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The correspondence columns are an important feature of the SAMJ. *Letters are often shortened and, as with all text received, subject to sub-editing to make them more reader-friendly. In the correspondence concerning Mikulicz-Radecki, we erred in inadvertently printing an explanatory covering letter to the Editor and not the correct response, hence the author's correction.* — Ed.

To the Editor: The article by J Kowalczyk on the biography of Professor Jan Mikulicz-Radecki[1] made us analyse this subject and we decided to compare it with our knowledge. In the years 1882 - 1887 Mikulicz-Radecki became a Director and Professor of Surgery at Jagiellonian University in Kraków, Poland. In 1887 he became Director of the Clinic and Professor of Surgery in Königsberg and afterwards in Wroclaw (Breslau). Presumably Jan Mikulicz-Radecki belonged to both cultures and nationalities: he was Polish by family origin and native language, and German by his study and work in Vienna, Königsberg and Wroclaw, as well as by his marriage to Henrietta Pacher.

Mikulicz-Radecki was of course a famous surgeon, but we would like to remind readers of his contribution to the development of otorhinolaryngology. One of this earliest articles was on scleroma and epidermoid cyst — one of the first descriptions of cholesteatoma.[2] In 1883 Mikulicz-Radecki gave a method of radical resection of the tonsil carcinoma by lateral pharyngotomy. He had led the section of the neck along the margin of the sternocleidomastoid muscle, and subsequently cut chewing muscles and resected the mandible body. In this way he exposed the lateral wall of the pharynx and the whole operation was done without opening the oral cavity and pharynx.[3] In 1886 he was the first to open the maxillary sinus from the medial nasal meatus and to evacuate empyema from the maxillary sinus. During his work in Kraków and Wroclaw he constructed the skolizoymeter and more frequently used Mikulicz's compressorium and devices for intrathoracic operations. He was the first to undertake an operation in a large hypobaric chamber on a patient with neoplasm of the upper part of the oesophagus.[4] He published several articles on the aseptics of surgical procedures and was a devotee of iodoform usage. In 1892 Mikulicz-Radecki published work in which he paid attention to disease with symmetrical, bilateral oedema and enlargement of the salivary and lacrimal glands, and to microscopic examination of lymphocyte infiltrations. Later works described these symptoms as Mikulicz-Radecki syndrome. In 1893 in Wroclaw Mikulicz-Radecki implanted a glass faser wick from the ventricle through the subarachnoid space to the galea, which was simultaneously the first ventriculostomy and the first extrathecal shunt.[5]

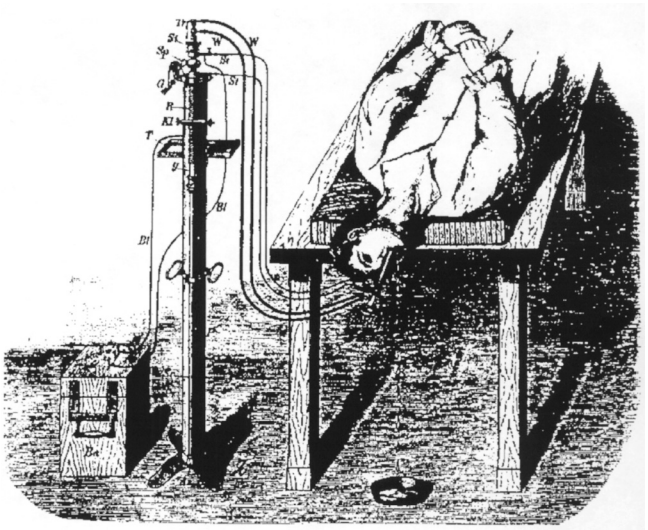

Fig. 1. Oesophagoscopy technique according to Mikulicz-Radecki (from Mikulicz J. Ueber Gastroskopie und Oesophagoskopie. Wien Med Presse *1881; **45:** 1405-1408).*

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The possibilities of hormone replacement therapy started at the critical time

To the Editor: In 'Hormone replacement therapy — finally, good data',[1] Rosenberg and Hoffman disagree with two recent articles in the *SAMJ*[2,3] as well as with Herrington *et al*.[4] in the Estrogen Replacement and Atherosclerosis (ERA) study who state 'Another possible explanation for our results are that estrogen is more effective in preventing atherosclerosis than in slowing the progression of the disease once it is established.'

