter to
the OHRP, Hopkins officials said that the
IRB “relied on the information submit-
ted by the investigator who was known
to them as an experienced researcher”.
And in a letter to the Food and Drug
Administration, Daniel Kracov, Togias’s
attorney, claimed Togias was relying on
the Hopkins review board to guide him
on whether to seek approval from the
FDA before using the substance.

A federal investigation also found that
the study was not reviewed at a properly
convened meeting and volunteers were
not warned of the risks. The informed
consent document referred to hexam-
ethonium as a “medication” and did not
mention the fact that hexamethonium
used by inhalation was experimental.
Hexamethonium was withdrawn from
human use by the Food and Drug
Administration (FDA) in the 1970s and
had “never been approved by the FDA for
administration via inhalation”. And
finally, Togias failed to report the cough,
shortness of breath, and decreased lung
function experienced by an earlier sub-
ject in the study. Instead of doing more
research on the toxicity of the substance,
Togias decided the volunteer had caught
a cold.

In its evaluation of the human subject
protection system at Hopkins, the OHRP
found that the IRB was failing to properly
review research. Most protocols were
not individually presented or dis-
cussed at convened or properly consti-
tuted meetings. Research must be re-
viewed at a convened meeting including
at least one member whose primary con-
cerns are nonscientific areas and where a
majority of members are present. The
OHRP did not regard the executive
subcommittee review process relied on at
Johns Hopkins as “substantive and
meaningful IRB review”. The Hopkins
IRB was also criticised for not keeping
proper documentation to show attend-
ance at meetings and to show that
research was reviewed according to the
correct procedures. There were no min-
utes for 18 of the last 21 meetings of the
Hopkins IRB. The OHRP also concluded
that a lack of diversity in the current
membership of the IRB meant that it
might not promote respect for its advice
and counsel in safeguarding the rights
and welfare of human subjects as re-
quired by the regulations.

Hopkins officials responded to the
OHRP research suspension with outrage.
They claimed the action was “unwar-
ranted, unnecessary, paralyzing, and pre-
cipitous” and “an extreme example of
regulatory excess”. The university also
said that tens of thousands of people had
taken part in its medical research and
Ms Roche was the only one who had
died. On July 22, the OHRP authorised
Hopkins to resume research involving
“minimal risk” but studies in which
there is “greater than a minimal risk” to
subjects remain suspended and must be
“re-reviewed”. In order to resume
research the university was ordered to take
specific action. It had to restructure its
system for protecting subjects with an
enhanced institutional commitment to
human subject protections” and develop
a plan to make sure the ethics committee
and researchers are educated about the
requirements for protecting human
subjects.

The death of Ms Roche highlights
problems with the review of research
and the protection of subjects. There is a
problem with researchers not bothering
to properly research the literature and
assuming that everything will be avail-
able on the internet. According to Dr
Frederick Wolff, a professor emeritus at
the George Washington School of Medi-
cine, it was “foolish” and “lazy” that the
investigator and the Hopkins review
board failed to look up the 1950s medical
journal articles warning of lung damage
caused by inhaling hexamethonium.
“Anyone trained in academic medicine
knows how to do this research,” he said.
Another problem brought to light is adverse events that are not reported and not published. In a similar study using hexamethonium in 1978, two healthy volunteers suffered adverse reactions but these problems were not included in the published study because researchers conducting the experiment did not think they were related to the drug. This was one of the four studies Dr Togias used as evidence that inhaling hexamethonium was safe. “What is more, the four studies included only 20 patients and according to the report of an internal panel investigating the death at Hopkins the study should never have been approved: “Small clinical trials give uncertain estimates for even frequent adverse events, and may miss even relatively common toxicity.”

The circumstances of Ms Roche’s enrolment in the study have also been criticised. Because she was an employee at Hopkins there is a potential for coercion or consent under duress. And although Ms Roche has been described as a volunteer her name was in fact obtained from a registry of people who had participated in past studies. A doctor called her to ask if she wanted to take part.

Dr Sidney Wolfe, of the Public Citizen Health Research Group said that “if protections are flawed at esteemed places such as Hopkins, they are likely flawed elsewhere.” According to bioethicist Arthur Caplan, the United States system for protecting human subjects “is not simply sick—it is dead”. Johns Hopkins is not the culprit, he claims. It is “an indictment of our societal failure to attend seriously to a crisis that has been building for years...” Michael A Susko, president of Citizens for Responsible Care and Research (CIRCARE) argues for independent review boards made up of people not employed by the research institutions. He claims that IRBs do not provide “truly independent review” because employees “tend to have a vested interest in not running up against their employer.”

EDITOR’S NOTE
You can respond to this piece by writing an eLetter. Log on to our website (www.jmedethics.com), find this paper, click on “full text” and send your response by email by clicking on “submit a response”.

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ADDITIONAL REFERENCES

LINKS