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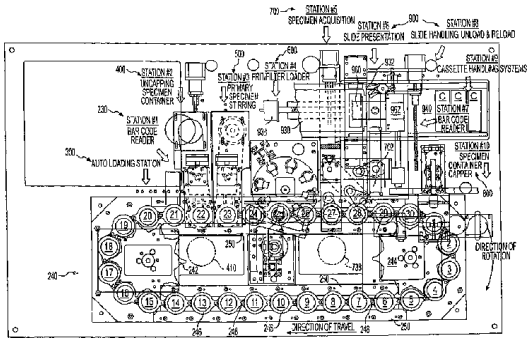
(54)【発明の名称】複数の液体ベース検体を処理するための自動式システムおよび方法

(57)【要約】
複数の粒状物質含有液体検体を各容器中で個別に処理するための自動式の装置および方法。容器は、処理経路に沿って順次搬送され、少なくとも予備処理装置（たとえば混合ヘッド）に対して呈示され、その後、 検体取得ヘッドに対して呈示される。検体取得ヘッドは、その後の分析検査または評価に備えて、検体取得ヘッドに対して呈示される容器から、予め混合しておいた粒状物質含有液体を採取する。各装置は、各装置に容器が呈示されるのに応答して作動し、各装置それぞれの操作を独立して実施する。システムの一例には、容器の搭載および取り出しを行うステーション、容器のキャップを取り外して廃棄するステーション、検体の混合を行うステーション、フィルターを装填するステーション、検体を取得する(たとえば、吸引してからスライドに押圧転写することにより)ステーション、フィルターを廃棄するステーション、および容器を再封止するステーションを、この順番で含みうる。



【特許請求の範囲】
【請求項１】
複数の粒状物質含有液体検体を各容器中で個別に処理するための自動式の方法であって、容器を処理経路に沿って順次搬送して、混合ヘッド、ついで検体取得ヘッドに対して容器を呈示する工程であって、混合ヘッドは、呈示される任意の容器中で検体を混合するよう適用され、かつ検体取得ヘッドは、呈示された容器から、予め混合しておいた粒状物質含有液体を吸引し、吸引された液体をそれぞれのフィルターの通過させて、フィルター表面上に粒状物質の試料を捕集するよう適用される、工程、
容器が混合ヘッドに対して呈示されるのに応答して混合ヘッドを作動させて、混合操作を個別に実施する工程、および
容器が検体取得ヘッドに対して呈示されるのに応答して検体取得ヘッドを作動させて、吸引操作を個別に実施する工程
を含む自動式の方法。
【請求項２】
混合ヘッドが、混合ヘッドに対して呈示された検体に特有のプロトコールにしたがって作動し、かつ検体取得ヘッドが、検体取得ヘッドに対して呈示された検体に特有のプロトコールにしたがって作動する、請求項1記載の自動式の方法。
【請求項３】
吸引した液体が通過した各フィルターを、処理経路に近接して位置する各スライドに順次押しつけて粒状物質試料をスライドに転写する工程をさらに含む、請求項1または2記載の自動式の方法。
【請求項４】
検体取得ヘッドが、検体取得ヘッドに呈示される各容器に入った検体を混合するよう適用され、この方法が、検体取得ヘッドを作動させて、吸引操作の直前に検体を混合する工程を含む、請求項1または2記載の自動式の方法。
【請求項５】
検体取得ヘッドが、混合ヘッドよりもゆっくりと検体を混合する、請求項4記載の自動式の方法。
【請求項６】
吸引した液体が通過した各フィルターを、処理経路に近接して位置する各スライド順次押しつけて粒状物質試料をスライドに転写する工程をさらに含む、請求項5記載の自動式の方法。
【請求項７】
複数の粒状物質含有液体検体をそれぞれの容器中で個別に処理するための自動式の方法であって、各容器が容器中に混合手段を有し、この混合手段が、上側の、フィルターを格納する粒状物質分離チャンバーと、ここから懸垂し、分離チャンバーに連通している吸引チューブとを有しており、上記方法が、
同時に別の検体を操作しうるよう間隔をおいてそれぞれ配置された複数の操作ヘッドに、容器を処理経路に沿って順次搬送する工程と、
各操作ヘッドを、各ヘッドへの容器の呈示に応答して作動させて、各操作ヘッドの操作を独立に実行する過程とを含み、
ここで上記の複数の操作ヘッドには、
呈示される任意の容器中の混合手段に係合して混合手段を動かし、容器中の検体を混合するよう適用された混合ヘッドと、
混合ヘッドの下流に設けられ、フィルターマガジンを有するフィルター搭載ヘッドであって、呈示される任意の粒状物質分離チャンバーにフィルターを供給するよう適用されたフィルター搭載ヘッドと、
フィルター搭載ヘッドの下流に設けられた検体取得ヘッドであって、呈示される粒状物質分離チャンバーを封止して陰圧をかけることにより、あらかじめ混合しておいた粒状物質含有液を容器から吸引し、分離チャンバー内のフィルターを通過させて、フィルター表面

