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Review article

100 years of iodine testing of the cervix: A critical review and implications for the future

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ABSTRACT

Objectives: We aim to describe the history of iodine testing of the cervix and identify areas where further work is required.
Study design: We conducted a search of PubMed and Google Scholar. Full article texts were reviewed. Reference lists were screened for additional articles and books. 37 basic articles in journals including ones written in German and three basic articles in books were identified.
Results: Glycogen staining of the ectocervical squamous epithelium with iodine goes back to Paul Ehrlich (1854–1915). Walter Schiller (1887–1960) examined nearly 200 different dyes and found that vital staining of the cervical squamous epithelium was best achieved with Lugol's iodine solution, which was indicated by Jean Guillaume Lugol (1786–1851) for disinfection of the vagina. In 1928 W. Lahm observed that the glycogen content of a squamous epithelium cell decreases as anaplasia increases. From the outset, H. Hinselmann included the iodine test in the minimum requirements for colposcopy. In 1946 H. J. Wespi first mentioned the finding of an "*uncharacteristic iodine negative area.*" The first international colposcopic terminology from Graz in 1975 lists the "*iodine light area*" among the different colposcopy findings. The IFCPC nomenclatures from Rome 1990, Barcelona 2002, and Rio de Janeiro 2011 have evaluated the iodine test and classified their findings differently. A breakthrough to effective cervical cancer screening in resource-limited settings in Africa, India, and Latin America was achieved with R. Sankaranarayanan's publication on naked-eye visual inspection of the cervix after application of Lugol's iodine.
Conclusions: This paper is a step toward a better understanding of what we think and do today with iodine testing and what problems and upcoming tasks will arise in future.
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Contents

Introduction

Today standard colposcopy without iodine testing misses up to 40 % of prevalent precancers, which is a poor level of sensitivity [1]. Furthermore, the iodine test is no longer applied in many places or only selectively applied in the event of ambiguous findings or as

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part of excisional treatments [2]. Only in a few countries is its result still equal to that of the acetic acid test and the inspection of blood vessels in the colposcopic finding [3]. Forgoing the iodine test in the determination of the ectocervical resection line in conizations and the currently common practice of only removing *major changes* following an acetic acid test are associated with an increased rate of conizations *non in sano* and thus substantial undertreatment [4,5]. This is the opposite of what was initially intended when colposcopy was introduced. In the beginning, the iodine test was an integral component of every colposcopic examination and an important aid in excising cervical precancers *in sano*. In 1954 H. Hinselmann wrote in his atlas and textbook: "Indeed, it must still be considered that in addition to the samples, we conduct an iodine test, for which we have Walter Schiller to thank." Further: "During the operation, Schiller's iodine solution should always be available in order to ensure that no area is missed" [6].

We aim to provide a general picture of the iodine test from its beginnings up to the present, discuss points of view that are open to debate, and make suggestions for improvements in future terminology.

Study design

We conducted a search of PubMed and Google Scholar. Full article texts were reviewed. Reference lists were screened for additional articles and books. In this review, the authors refer to H. Hinselmann's name for a factual description of his contributions to our specific field of interest. The aim was not to assess the ethical concerns surrounding his research. We only searched for articles and abstracts published in English and German.

Results

37 basic articles in journals including ones written in German and 3 basic articles in books were identified. The following topics are highlighted and discussed: Walter Schiller and the history of iodine testing, iodine testing in colposcopic terminologies, scientific evidence, problems, upcoming tasks, and progress.

Discussion

Walter Schiller and the history of iodine testing

In 1954 Hans Hinselmann put forward the requirement that every woman over the age of 30 who has given birth should receive a colposcopic examination including an iodine test every one to two years in order to prevent cervical carcinoma [6]. It became clear early on that contrary to original hopes, the iodine test is only a method for searching for changes in the ectocervix that may be (pre)cancerous. Definitive histological diagnosis with all its therapeutic consequences should involve cell removal or sample excision [7,8]. Adopted by H. Hinselmann, the Schiller iodine test spread with colposcopy through his students (*Mestwerdt, Ganse, Limburg, Wespi, Glatthaar*), starting in the German-speaking countries and reaching Scandiavia (*Kolstad*), France (*Palmer, Funck-Brentano, de Watteville, Bret, Coupez*), Italy (*Masciotta, Cattaneo*) and Spain (*Martinez de la Riva, Dexeus*). *Hinselmann* himself ultimately brought it to Latin America (*Rieper, Jürgens, Jakob, De Morales in Argentina and Brazil as well as Santiago-Pineda* in Mexico).

