Case Report/Case Series

Activating *HRAS* Mutation in Agminated Spitz Nevi Arising in a Nevus Spilus

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IMPORTANCE Spitz nevi are benign melanocytic proliferations that can sometimes be clinically and histopathologically difficult to distinguish from melanoma. Agminated Spitz nevi have been reported to arise spontaneously, in association with an underlying nevus spilus, or after radiation or chemotherapy. However, to our knowledge, the genetic mechanism for this eruption has not been described.

OBSERVATIONS We report a case of agminated Spitz nevi arising in a nevus spilus and use exome sequencing to identify a clonal activating point mutation in *HRAS* (GenBank 3265) (c.37G→C) in the Spitz nevi and underlying nevus spilus. We also identify a secondary copy number increase involving *HRAS* on chromosome 11p, which occurs during the development of the Spitz nevi.

CONCLUSIONS AND RELEVANCE Our results reveal an activating *HRAS* mutation in a nevus spilus that predisposes to the formation of Spitz nevi. In addition, we demonstrate a copy number increase in *HRAS* as a "second hit" during the formation of agminated Spitz nevi, which suggests that both multiple Spitz nevi and solitary Spitz nevi may arise through similar molecular pathways. In addition, we describe a unique investigative approach for the discovery of genetic alterations in Spitz nevi.

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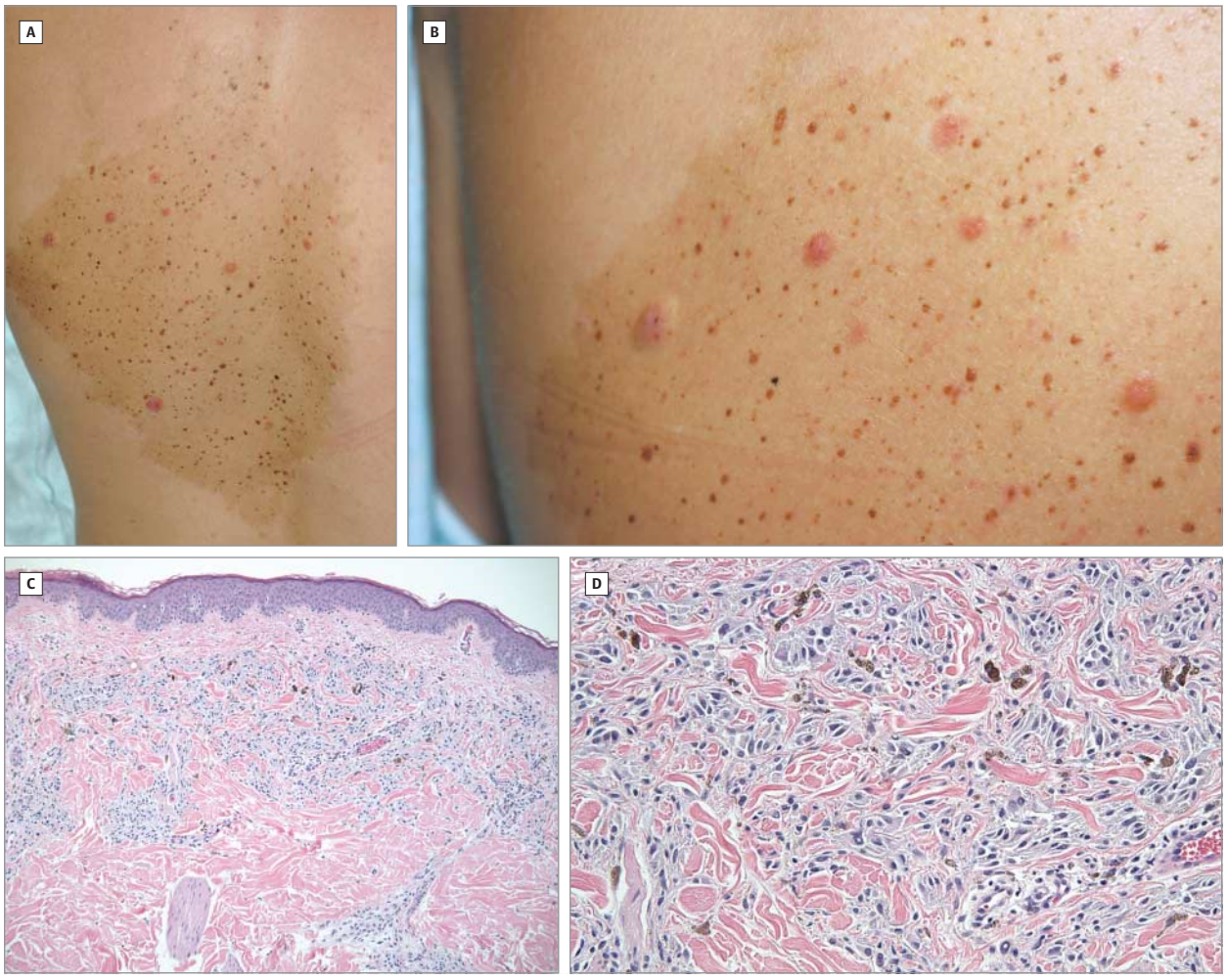
Spitz nevi are benign melanocytic neoplasms composed of epithelioid or spindle cell melanocytes. While Spitz nevi have distinct histologic criteria for diagnosis, a subset of Spitz nevi can be clinically and histopathologically difficult to distinguish from malignant melanoma, leading to controversy regarding the nature of these lesions.[1,2] Some Spitz nevi harbor activating mutations in *HRAS* (GenBank 3265) and *BRAF* (GenBank 673), serine-threonine kinases in the mitogen-activated protein kinase pathway that play a critical role in epidermal development, homeostasis, and tumor progression.[3-5] In addition, approximately 20% of Spitz nevi, predominantly those harboring *HRAS* mutations, have an increased copy number of chromosomal locus 11p, where *HRAS* resides.[3,6] These *HRAS* mutations can be a favorable prognostic biomarker since *HRAS* is rarely mutated in melanoma.[6,7]