上に粒状物質の試料を捕集する検体取得ヘッドとが含まれる、自動式の方法。
【請求項８】
混合ヘッドが、混合ヘッドに対して呈示された検体に特有のプロトコールにしたがって作動し、検体取得ヘッドが、検体取得ヘッドに対して呈示された検体に特有のプロトコールにしたがって作動する、請求項7記載の自動式の方法。
【請求項９】
吸引した液体が通過した各フィルターを、処理経路に近接して位置する各スライドに順次押しつけて粒状物質試料をスライドに転写する工程をさらに含む、請求項7または8記載の自動式の方法。
【請求項１０】
フィルター搭載ヘッドのフィルターマガジンが、少なくとも2種のフィルターを格納するよう適用され、かつ粒状物質分離チャンバーに供給されるフィルターの種類が、呈示された検体に特異的な情報に応じて決定される、請求項7記載の自動式の方法。
【請求項１１】
検体取得ヘッドが、検体取得ヘッドに呈示される各容器に入った検体を混合するよう適用され、この方法が、検体取得ヘッドを作動させて、吸引操作の直前に検体を混合する工程を含む、請求項7、8、または10記載の自動式の方法。
【請求項１２】
検体取得ヘッドが、混合ヘッドよりもゆっくりと検体を混合する、請求項11記載の自動式の方法。
【請求項１３】
吸引した液体が通過した各フィルターを、処理経路に近接して位置する各スライドに順次押しつけて粒状物質試料をスライドに転写する工程をさらに含む、請求項12記載の自動式の方法。
【請求項１４】
各容器は、取り外し可能なカバーを有し、そしてカバーが所定位置に装着された状態で処理経路に搭載され、かつ複数の操作ヘッドには、処理経路上の混合ヘッドの上流に設けられたキャップ取外しヘッドがさらに含まれ、このキャップ取外しヘッドは、呈示される容器のカバーを把持して取り外すよう適用されている、請求項7、8、または10記載の自動式の方法。
【請求項１５】
複数の操作ヘッドが容器キャップ再装着ヘッドをさらに含み、この容器キャップ再装着ヘッドは、処理経路上の検体取得ヘッドの下流に設けられ、呈示されるキャップの外された容器に対して封止キャップを取付けるよう適用されている、請求項14記載の自動式の方法。
【請求項１６】
処理が行われてキャップが再装着された容器を処理経路から取り出し、処理後のキャップ再装着容器がそれまで搭載されていた、処理経路上の空となった位置に、未処理の検体容器を搭載する工程をさらに含む、請求項15記載の自動式の方法。
【請求項１７】
容器の取り出しおよび搭載を、処理経路に沿った全容器の動きを止めている間に行う、請求項16記載の自動式の方法。
【請求項１８】
複数の粒状物質含有液体検体をそれぞれの容器中で個別に処理するための自動式装置であって、
容器を支持し、処理経路に沿って順次前進させる、間隔をおいて配置された複数の容器支持手段を有するコンベヤ、
処理経路に沿って配置され、コンベヤによって呈示される任意の容器に入った検体を混合する混合ヘッド、
処理経路に沿って混合ヘッドの下流に配置され、コンベヤによって呈示される任意の容器