In contrast to the relatively rapid spread of colposcopy in Europe and South America before and above all after World War II, colposcopy (including iodine testing) was accepted rather reluctantly in the English-speaking countries and especially in the United States after an initial period of enthusiasm. Proponents of colposcopy in the United States, for example *Adolf Stafl* (1931–2020), emphasized that iodine testing did little or nothing at all for colposcopy. One reason for its delayed acceptance in the English-speaking countries appears to be the difficulty in applying Hinselmann's nomenclature, which was unwieldy and not founded in histopathology. Furthermore, colposcopy was viewed as a method in competition with cytology, which was easier to practice; the latter had been introduced primarily in the U.S. by Papanicolaou, Traut, and Ayre for early detection of cervical carcinoma [9]. It was not until 1963 that a society for colposcopy was established in the U. S. 1971 was the year in which the British Colposcopy Group was founded. Since 1958, only the Australian colposcopy group under the direction of Malcolm Coppleson (1927–2017) and Richard Reid (1944) has dedicated itself to this discipline without any reservations [10].

Walter Schiller (Fig. 1) was born in Vienna on December 3, 1887. During his medical studies at the University of Vienna, he worked as a demonstrator at the Institute of Physiology under *Siegmund Exner von Ewarten* (1846–1926, known for the Call-Exner bodies in granulosa cell tumors named after him) and at the Institute of Pathological Anatomy under *Anton Weichselbaum* (1845–1920). The latter is regarded as the founder of microbiological research and diagnostics in pathology. The greatest achievement of *Weichselbaum*'s group is the discovery of blood groups by his collaborator *Karl Landsteiner* (1868–1943). Upon receiving his doctorate in 1912, *Walter Schiller* became an assistant at this institute and received a basic education in pathological anatomy and histology. His first scientific publication, a paper written with *Robert Koch* on the reaction of tuberculous skin to tuberculin, dates back to this time. During World War I, *Schiller* served as a

Fig. 1. Walter Schiller (1887–1960).

bacteriologist in the Austro-Hungarian Army. From 1918 to 1921 he worked as a pathologist at the Second Military Hospital in Vienna.

In 1921 *Walter Schiller* was appointed to succeed *Julius Schottländer* as director of the laboratory at the Second Gynecological Clinic in Vienna, which was led by *Fritz Kermauner* (1892–1931). He remained in this position until 1936. During this time, he produced a large number of important and internationally recognized scientific papers, making him one of the three leading experts in gynecological pathology in the German-speaking world along with *Robert Meyer* (1864–1947) in Berlin and *Oscar Frankl* (1873–1938) in Vienna [7,8,11–15]. His international reputation at that time is documented above all in the English-speaking countries, where he gave lectures and taught at Trinity College and the Royal Academy in Dublin and then in London, Manchester, Birmingham, and other cities in England and Scotland. From September 1926 to May 1937, he also gave many lectures in the United States and in Canada.

Schiller was Jewish. Due to ominous political developments in Europe, he decided to emigrate and left his hometown of Vienna in 1937. He emigrated via Canada to the United States, where he received U.S. citizenship in 1943. From 1937 to 1939 he worked as laboratory director at Jewish Memorial Hospital in New York. In 1938 he was appointed director of the Institute of Pathology at Cook County Hospital in Chicago, where in 1944 he was succeeded by the very famous liver pathologist *Hans Popper* (1903–1988), who had also emigrated from Vienna. *Popper* describes his predecessor and sponsor Walter Schiller as “a world authority in gynecological pathology and a superb teacher.” After leaving Cook County Hospital, *Walter Schiller* worked at State Hospital, at Roseland Community Hospital, and as director of laboratories at Women’s and Children’s Hospital. He was a renowned member of a number of American scientific societies and received high honors. In 1944 *Walter Schiller* exhibited the first signs of Parkinson's disease. On May 2, 1960, *Walter Schiller* died as a result of this disease and secondary pneumonia. He left behind his spouse Marie, with whom he had been married since 1923 and had two daughters.