Spitz nevi usually present as solitary skin tumors but can occur in multiple patterns, having agminated, dermatomal, and disseminated forms.[8-10] Agminated Spitz nevi occur rarely, with fewer than 50 cases reported in the literature. They have been reported to arise spontaneously, in association with an underlying nevus spilus, and after radiation or chemotherapy.[10-12] Despite the clinical and histopathologic resemblance to solitary Spitz nevi, the genetic alterations in these lesions remain unknown. It is unclear if these agminated lesions harbor the same mutations as solitary Spitz nevi or arise from an alternate pathway. These lesions represent a compelling approach to studying Spitz nevi since they may potentially arise from an early mutation, producing a clone of melanocytes predisposed to developing into Spitz nevi. Herein, we applied exome sequencing to identify genetic changes in agminated Spitz nevi arising in a nevus spilus and demonstrate a common mosaic mutation among them.

Report of a Case

A 25-year-old man presented to the Stanford Pigmented Lesion and Melanoma Clinic with a 4-year history of pink papules emanating in a large congenital pigmented tan patch on his left lower back. Clinical examination revealed a more than 20-cm tan patch speckled with 1- to 2-mm hyperpigmented macules, characteristic of a nevus spilus, and containing fifteen to twenty 4- to 6-mm pink papules, characteristic of Spitz nevi (**Figure 1**A and B). The patient was otherwise healthy, with no personal or family history of malignant melanoma. Histopathologic specimens of 2 pink papules revealed symmetric, well-demarcated melanocytic proliferations consisting of spindle cell melanocytes with large vesicular nuclei splayed

Figure 1. Clinical and Histopathologic Features of the Agminated Spitz Nevi Arising in a Nevus Spilus



A and B, Photograph of a large tan patch on the left lower back with 1- to 2-mm hyperpigmented macules and 4- to 6-mm pink papules. C, Pink papule showing plump melanocytes splayed through desmoplastic collagen, consistent with Spitz nevi (hematoxylin-eosin, original magnification ×10). D, Melanocytes with amphophilic cytoplasm in the dermis (hematoxylin-eosin, original magnification ×20).

