A 71-year-old woman was admitted to the hospital due to progressive dyspnoea over the previous two weeks. Five years ago one of her breasts had been removed because of cancer and the area was irradiated. She had undergone aortic valve replacement four years earlier because of calcific aortic stenosis. A post-operative echocardiographic assessment suggested a residual pressure gradient of 40 mm Hg across the valve. On admission, a transthoracic echocardiogram showed a pressure gradient of approximately 100 mm Hg with a valve area estimated as <1 cm. A chest roentgenogram indicated a diagnosis of congestive heart failure. Laboratory values yielded haemoglobin (Hb) levels of 9.7 grams per decilitre (g/dL), a hematocrit level of 31 volume per cent, a mean cell volume of 93 femtoliters (fL), mean corpuscular haemoglobin levels of 29.1 picogram (pg), a mean corpuscular haemoglobin concentration of 31.7 g/dL, with normal leukocyte and platelet counts. The haptoglobin level was <20 mg/dl, although no paravalvular leak was observed. The ferritin concentration was 56 nanograms per millilitre (ng/mL), while the transferrin saturation was seven per cent. The serum iron concentration was 4.2 micromoles per litre of blood (µmol/L). The creatinine concentration was 0.72 milligrams per decilitre (mg/dL). The patient had anaemia and iron deficiency appeared to be present. An upper and lower endoscopy were performed and showed no bleeding sites or suspicious lesions. We found no basis for haemolysis.

On careful re-examination of the patient, we observed a single, raised, reddish lesion on the patient’s left internal buccal area as well as on one of her fingers. A review of her family history indicated that the patient’s father had similar skin lesions that were occasionally prone to rupture. Our patient had two daughters and both had recurrent nosebleeds. A more careful abdominal examination disclosed a systolic murmur that was audible in the upper abdomen. We reviewed the Curacao criteria for hemorrhagic hereditary telangiectasia (HHT, also known as Osler-Weber-Rendu syndrome): epistaxis, telangiectasia, visceral malformations and a positive family history of the disease. To clarify the abdominal bruit, we performed a computed tomography (CT) angiogram of her viscera (Figures 1A and 1B).
issues, insurance consequences and other concerns are
last 20 years and could again in the next. Invasion of privacy
Genetic diagnostic tests have changed dramatically in the
them to decide at a later date what should be done.
Genetic testing provided the surgeons, who
were faced with replacing the patient's aortic valve, with
detailed information about the challenge they faced. The
patient was satisfied with a diagnosis of a rare genetic
disease, the cause of which was now known. The
physicians and students established a genetic disease
down to the last base pair; showing the value of taking a
detailed history and performing a physical examination,
as well as looking to molecular biology for the answers.
There were however some negative consequences to
the decision to perform genetic testing: the body
responsible for the financial implications refused to pay the
€4,000 sequencing bill even though a disease-
relevant mutation was found. Our university public
hospital was forced to pay the cost and we received
official reprimands for our decision.

LITERATURE REVIEW

The terms ‘gene tests and diagnosis-related groups’ resulted in 198 entries. In the most recent paper, Antonanzas et al studied the economic relevance of genetic testing in the European Union.1 They conducted a systematic literature review and found approximately 3,500 papers relevant to their topic. The most studied
diseases were cystic fibrosis, breast and ovarian cancer,
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cancer and thrombophilia. Genetic tests were mostly
used for screening purposes and cost-effectiveness
analysis is the most common type of economic study.
There appear to be few studies examining medical
students’ attitudes or concerns raised by other
healthcare professionals.7 Physicians will continue to be
required to incorporate new genetic findings into
patient care, which will hopefully improve because
therapy will be tailor-made for both the disease and the
patient. Improved patient care should be a primary goal
for any national healthcare system, and the challenge
now is to ensure that budgets are allocated for this type
of testing. We wonder what Sir William would have done
under the circumstances. Would he have been satisfied
with a 99% positive result or would he have continued to
investigate? Although eclectic, Osler was a stickler for
clinical exactness. We doubt he would have been intimidated
by gaining approval for the cost of establishing a DNA
sequence. We believe he would have put the patient and the
aim of a detailed diagnosis, as well as the potential learning
experience for physicians, first.

DISCUSSION

Based on the clinical evidence, we believed that our
patient had HHT and that the next stage was to establish
a genetic diagnosis. However, Shovlin et al.3 state that ‘for
patients with definite clinical HHT, molecular testing is
not required to establish the diagnosis’. They suggested
that a clinically obvious case does not require genetic
analysis, except when a mutation is suspected in the
SMAD4 gene; how this rare possibility is to be confirmed
clinically is less clear. Shovlin also discussed the different
types of screening:8 when there is a benefit and no harm,
when there is a benefit but possible harm, when there is
no benefit to screening, but no harm, when there is no
benefit and possible harm. In our case we established
that screening would cause no harm but would have no
benefits for the patient; the only benefit might be for
subsequent grandchildren. We believed that our students
on the other hand would benefit by making the
association between this patient’s test results and the
precise pathophysiology of her condition. However,
directing them to a textbook or to the Internet may
have achieved the same result. On making our final
decision to undertake expensive genetic testing, we
relied on Sir William Osler’s belief that: ‘To study the
phenomenon of disease without books is to sail an
uncharted sea, while to study books without patients is
to not go to sea at all.’4 We discussed the screening
options with our patient; the gene test would have little
consequence for her and her children, but there might
be some benefits for her grandchildren, although this
could not be guaranteed. The patient agreed to genetic
testing. We could have taken her blood for DNA storage
on behalf of her future family members and allowed
them to decide at a later date what should be done.
Genetic diagnostic tests have changed dramatically in the
last 20 years and could again in the next. Invasion of privacy
issues, insurance consequences and other concerns are
reiterated elsewhere by Becker et al.2 Physicians and
students caring for this patient examined her endoglin
levels, the activin receptor-like kinase (ALK1) levels and
her SMAD4 genes. They investigated the transforming
growth factor beta (TGF-β) signalling pathway in order
to establish how this mutation worked in their patient, a
woman with multiple medical problems, undiagnosed for
so long. We elected to sequence the genes in question
and identified a previously known ALK1 (ACVRL1) mutation. Genetic testing provided the surgeons, who
were faced with replacing the patient’s aortic valve, with
detailed information about the challenge they faced. The
patient was satisfied with a diagnosis of a rare genetic
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CONCLUSIONS

We believe that cost constraints inhibit ‘Oslerian’ teaching to the detriment of patient care. For our patient, the clinical diagnosis of her genetic disease was delayed for seven decades. However, the diagnosis was apparent and could have been made with a stethoscope and a flashlight. We performed a gene test that elucidated a signal transduction pathway that is highly relevant for the understanding of angiogenesis by medical students. However, the healthcare system will not defray the costs for these diagnoses, which interferes with our teaching obligations. We are curious how William Osler would have reacted to this issue and regret that we cannot ask him.

Postscript

Since preparing this report (2011), the topic has become largely irrelevant due to the dramatic reduction in sequencing costs. Currently, the total human genome can be sequenced for US$5,000 (we paid almost that much) and the costs are predicted to approach US$1,000 in the near future.1 We could have had the other 20,000 genes and everything in between for approximately the same price. The more complex area now is what genomic medicine will do for our patients, but that remains to be seen.

REFERENCES