Walter Schiller published just over 100 scientific papers and significantly enriched our knowledge of the pathology of the female genital tract. In 1928 and 1929 he reported that cellular atypia can be detected on the ectocervical epithelium before there are any signs of invasiveness, thus supporting the concept of a preinvasive stage, or carcinoma in situ [12,13]. Such changes had already been described by *John Williams* in 1886, *Thomas Cullen* in 1900 and by *Walther Schauenstein*, *Karl Pronai*, *Isidor Rubin*, and *Julius Schottlaender* between 1908 and 1912 [16,17].

Selective intravital staining for glycogen in the ectocervical squamous epithelium with iodine was already anticipated by *Paul Ehrlich* (1854–1915) (18). Yet *Walter Schiller* was the first to find in experiments with more than 200 different dyes that the most potent vital staining of the ectocervical squamous epithelium was only possible with Lugol's iodine solution [7], (Schiller's original recipe: iodine 1.0, potassium iodide 2.0, water 300.0 g). All other vital staining, for example with Best's carmine and with fluorescent dyes, have not been able to call into question the primacy of the iodine solution. The iodine solution was originaly indicated for disinfection and detection of starch by the French physician *Jean Guillaume Lugol* (1786–1851) (Fig. 2).

W. Lahm's observation in 1928 [18] that the glycogen content of squamous epithelium cells decreases as anaplasia increases was confirmed by Schiller in the same year on cervical carcinoma; this led to his development of the iodine test associated with his name [12,13]. He recommended this test as a screening method but was aware that the loss of glycogen in the cells can also be observed in other non-neoplastic cell changes. The test merely proves the existence of a deviation from the norm, not its nature. He also proved that different histological cell changes could lie behind the colposcopic finding of leukoplakia and that it is not a definable entity.

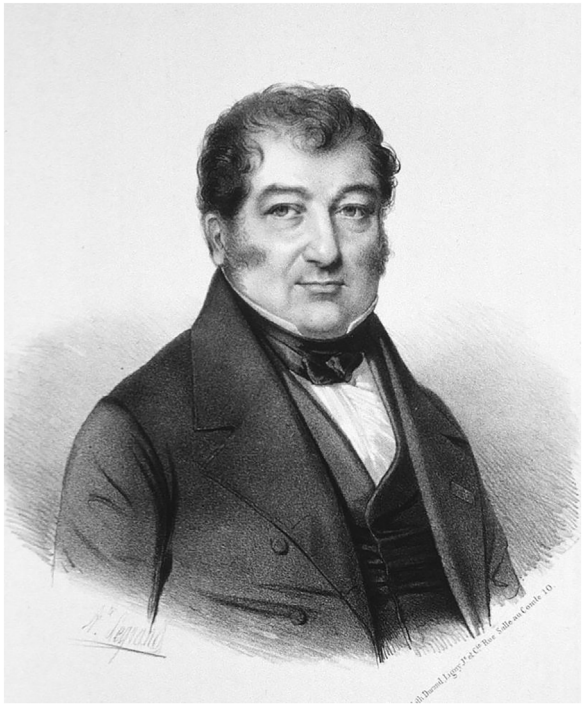

Fig. 2. Jean Guillaume Lugol (1786–1851).

Iodine test in colpsocopic teminologies

In the first colposcopic terminology, *Hans Hinselmann* included the iodine test in the minimum requirements of colposcopy in 1954 and associated it with the term “expanded colposcopy.” However, he did not provide a separate classification of the various reactions to iodine testing of the cervix. In 1946 the first mention was made of the finding “*uncharacteristic iodine-negative area*” [19] by the Swiss H. J. Wespi (1906–1995), who graded this as a colposcopic finding that required monitoring. The history of international colposcopic nomenclatures is closely connected with the IFCPC, which was founded at its first world congress in Mar del Plata, Argentina, in 1972. The first international colposcopic teminology was proposed at the Second IFCPC World Congress in Graz, Austria, in 1975. For the first time, an “*iodine light area*” was described as an “*abnormal colposcopic finding*” under iodine in an international terminology and listed under “*miscellaneous findings*” [20,21]. *Erich Burghardt* (1921–2006), the president of the congress at that time, was not successful in getting the iodine test accepted into the classification as an integral part of the colposcopic examination procedure. In 1976 the American Society of Colposcopy and Cervical Pathology [22] accepted the Graz classification with several changes. The “*iodine light area*” received no mention. In the following years, it became increasingly accepted in most countries to classify “*iodine yellow epithelium*” as “*iodine-negative*” and to consider this finding worthy of clarification. The IFCPC terminology from Rome 1990 [23] no longer ordered “*iodine negativity*” under “*miscellaneous findings*” as in Graz 1975 [20]; it now appeared under “*abnormal findings*.” “*Iodine negativity*” is also found in the IFCPC teminology from Barcelona 2002 [24] under “*abnormal findings, major changes*.” In addition, the category “*iodine partial positivity*” was created and listed under “*abnormal findings, minor changes*.” The IFCPC terminology from Rio 2011 [25],

Table 1
Staining pattern of different histological findings after iodine testing by glycogen content of epithelium.