から、予め混合しておいた粒状物質含有液体を吸引し、吸引された液体をそれぞれのフィルターへ通過させる検体取得ヘッド、ならびに
混合ヘッドの操作、検体取得ヘッドの操作、およびコンベヤの動きを支配するコントローラであって、混合ヘッドに対する容器の呈示に応答して、混合ヘッドに、呈示される容器中の検体の混合を個別に行わせ、また、検体取得ヘッドに対する容器の呈示に応答して、検体取得ヘッドに、呈示される容器から、予め混合しておいた粒状物質含有液体の吸引を行わせるコントローラ
を備える自動式装置。
【請求項１９】
コントローラによって、混合ヘッドが、混合ヘッドに対して呈示された検体に特有のプロトコールにしたがって作動し、検体取得ヘッドが、検体取得ヘッドに対して呈示された検体に特有のプロトコールにしたがって作動する、請求項18記載の自動式装置。
【請求項２０】
検体取得ヘッドの近傍にスライド呈示ステーションをさらに備えており、このスライド呈示ステーションでは、検体取得ヘッドが処理経路に対して可動であり、かつ検体取得ヘッドは、液体検体の吸引後に、分離チャンバーからフィルターを取得して取り除き、スライドにフィルターを押しつけて粒状物質試料をスライドに転写するよう適用され、そしてコントローラが、検体取得ヘッドによってフィルターが取り除かれた後にコンベヤーを前進させる、請求項18または19記載の自動式装置。
【請求項２１】
検体取得ヘッドが、検体取得ヘッドに呈示される各容器に入った検体を混合するよう適用され、コントローラが、検体取得ヘッドを作動させて、吸引操作の直前に検体を混合する、請求項18または19記載の自動式装置。
【請求項２２】
検体取得ヘッドが、混合ヘッドよりもゆっくりと検体を混合する、請求項21記載の自動式装置。
【請求項２３】
複数の粒状物質含有液体検体をそれぞれの容器中で個別に処理するための自動式装置であって、各容器が容器中に撹拌手段を有し、この撹拌手段が、上側の、フィルターを格納する粒状物質分離チャンバーと、ここから懸垂し、分離チャンバーと連通している吸引チューブとを有しており、装置が、
容器を支持し、処理経路に沿って順次前進させる、間隔をおいて配置された複数の容器支持手段を有したコンベヤと、
処理経路に沿って配置された複数の操作ヘッドであって、一つの容器支持手段が操作ヘッドの一つに位置しているときには、他の容器支持手段はそれぞれ他の操作ヘッドに位置しているため、別の検体を同時にそれぞれ操作することができる複数の操作ヘッドと、
混合ヘッドの操作、検体取得ヘッドの操作、およびコンベヤの動きを支配するコントローラであって、混合ヘッドに対する容器の呈示に応答して、混合ヘッドに、呈示される容器中の検体の混合を個別に行わせ、かつ検体取得ヘッドに対する容器の呈示に応答して、検体取得ヘッドに、呈示される容器から、予め混合しておいた粒状物質含有液体の吸引を行わせるコントローラとを備え、
ここで上記の複数の操作ヘッドには、
呈示される任意の容器中の撹拌手段に係合して撹拌手段を動かし、容器中の検体を撹拌するよう適用された回転可能な把持手段を有する撹拌ヘッドと、
撹拌ヘッドの下流に設けられ、フィルターマガジンを有するフィルター搭載ヘッドであって、呈示される任意の粒状物質分離チャンバーにフィルターを供給するよう適用されたフィルター搭載ヘッドと、
フィルター搭載ヘッドの下流に設けられた検体取得ヘッドであって、呈示される粒状物質分離チャンバーを封止して陰圧をかけることにより、あらかじめ撹拌しておいた粒状物質含有液を容器から吸引し、分離チャンバー内のフィルターを通過させて、フィルター表面