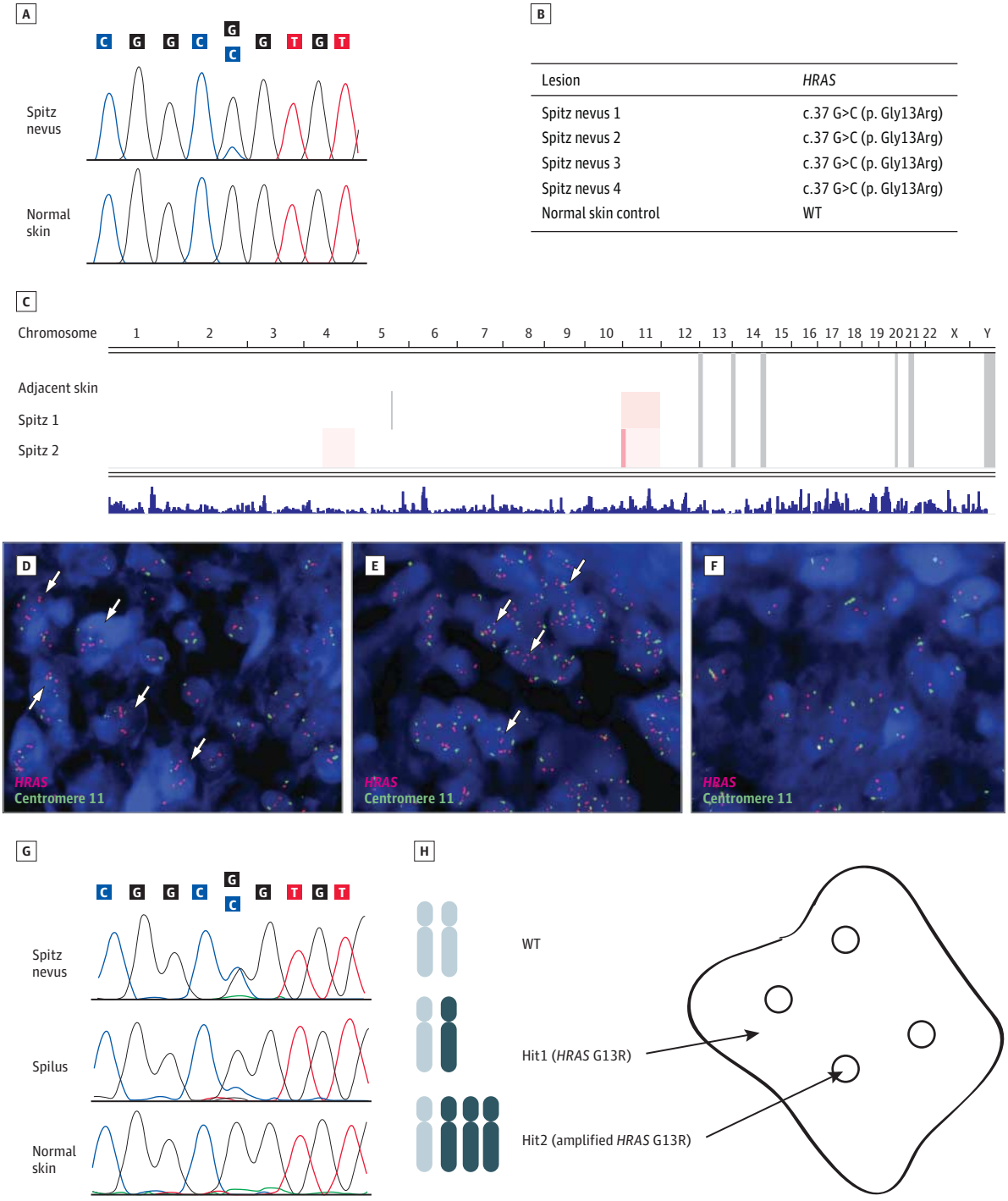
through the dermis, consistent with intradermal Spitz nevi (Figure 1C and D). To identify underlying genetic alterations, we obtained specimens from 2 additional pink papules, with histopathologic features also confirming the diagnosis of Spitz nevi. Our study complied with the Declaration of Helsinki and was approved by the institutional review board at Stanford University School of Medicine. Genomic DNA was isolated from these 2 lesional samples along with the adjacent normal skin, 1 cm outside the boundaries of the nevus spilus, and subjected to exome sequencing (eMethods and eTable in the Supplement).