To justify the idea that HRT is not protective against heart disease one of the three studies quoted[1] is the Herrington ERA

study[4] in which women (average age 65.8 years) with angiographically verified coronary disease showed no reduction in atherosclerosis but also no increase in clinical cardiovascular disease.

It is agreed that randomised trials are the gold standard.[1] They must, however, not be generalised to a population they were not designed to study. Possible cardiovascular benefits of HRT requires cardiovascularly healthy women with no atherosclerosis within 5 - 10 years of the menopause[3] before downregulation of oestrogen receptors. This may also apply to Alzheimer's disease and dementia[2] as demonstrated in the Cache County study[5] and the study by Resnick *et al*.[6]

This excludes the ERA study[4] and a secondary prevention study, viz. the Heart and Estrogen/Progestin Study (HERS).[7] The third study quoted is the Women's Health Initiative (WHI)[8] which by design limited the intake of symptomatic women in the early years of the menopause. Statistics from the follow-up[9] show the hazard ratio (HR) of coronary heart disease (CHD) in the first 10 years since the menopause to be 0.86 but not statistically significant by 95% confidence interval (CI). But then neither was the HR for CHD in the entire cohort (HR 1.29, adjusted CI: 0.85 - 1.97).

Criticism of the statistics in the WHI is ongoing,[3] with Shapiro and Tucker[10] having differing views.

Was the WHI Data and Safety Monitoring Board biased in stopping the WHI trial mainly on the basis of breast cancer harm? At baseline over 25% of the women were previous HRT users, with about 12% of these women using HRT for more than 10 years before the start of the WHI trial and about 6% being current users. Exclusion of this group decreases the HR from 1.26 to 1.06.

Is it biased to compare HRT users who had started HRT prior to the commencement of the trial with placebo (average duration 5.2 years) and then to suggest that breast cancers are more advanced in the HRT group?[11] The follow-up article does not give a breakdown on previous versus no previous HRT use.[11]

To support their argument Rosenberg and Hoffman[1] also use a pooled meta-analysis[12] of 22 small (total 4 124), short-duration (3 months - 3 years) trials of HRT use in mostly young women where cardiovascular disease was a secondary endpoint and had an odds ratio of 1.39 (CI: 0.48 - 3.59). Rosenberg and Hoffman[1] don't mention that this pooled analysis showed that the rate of breast cancer was lower in the hormone group.[12]

Also not mentioned was a meta-analysis of 22 studies by Barrett-Connor *et al*.[13] up to 1997 which showed a relative risk (RR) of 0.7 (CI: 0.65 - 0.75) for cardiovascular events in 'ever-users' of mainly unopposed oestrogens over 'never-users'. In 7 studies using opposed oestrogen, mainly medroxyprogesterone acetate, the RR was 0.66 (CI: 0.53 - 0.84). Is one of the oestrogens used in the Million Women Study (MWS)[14] ethinyl oestradiol, as suggested in Fig. 3? It has not been used for HRT for many years. This trial differs from most other studies on breast cancer, including the WHI.

Is it statistically correct, as in the MWS, to exclude women with a history of breast cancer at baseline, total number unknown, who had registered before recruitment? There were 485 breast cancer deaths reported in this excluded group, with only 3% using HRT.[14] As incident breast cancers were diagnosed on average 1.2 years after recruitment and because breast cancer generally requires several years (7 - 10) to grow to a clinically or radiologically detectable size,[15] it makes biological as well as epidemiological sense to include this group in the final analysis despite counter-suggestions by the collaborators. There were 637 breast cancer deaths included in the study summary and 517 in Fig. 6. Current users of HRT at baseline had a RR of breast cancer of 1.22, which according to the collaborators is of 'borderline significance'.[14] What would the RR be if the excluded group was included?