上に粒状物質の試料を捕集する検体取得ヘッドとが含まれる、自動式装置。
【請求項２４】
コントローラによって、撹拌ヘッドが、撹拌ヘッドに対して呈示された検体に特有の撹拌プロトコールにしたがって作動し、検体取得ヘッドが、検体取得ヘッドに対して呈示された検体に特有の吸引プロトコールにしたがって作動する、請求項23記載の自動式装置。
【請求項２５】
フィルター搭載ヘッドのフィルターマガジンが、少なくとも2種のフィルターを格納するよう適用され、コントローラによって、少なくとも2種の該フィルターのうちの1種が、呈示された検体に特異的な情報に応じて供給される、請求項24記載の自動式装置。
【請求項２６】
検体取得ヘッドが、呈示された任意の容器に入った検体を混合するよう適用され、コントローラが、検体取得ヘッドを作動させて、吸引操作の直前に検体を混合させる、請求項23、24、または25記載の自動式装置。
【請求項２７】
検体取得ヘッドが、混合ヘッドよりもゆっくりと検体を混合する、請求項26記載の自動式装置。
【請求項２８】
検体取得ヘッドの近傍にスライド呈示ステーションをさらに備えており、このスライド呈示ステーションでは、検体取得ヘッドが処理経路に対して可動であり、かつ検体取得ヘッドが、液体検体の吸引後に、分離チャンバーからフィルターを取得して取り除き、スライドにフィルターを押しつけて粒状物質試料をスライドに転写するよう適用され、そしてコントローラが、検体取得ヘッドによってフィルターが取り除かれた後にコンベヤーを前進させる、請求項23記載の自動式装置。
【請求項２９】
各容器は、取り外し可能なカバーを有しており、そしてカバーが所定位置に装着された状態でコンベヤに搭載され、かつ複数の操作ヘッドには、処理経路上の撹拌ヘッドの上流に設けられたキャップ取外しヘッドがさらに含まれ、このキャップ取外しヘッドは、呈示される容器のカバーを把持して取り外すよう適用された把持手段を有している、請求項23、24、または25記載の自動式装置。
【請求項３０】
複数の操作ヘッドが容器キャップ再装着ヘッドをさらに含み、この容器キャップ再装着ヘッドは、処理経路上の検体取得ヘッドの下流に設けられており、呈示されるキャップの取り外された容器に対して封止キャップを取付けるよう適用されている、請求項29記載の自動式装置。
【請求項３１】
検体容器搭載および取外しステーションをさらに含み、この検体容器搭載および取外しステーションが、処理後のキャップ再装着容器を把持してコンベヤ上の容器支持手段から容器を取り外し、未処理の検体容器を把持してコンベヤ上の空となった容器支持手段に装填するピック＆プレース・アームを備える、請求項30記載の自動式装置。
【請求項３２】
コントローラによって、ピック＆プレース・アームは、キャップを再装着した容器をコンベヤ上の容器支持手段から取り除き、未処理の検体容器を把持して、コンベヤ上の同一の容器支持手段へと装填を行い、この間、コンベヤの動きは止められている、請求項31記載の自動式装置。
【請求項３３】
複数の粒状物質含有液体検体をそれぞれの容器中で個別に処理するための自動式の方法であって、各容器が取り外し可能なカバーを有しており、この自動式の方法が、
容器を処理経路に沿って順次搬送して、同時に別の検体を操作しうるよう間隔をおいてそれぞれ配置された複数の操作ステーションに容器を呈示する過程と、
各操作ステーションを、各操作ステーションに対して容器が呈示されるのに応答して作動

させて、各操作ステーションのそれぞれの操作を個別に実施させる
工程とを含み、
ここで上記の複数の操作ステーションには、順番に、
呈示される容器のカバーを取り外すキャップ取外しステーションと、
呈示される容器中の検体を混合する混合ステーションと、
呈示される容器頂部に隣接して配置された粒状物質分離チャンバーに、フィルターを搭載するフィルター搭載ステーションと、
あらかじめ撹拌しておいた粒状物質含有液を容器から吸引し、分離チャンバー内のフィルターを通過させて、フィルター表面上に粒状物質の試料を捕集する検体取得ステーションとが含まれる、自動式の方法。

【請求項３４】
検体取得ステーションの下流に、呈示される容器にキャップを再装着する容器キャップ再装着ステーションをさらに備える、請求項33記載の自動式の方法。

【請求項３５】
検体取得ステーションが、粒状物質含有液体を容器から吸引する前に、粒状物質含有液体の再混合を行う、請求項33記載の自動式の方法。

【請求項３６】
処理経路および検体取得ヘッドの近傍にスライド呈示ステーションが位置しており、自動式の方法が、吸引された液体が通過した各フィルターをスライドに順次押しつけて粒状物質試料をスライドに転写する工程をさらに含む、請求項33または35記載の自動式の方法。