Glycogen Content of Epithelium	Type of epithelium	Staining pattern
Glycogenated	• Mature glycogenated squamous epithelium	• Brown *
Partially glycogenated	• Immature metaplastic squamous epithelium; incomplete atrophic squamous epithelium	• Different shades of brown to yellow
	• LSIL	• Brown to yellow
Non-glycogenated	• Columnar epithelium; early immature metaplastic squamous epithelium; complete atrophic squamous epithelium, erosion; leukoplakia; cancer	• Unstained **
	• Mature non-glycogenated squamous epithelium	• Yellow
	• HSIL	• Yellow to ocher

* Mahogany to black.
** May appear slightly discolored due to a thin film of iodine.

however, did away with the diagnostic term "*iodine-negative*," which had been used for over 20 years, and replaced it with the term "*non-stained*" [25]. Other descriptions and assignments of abnormal iodine test findings are used in colposcopic scores (Swede score, Reid colposcopic index): point faintly yellow, patchy yellow, partial iodine uptake, yellow staining [26,27].

Scientific evidence

The scientific evidence for colposcopy including the iodine test is poor. This is due to the fact that no prospective randomized studies are possible or available and that reports on colposcopic findings in nomenclatures and scores are varied and partly contradictory. On the other hand, it is accepted that colposcopy plays a central role in the diagnostic investigation of women with premalignant diseases of the cervix and vagina as well as disease management. It is surprising and unfortunate that large screening studies in previous years in the U.S., England, and Germany have only considered inspection of blood vessels and the acetic acid test, not iodine testing in colposcopy, i.e. Trial of management of borderline and other low-grade abnormal smears (TOMBOLA), ASC-US-LSIL triage study (ALTS), Kaiser Permanente trial, Wolfsburg trial [28–31]. False positive and false negative rates of iodine testing in retrospective single center studies vary considerably and are of limited value [32,33].

Clearly better is the evidence for iodine testing in "*naked-eye visual inspection of the cervix*" after application of iodine. This method provided a breakthrough to effective cervical cancer screening in resource-limited settings of Africa, India, and Latin America [34–36]. A meta-analysis that included 23 studies comprising 101,273 women compares the accuracy of visual inspection with acetic acid (VIA) and visual inspection with Lugol's iodine (VILI), alone and in combination, for detection of cervical precancer. The meta-analysis showed that VILI was more sensitive than VIA at comparable specificity and concluded that VILI alone appeared to be the most useful visual screening strategy [36]. The LAMS (Latin American Screening) study of 11,834 healthy women has been compared to VIA, VILI, cytology and HPV testing. The authors concluded that combined use of VIA or VILI with cytology or HPV testing allows specific detection of HSIL+ [35]. A cross-sectional study involving 4,444 women in India reported a sensitivity of 87.2 % and specificity of 84.7 % for VILI in the detection of HSIL+ [34]. This study is important because only detection of definite yellow iodine non-uptake areas inside the transformation zone close to or touching the squamocolumnar junction constitute a positive VILI test. The result is a clear improvement in the sensitivity and specificity of the iodine test [34].

Problems, upcoming tasks, and progress

The first step in solving a problem is recognizing that there is one. We are of the opinion that the most eminent problem is that the evaluation of the iodine test in the current Rio classification from 2011 [25] with the terms "*stained*" and "*non-stained*" does not permit a clear differentiation from physiological and pathological findings. The brown reactions of normal squamous epithelium and the yellow or ocher colored reactions of SIL could both be interpreted as "*stained*." It is not taken into account that "*iodine yellow epithelium*" within the transformation zone has a different value than that outside the transformation zone. "*Non-stained*," however, can be associated not only with normal columnar

Table 2
Colposcopic classification after the application of Lugol's iodine to the cervix suggested by the authors for a revised (new adaptation) of IFCPC nomenclature.