Results

Comparison of recurrent variants from the exome sequencing identified an *HRAS* point mutation (c.37G→C, p.Gly13Arg) in both Spitz nevi that was absent in the adjacent normal skin (**Figure 2**A). No other recurrent somatic mutations were detected (eMethods in the Supplement). Sanger sequencing confirmed the presence of the *HRAS* mutation in both Spitz lesions. We performed Sanger sequencing on DNA derived from 2 additional formalin-fixed, paraffin-embedded Spitz nevi obtained from the same patient that also demonstrated the *HRAS* point mutation (Figure 2B). Therefore, all 4 Spitz nevi obtained from our patient harbored the same single-nucleotide variation.

To evaluate for copy number changes, we used SeqGeneCNV on the exome sequencing data.[13] This algorithm detects regions with abnormal copy number changes using circular binary segmentation. This revealed a copy number increase in chromosome 11p in both Spitz nevi compared with the normal skin control (Figure 2C). We then performed fluorescent in situ hybridization using an *HRAS* probe that confirmed amplification of *HRAS* in the melanocytes from 2 Spitz nevi (Figure 2D) and polysomy in the melanocytes from a third Spitz nevus (Figure 2E). No *HRAS* amplification was detected in adjacent fibroblasts or epidermal keratinocytes (Figure 2F).

Figure 2. Activating *HRAS* Mutations and Amplification of Chromosome 11p in Agminated Spitz Nevi



A, Sanger sequencing of a representative Spitz nevus and adjacent unaffected skin demonstrates a c.37G→C, p.Gly13Arg mutation specific to the lesional tissue. B, Table of *HRAS* mutations showing the *HRAS* mutation is present in all 4 Spitz nevi but undetectable in the adjacent normal skin. C, Chromosomal amplifications predicted by SeqGene CNV and displayed with an Integrative Genomics Viewer (http://www.broadinstitute.org/igv/). Both Spitz nevi have a predicted amplification (red bars) over chromosome 11p. D, Dual-color fluorescent in situ hybridization (FISH) with *HRAS* probe (red signals) and a reference centromeric probe for chromosome 11 (green signals) showing a focus of melanocytes with increased red signal significantly above reference green signals, indicating *HRAS* amplification (arrows). E, Dual-colored FISH showing a focus of melanocytes with polysomy demonstrated by increased *HRAS* (red) and centromeric (green) signals in the nucleus (arrows). F, Dual-color FISH showing epidermal keratinocytes and papillary dermal fibroblasts with equivalent red and green signals. G, Sanger sequencing of AciI1-digested DNA from a Spitz nevus, nevus spilus, and the adjacent normal skin demonstrating the *HRAS* mutation in the nevus spilus and Spitz nevus but not in the normal skin. H, Diagram of 2-hit model of a nevus spilus, with the first hit leading to the macular portion of the nevus spilus and the second hit leading to the formation of Spitz nevi. WT indicates wild type.

Spitz nevi are heterogeneous melanocytic tumors, with less than 20% of these lesions harboring *HRAS* activating mutations and even fewer containing the *HRAS* point mutation.[3] Thus, it would be highly improbable for all Spitz nevi obtained from our patient to develop identical mutations if they represented independent lesions. We hypothesized that these Spitz nevi arose in an agminated fashion from a common postzygotic clone of melanocytes, likely demarcated by the nevus spilus. To improve our sensitivity to detect this mutation in the nevus spilus, we performed polymerase chain reaction amplification of the genomic DNA followed by enzymatic digestion with Aci1, which digests the wild-type sequence but not the mutant sequence (eMethods and eFigures 1 and 2 in the Supplement). Subsequent Sanger sequencing reproducibly detected the *HRAS* point mutation in the nevus spilus and Spitz nevi but not in the adjacent normal skin (Figure 2G). This implicates the *HRAS* point mutation as the initiating mutation predisposing melanocytes to develop into Spitz nevi. In this model, a "second hit" may be required for the formation of Spitz nevi (Figure 2H). Our data support *HRAS* amplification as a secondary change because its mechanism was not identical in all Spitz nevi, with 1 nevus demonstrating polysomy of chromosome 11.