Another MWS media headline 'Oestrogen-progestogen increases incident invasive breast cancer in year one' is due to a statistical variation used by the collaborators, and if worked out in the same way as the WHI and most other trials, i.e. number of breast cancers in the whole cohort taking HRT for that year(s) and not just women using HRT in that year(s) only as done in the MWS, the RR for less than 1 year is < 0.10, for 1 - 4 years 0.61, for 5 - 9 years 1.43, and for more than 10 years 2.08 — and not 1.45, 1.74, 2.17 and 2.31 as suggested by the collaborators.[14]

Another statistic not in agreement with previously held views is the RR of invasive breast cancer according to menopausal status among never-users of HRT:[14] premenopausal women 1.00, perimenopausal women 0.75 (CI: 0.68 - 0.82) and postmenopausal women 0.63 (CI: 0.58 - 6.8).

No trial has previously shown tibolone (Livifem) to increase the risk of breast cancer, but in the MWS the RR is 1.45 (CI: 1.25 - 1.68) based on 184 cases, and 1.48 (1.20 - 1.83) based on 88 incident breast cancer patients who used tibolone exclusively.

A suggestion is that it is because of preferential prescribing of tibolone for high-risk breast cancer women. Incident breast cancer was diagnosed in tibilone and HRT users on average 1 - 2 years after recruitment, suggesting the presence of cancer at recruitment.

Tibolone and its metabolites are selective oestrogen enzyme modulators (SEEM) and inhibit sulfatase and 17B-hydroxy-steroid dehydrogenase in hormone-dependent breast cancer cells as well as increasing sulfotransferase activity. Biologically, therefore, it should decrease and not increase breast cancer risk.

What is required is a randomised case-controlled trial on a population that may benefit from HRT, which may be women in the first 5 - 10 years of the menopause, and assessment of contraindications from this and previous trials.

Possibly the results of the WHI would have been very different if the contraindications to the HRT suggested[3] had been used.

The International Menopause Society Workshop position statement of HRT (Vienna, December 2003) will be published soon and will constitute an unbiased opinion by the world's experts.

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Rosenberg and Hoffman reply: Dr Cheifitz criticises various aspects of the Women's Health Initiative (WHI) (a randomised controlled trial)[1] and of the Million Women Study (an observational study).[2] Both indicate that combined oestrogen/progestin therapy (HRT) increases the risk of breast cancer. Rather than respond to each of Dr Cheifitz's comments, we note that the weight of evidence that HRT causes breast cancer is appreciable and comes from numerous studies, many of excellent quality and with large sample sizes.[3] Moreover, the randomised trial data and observational data are in agreement.

As for coronary heart disease (CHD), the randomised trials indicate that HRT does not protect against CHD in healthy women,[1] recurrent CHD,[4] or progression of atherosclerosis.[5] Indeed, the WHI and HERS trials suggest that risk of CHD is increased acutely within a year or so after the beginning of HRT use (which suggests a prothrombotic mechanism, which may also account for the increases in deep-vein thrombosis and stroke in HRT users). Dr Cheifitz argues that the results of these randomised trials on CHD should not be generalised to a population that they were not designed to study, i.e. healthy women with no atherosclerosis who are within 5 - 10 years of their menopause. He suggests that what is required is a randomised controlled trial of HRT and CHD in such a population. However, in a trial among younger women, the increased risk of breast cancer would come at a younger age than the putative benefits against CHD, osteoporotic fractures, and Alzheimer's disease.[1,6-9] Therefore, if such a trial were found to be ethical and feasible among younger women, it would probably be stopped early because of an excess of risk over benefit.

In our commentary we stated our belief that it is unjustified to increase the risk of breast cancer, stroke, deep-vein thrombosis and other serious diseases in healthy women in order to decrease their risk of other illnesses.[10] It is even more unjustified when the risks come at an earlier age than the proposed benefits, and when there are other proven safer ways of disease prevention.

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