Interpretation Iodine testing	Description/ Reaction of epithelium to iodine	Type of epithelium/lesion	Colposcopic classification suggested by authors
Iodine positivity	Different shades of brown *	Squamous epithelium (glycogenated)	Normal finding
Iodine negativity inside TZ	Iodine yellow (Iodine ocher) **	HSIL	Abnormal finding, major change
Iodine negativity outside TZ	Iodine yellow ***	Squamous epithelium (non-glycogenated)	Abnormal finding, non-specific change
		LSIL	
		Congenital TZ	

* Iodine-positive punctuation and iodine-positive mosaic appearance in an area with slight acetowhite change may represent not only a normal finding (immature metaplasia) but also LSIL.
** An iodine-yellow to iodine-ocher reaction inside the transformation zone in an area that has appeared strongly acetowhite is specific and highly suggestive of HSIL.
*** An iodine-yellow reaction outside the transformation zone is unspecific and may represent normal non-glycogenated squamous epithelium, LSIL, or a congenital transformation zone.

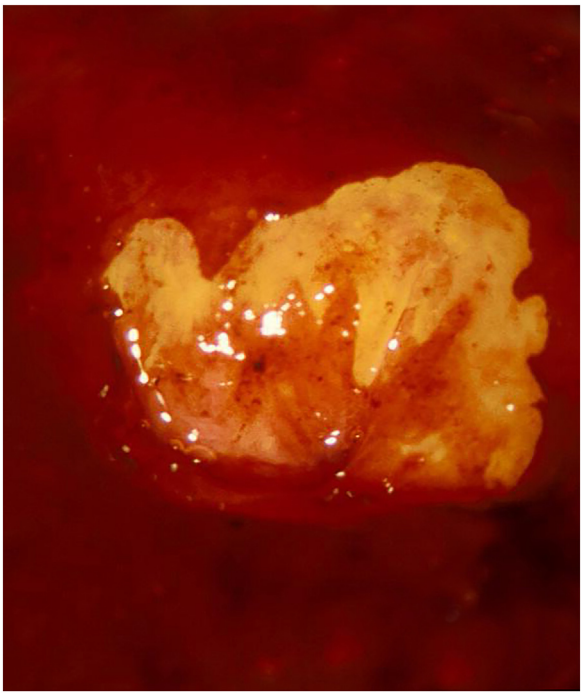

Fig. 3. Iodine negativity inside the transformation zone: Iodine staining shows a iodine-ocher reaction in a slightly elevated epithelium. Such a slight elevation is highly suggestive for HSIL. HSIL was confirmed by histology. It is suggested by the authors to classify such a finding as major change in a new adaption of IFCPC terminology.
From: Reich O, Girardi F, Tamussino K, Pickel H. Burghardt's Primary Care Colposcopy. Textbook and Atlas. Second Edition. Thieme, Stuttgart 2017.

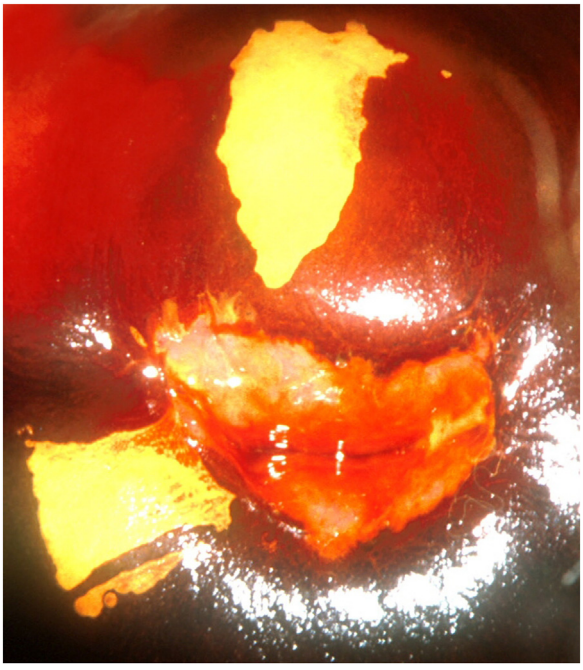

Fig. 4. Iodine negativity outside the transformation zone. Such a iodine yellow reaction is unspecific and may represent normal non-glycogenated squamous epithelium or LSIL. Histology of this case shows normal non-glycogenated squamous epithelium. It is suggested by the authors to classify such a finding as "abnormal non-specific changes" in a new adaption of IFCPC terminology.
From: Reich O, Girardi F, Tamussino K, Pickel H. Burghardt's Primary Care Colposcopy. Textbook and Atlas. Second Edition. Thieme, Stuttgart 2017.