Discussion

Multiple Spitz nevi can occur rarely in agminated and disseminated forms, but the genetic alterations that lead to these occurrences are unknown. To our knowledge, this is the first report demonstrating mosaicism in agminated Spitz nevi and identifying an activating *HRAS* mutation in agminated Spitz nevi. Mosaic *HRAS* mutations were recently recognized in the nevi sebacei and nevi spili in patients with phacomatosis pigmentokeratotica.[14] This report extends this finding by demonstrating an *HRAS* mutation in a sporadic nevus spilus. Interestingly, the *HRAS* point mutation, in particular, has been detected in a variety of benign skin neoplasms, including epidermal and sebaceous nevi, Spitz nevi, and nevi spili, providing a unique example of genetic pleiotropy within the ectodermal lineage.[15]

Our data indicate that multiple Spitz nevi may have a similar pathogenesis to that of solitary Spitz nevi since a subset of solitary Spitz nevi also harbors activating mutations in *HRAS* and copy number increases in chromosome 11p.[3] However, similar to solitary Spitz nevi, other genetic alterations also may play a role in the pathogenesis of multiple Spitz nevi. Gantner et al[9] recently demonstrated the absence of *HRAS*-activating mutations in a patient with eruptive Spitz nevi, suggesting that alternate genetic alterations may be responsible for the lesions in this patient. It is tempting to speculate that many cases of multiple Spitz nevi may result from an early clonal mutation, as demonstrated in our patient.

Recently, significant progress has been made in understanding the genetic alterations in cutaneous tumors, in part due to the advances in sequencing technology. Many of these technologies rely on a large number of samples to determine recurrent mutations. This approach may be difficult in solitary Spitz nevi since the lesions are uncommon and possess heterogeneous mutations. Identifying clonal mutations in patients with multiple Spitz nevi presents a promising approach to distinguish genetic alterations in all Spitz nevi. Insight into these genetic changes is critical to improve our ability to diagnose and manage these controversial lesions.

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NOTABLE NOTES

Euphorbia peplus: 18th-Century Insights on a 21st-Century Therapy

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In 2012, the US Food and Drug Administration approved a new therapeutic agent, ingenol mebutate, for the topical treatment of actinic keratoses. Ingenol mebutate is a diterpene ester with the chemical formula $C_{25}H_{34}O_6$ and is extracted from the sap of the plant species *Euphorbia peplus*, also known as the petty spurge. *Euphorbia peplus* extract has been used for centuries as a topical agent for the treatment of a variety of skin conditions in traditional medicine systems from around the world.

Euphorbia peplus was first taxonomically categorized in the Western scientific community by Carl Linnaeus in the 1750s and presented in a thesis defended by his student Johannes Wiman at Uppsala University in Sweden.[1] Linnaeus described a variety of medicinal uses for the genus of *Euphorbia* plants as topical treatments and systemic agents for gastrointestinal tract purging. Members of this genus were known to cause skin irritation on contact with the plant's sap. The genus was named after the ancient Greek physician Euphorbus, who in the first century AD documented the laxative properties of the spurges.

A monograph published in London, England, circa 1770 highlights specific insights into several plants, including *E peplus*.[2] The manuscript (**Figure**), published in both Latin and English, likely represents one of the earliest documentations of the dermatologic applications after Linnaean classification. The monograph authors describe "the milky fluid which it abounds with, is by some applied to Warts, which it is said to destroy."[2] The other members of the *Euphorbia* genus, particularly *Euphorbia helioscopia*, or sun spurge, were also recognized to have sap with similar properties in the monograph.

A later selection from the same monograph discusses the sun spurge or "wart-wort" species in greater detail, including its toxicity. "My friend Mr William Wavell lately informed me of a case which fell under his notice in the Isle of Wight, where from the application of the juice of this Spurge [*E helioscopia*] to some Warts near the eye of a little girl, the whole face became inflamed to a very great degree," noted the author of the monograph.[2]

Consistent with these case reports from more than 2 centuries earlier, most patients enrolled in clinical trials demonstrating the efficacy of ingenol mebutate for actinic keratoses developed clinically significant erythema at the site of application.[3] It is also notable that a lower concentration of the drug is approved for treatment of the face and that the most common adverse effects of ingenol mebutate in the aforementioned clinical trials were pruritus, irritation, and pain—echoing the cautionary case described in the monograph. As future work unfolds examining additional applications for topical ingenol mebutate, looking back into the past may help uncover other natural remedies awaiting our rediscovery.