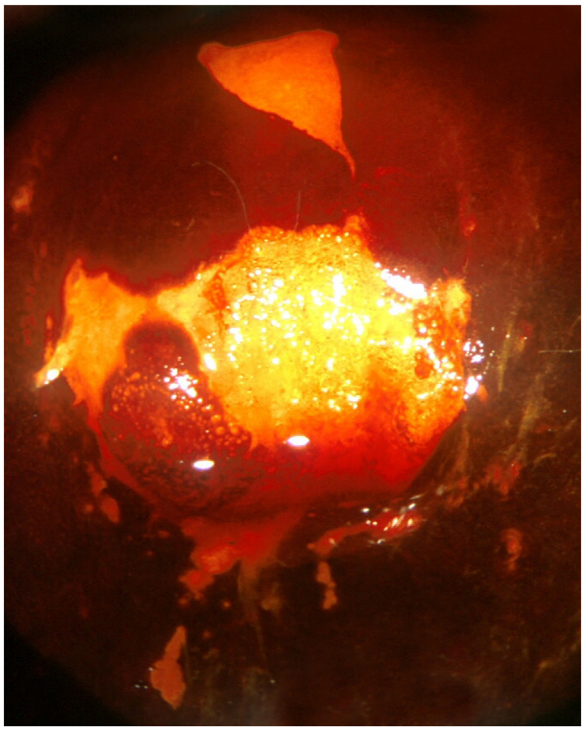

Fig. 5. Iodine negativity inside and outside the transformation zone and iodine positive punctation: The epithelium inside the transformation zone corresponds to HSIL. The area at 12 o'clock with a iodine yellow reaction outside the transformation zone shows normal non-glycogenated squamous epithelium by histology. On the left, within the transformation zone, there is an area of iodine-positive punctation due to LSIL.
From: Reich O, Girardi F, Tamussino K, Pickel H. Burghardt's Primary Care Colposcopy. Textbook and Atlas. Second Edition. Thieme, Stuttgart 2017.

epithelium of ectopy but also with erosion, leukoplakia, and cancer. This means that the descriptions "*stained*" and "*non-stained*" are ambiguous and in the authors' opinion unsuitable for the classification of iodine test findings.

It is well known that the staining pattern of iodine testing depends on the interaction between iodine and glycogen. The staining of different cervical epithelia und lesions is variegated. Deep brown staining of glycogenated squamous epithelium should diminish suspicions of precancer and has a very high negative predictive value for precancer. The various shades of brown of partially glycogenated epithelium in the normal transformation zone depends on the maturity of metaplastic squamous epithelium. Postmenopausal cervical and vaginal squamous epithelium stains light brown to yellow. "*Iodine yellow epithelium*" of non-glycogenated epithelia and lesions, however, is ambiguous (Tables 1 and 2).

For a colposcopic terminology to be applicable in both daily clinical practice and research and to be accepted around the world, it (I) must be relevant and comprehensible, (ii) requires a descriptive and pragmatic approach, and (iii) should avoid descriptions that are too complicated in order to allow a simple triage of women with "*abnormal colposcopic findings*." This is also necessary for future advances in colposcopy such as the development of learning models to automatically classify cervical lesions on colposcopic photographs in computer-aided diagnosis by artificial intelligence [37,38].

It is widely accepted that "*iodine brown epithelium*" should be classified as "*iodine positivity*" and belongs to "*normal colposcopic findings*" (Table 2). Current thinking suggests that the categorization of "*abnormal colposcopic findings*" after iodine testing depends not only on the general color changes observed on the cervix during colposcopy but also on (i) the location of the abnormal

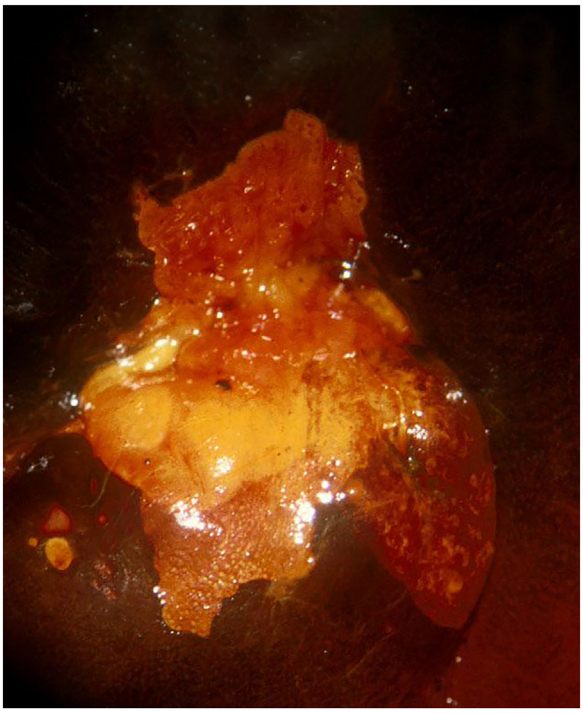

Fig. 6. Complex colposcopic picture after iodine-staining: Iodine-positive mosaic at 7 o'clock is due to LSIL. The well demarcated brown areas at 12 o'clock and 5 o'clock are metaplastic squamous epithelium of different degrees of maturity. The iodine-ocher reaction at the external os corresponds to HSIL.
From: Reich O, Girardi F, Tamussino K, Pickel H. Burghardt's Primary Care Colposcopy. Textbook and Atlas. Second Edition. Thieme, Stuttgart 2017.

iodine pattern inside or outside the transformation zone, (ii) acetowhitening before the iodine test (thin/dense/no reaction), and (iii) the color of the abnormal iodine pattern (yellow vs. ocher). As authors from an institution at which the iodine test has been included in every colposcopy since 1946, we strongly advocate for "*iodine yellow epithelium*" to be classified once again as "*iodine negative*" for pragmatic reasons (Table 2). This term has already been used by the IFCPC in the Rome 1990 [23] and Barcelona 2002 [24] nomenclatures and was well-established. Investigations on the sensitivity and specificity of the iodine test by R. Sankaranarayanan et al. [34] further justify differentiation between "*iodine negativity inside the transformation zone*" and "*iodine negativity outside the transformation zone*." "*Iodine negativity inside the transformation zone*" in an area that has appeared densely acetowhite is a "*specific colposcopic finding*." It is highly suggestive of HSIL and thus corresponds to "*abnormal, major change*" (Fig. 3). In contrast, "*iodine negativity outside the transformation zone*" is an unspecific colposcopic finding and may represent normal non-glycogenated squamous epithelium, LSIL, or a congenital transformation zone. In these findings, the acetic acid test shows thin acetowhitening or no reaction before iodine. As a result, the authors feel that "*iodine negativity outside the transformation zone*" belongs in the category "*abnormal non-specific changes*" (Fig. 4). Colposcopists who use iodine often see such sharply demarcated fields of non-glycogenated squamous epithelium outside the transformation zone that stain "*iodine yellow*." The histogenesis of this variant of normal cervical epithelium is just as unclear as that of the "*congenital transformation zone*" [39]. "*Iodine negativity inside the transformation zone*" and "*iodine negativity outside the transformation zone*" may appear on the same cervix (Fig. 4). Most expert colposcopists agree that HSIL stains "*iodine ocher*" whereas LSIL stains "*iodine yellow*" or showing "*iodine positive punctuation*" or "*iodine postive mosaic*" (Figs. 5 and 6).

The 2021 European consensus statement on essential colposcopy defined colposcopy as a diagnostic procedure to visualize the epithelia of the lower genital tract with magnification and adequate illumination before and after application of acetic acid and Lugol's iodine [40]. The EFC has spoken in favor of a three-part colposcopic examination: inspection of blood vessels (first colposcopic examination), an acetic acid test (second colposcopic examination), and an iodine test (third colposcopic examination). This corresponds to a recent revaluation of iodine testing in Europe.

In summary, it is important to present the medical history of iodine testing that has led to the current "state of the art"—especially to younger colleagues. Further work is required to revise the ordering of the iodine test findings in the IFCPC classification and to reevaluate the role of iodine application in defining the ectocervical excision line during excisional treatment of cervical precancer.

Declaration of Competing Interest

Olaf Reich and Hellmuth Pickel have no conflicts of interest to declare.

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