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Figure. Eighteenth-Century Monograph Describing the Dermatologic Use of *Euphorbia peplus*, the Plant From Which Ingenol Mebutate Is Derived

EUPHORBIA PEPLUS. SMALL GARDEN SPURGE.

EUPHORBIA *Linnæi Gen. Pl.* DODECANDRIA TRIGYNIA.
Raii Syn. Gen. 22. HERBÆ VASCULIFERÆ FLORE TETRAPETALO ANOMALÆ.
EUPHORBIA *(Peplus)* umbella trifida, dichotoma, involucellis ovatis, foliis integerrimis obovatis petiolatis. *Linn. Syst. Vegetab. p.* 375. *Fl. Suecic. p.* 163.
TITHYMALUS foliis rotundis, stipulis borabibus cordatis, obtusis, petalis argute corniculatis. *Haller. hist. vol. 2. p. 9. n.* 1049.
PEPLUS sive Esula rotunda. *Bauhin pin.* 292. *Parkinson. Gerard. emac.* 503.
TITHYMALUS parvus annuus, foliis subrotundis non crenatis, Peplus dictus. *Raii Syn. p.* 313. *n.* 9: Petty Spurge. *Hudson Fl. Angl. p.* 182.

RADIX annua, lignosa, simplex, fibrata, albida.
CAULIS, fuberculis, dodrantalis, teres, glaber, ramosus, basi durior, tenuior, subruber, foliosus, laciniosus.
RAMI pauci, sparsi, inferioribus longioribus oppositis.
UMBELLA trifida, dichotoma.
FOLIA obovata, petiolata, integerrima, sparsa, obtusiuscula, inferioribus subrotundis.
STIPULÆ *umbellæ tres*, ovato-acutæ, petiolis brevibus insidentes, *umbellulæ* alternæ oppositæ, sessiles, cordato-ovatæ, inæquales, integerrimæ, basi quâ tectæ germen quasi excavatæ.
CALYX ventricosus, persistens. *fig.* 1.
COROLLA nulla.
NECTARIA quatuor *bicorniculata*, *fig.* 2.
STAMINA pleromque duo, aut tria, vitilia, exserta: ANTHERÆ didymæ, subrotundæ, *fig.* 3.
PISTILLUM: GERMEN pedunculatum, nutans, triangulare, angulis longitudinaliter sulcatis, *fig.* 4, 6: STIGMATA tria, apice bifida, *fig.* 5.
PERICARPIUM: CAPSULA tricocca, trilocularis, trivalvis, valvulis lævibus, et dum adhuc virides diffilientibus, *fig.* 6.
SEMEN unicum in singulo loculamento, ovatum, enum, *obtusiusculum*, appendiculatum, *fig.* 7.
N. B. Omnes partes fructificationis lente augentur.

ROOT annual, woody, simple, fibrous and whitish.
STALK generally upright, about nine inches high, round, smooth, and branched: at bottom harder, more slender, and of a reddish colour, leafy and milky.
BRANCHES few, not growing in any regular order, the lower ones longeſt and oppoſite.
UMBEL firſt trifid, then dichotomous.
LEAVES ſomewhat oval, but narroweſt towards the baſe, having foot-ſtalks, entire at the edges, placed in no regular order, ſomewhat blunt, the lowermoſt leaves almoſt round.
STIPULÆ of the *large umbel* three in number, oval and pointed, placed on very ſhort foot-ſtalks: of the *ſmall umbel* alternately oppoſite, ſeſſile, of an heart-ſhaped-oval form, unequal, and entire, at bottom on that ſide to which the Germen tends as if cut away.
CALYX ſwelling out and continuing. *fig.* 1.
COROLLA wanting.
NECTARIES four, each having *two little horns*. *fig.* 2.
STAMINA ſeldom more than two or three, which are viſible, and placed without the Calyx: ANTHERÆ two on each filament joined together, of a roundiſh figure, *fig.* 3.
PISTILLUM: GERMEN placed on a foot-ſtalk, hanging down, triangular, the angles longitudinally grooved, *fig.* 4, 6: STIGMATA three, bifid at top, *fig.* 5.
SEED-VESSEL: a CAPSULE of three cavities, and three valves, the valves protuberant, ſmooth, and ſplitting with a kind of elaſticity even while they are of a green colour, *fig.* 6.
SEED one in each cavity, oval, grey, with *numerous depreſſions on its ſurface*, and a little white button at one end. *fig.* 7.
N. B. All the parts of fructification are magnified.

MANY of the Spurges conſiderably reſemble one another, and two of them that have this affinity, grow frequently together in Gardens, viz. the preſent Spurge, *Euphorbia Peplus*, and the Sun Spurge, *Euphorbia Helioſcopia*: they may be diſtinguiſhed however by the cloſeſt attention. In the *Helioſcopia* the leaves are *notched* or *ſerrated* at the edges, in the *Peplus* they are *entire*, in the *Helioſcopia* the Petals or rather Nectaria are *round* and *entire*, in the *Peplus* each is furniſhed with *two little horns*, *fig.* 2: there are other marks of diſtinction but theſe are the moſt ſtriking.
This ſpecies grows in Gardens and other cultivated ground, and flowers in Autumn.
The milky fluid which it abounds with, is by ſome applied to Warts, which it is ſaid to deſtroy.
Moſt if not all the plants of this Genus contain in them this milky and gummy ſubſtance, which to the taſte is exceedingly acrid: and this lacinious property, joined to the peculiarity of its parts of fructification, point out almoſt at firſt ſight this natural family of plants. But the botanic Student who would inveſtigate this ſpecies according to the principles of the Linnæan Syſtem, not having theſe characteriſtics to aſſiſt him, finds a conſiderable difficulty in learning even the *Claſs* to which it belongs, nor is it poſſible for him to aſcertain the Claſs by an examination of this or ſcarce any other Engliſh Spurge: the *Stamina* in the firſt place are very minute, it is ſeldom that more than *two* or *three* protrude beyond the Calyx, all the reſt lye concealed within it, they ſeldom amount to *twelve* in number, and even if they did amount to that exact number, their *minuteneſs* and the *milky juice* which flows from the diſſection, render the enumeration of them ſcarce practicable. The Student may however in a great degree ſurmount this difficulty, by an examination of ſome plant of this genus, which is larger in every reſpect, and the *Euphorbia Lathyris* improperly called the *Caper Tree*, (which is cultivated in many Gardens) will afford him a very good example, and tend to give him a clear idea of the flower and fruit of this ſingular genus of plants.
I would not be thought on account of this difficulty to inveigh againſt LINNÆUS's Syſtem, being ſenſible that difficulties occur, and muſt occur in all botanic arrangements, and inſtead of ſhifting faults inſeparable from every mode of claſſification, (which ſeems to have been a favourite amuſement of ſome Authors, and forms indeed the greateſt part of their writings) I would uſe every endeavour to make it more perfect.
It is too much the faſhion now, as well as formerly, for every Botaniſt as ſoon as he thinks he has ſome pretenſions to eminence, to ſet about the arduous taſk of framing a new Syſtem; he may by this means give the public ſome idea of his ſelf-conſequence, and be inrolled in the Catalogue of Syſtem-makers, but not one jot will he advance the Science of Botany. It is to be regretted that Botaniſts will not be contented with a Syſtem, a proof of whoſe ſuperiority is the almoſt general reception it has met with throughout Europe, and unite in their endeavours to render that Syſtem more complete, by giving us an accurate account of the hiſtory of thoſe plants not already given, their virtues and uſes: this appears to me to be the true method of advancing this delightful Science, and making it uſefull to Mankind.
When one Syſtem of Botany is generally followed as is nearly the caſe at preſent, Botaniſts in different kingdoms perfectly underſtand each others language, but when each adopts a ſeperate one, (which is frequently dictated by Pride or Caprice) all becomes Babel; and every one who wiſhes to acquire a knowledge of the plants treated of, muſt at conſiderable expence both of time and labour, acquire firſt the Authors new-created Syſtem-language, a tax which it is hoped every true Botaniſt will unite to oppoſe.

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