【請求項３７】
検体取得ステーションの下流に、呈示される容器にキャップを再装着する容器キャップ再装着ステーションをさらに備える、請求項36記載の自動式の方法。

【請求項３８】
複数の粒状物質含有液体検体をそれぞれの容器中で個別に処理するための自動式装置であって、各容器が取り外し可能なカバーを有しており、この自動式装置が、
容器を支持し、処理経路に沿って順次前進させるコンベヤと、
処理経路に沿って配置された複数の操作ステーションと、
操作ステーションとコンベヤの動きを支配するコントローラであって、各操作ステーションに対する容器の呈示に応答して、各操作ヘッドに、呈示される容器中の検体に対する操作を個別に行わせるコントローラとを備え、
ここで上記の各操作ステーションには、順番に、
呈示される任意の容器のカバーを把持して取り外すよう適用された把持手段を有するキャップ取外しステーションと、
呈示される任意の容器中の撹拌手段に係合して回転させるよう適用された回転可能な把持手段を有する撹拌ステーションと、
フィルターマガジンと、呈示される任意の容器頂部に隣接して配置され、粒状物質分離チャンバーにマガジンからフィルターを供給するよう適用された押し手段を有するフィルター搭載ステーションと、
呈示される粒状物質分離チャンバーを封止し、あらかじめ撹拌しておいた粒状物質含有液を容器から吸引し、分離チャンバー内のフィルターを通過させて、フィルター表面上に粒状物質の試料を捕集する吸引ヘッドを有する検体取得ステーションと、
呈示される任意の容器に対して封止キャップを取付ける可動ヘッドを有する容器キャップ再装着ステーションとが含まれる、自動式装置。

【請求項３９】
容器からの吸引を行う前に粒状物質含有液体を再撹拌できるよう、吸引ヘッドが回転可能である、請求項38記載の自動式装置。

【請求項４０】
処理経路および検体取得ヘッドの近傍にスライド呈示ステーションをさらに備えており、このスライド呈示ステーションでは、吸引ヘッドが処理経路に対して可動であり、かつ吸

引ヘッドは、液体検体の吸引後に、分離チャンバーからフィルターを取得して取り除き、スライドにフィルターを押しつけて粒状物質試料をスライドに転写するよう適用されている、請求項38または39記載の自動式装置。
【請求項４１】
吸引ヘッドによるフィルターの除去後に、コントローラによってコンベヤが前進する、請求項40記載の自動式装置。
【請求項４２】
複数の流体状生体物質検体をそれぞれの容器中で個別に処理するための自動式の方法であって、
容器を処理経路に沿って順次搬送して、容器を予備処理装置、ついで検体取得装置に対して呈示する工程であって、予備処理装置は、呈示される任意の容器中の検体を予備処理するよう適用され、かつ検体取得装置は、呈示される任意の容器から、その後の分析検査または評価に備えて、予備処理された検体流体を採取するよう適用されている、工程、
予備処理装置を、この予備処理装置に対して容器が呈示されるのに応答して作動させて、予備処理操作を個別に実施させる工程、および
検体取得装置を、この検体取得装置に対して容器が呈示されるのに応答して作動させて、流体取り出し操作を個別に実施させる工程
を含む自動式の方法。
【請求項４３】
予備処理装置が、検体流体の粒状成分を分散させる、請求項42記載の自動式の方法。
【請求項４４】
検体取得装置が、細胞診断用試料を捕集する、請求項43記載の自動式の方法。
【請求項４５】
検体取得装置が、採取した検体流体を濾過する、請求項43記載の自動式の方法。
【請求項４６】
検体取得装置が、細胞診断用試料を捕集する、請求項45記載の自動式の方法。
【請求項４７】
検体取得装置が、細胞診断用試料をスライド上に載置する、請求項46記載の自動式の方法。
【発明の詳細な説明】
【技術分野】
【０００１】
関連出願の相互参照
本出願は、本出願と出願人が同一である2001年10月19日に出願された米国仮出願第60/330,092号、2002年4月15日に出願された米国仮出願第60/372,080号、および2002年4月19日に出願された米国仮出願第60/373,658号に対して、優先権を主張する。これらの出願は、参照として本出願に組み入れられる。本出願は、本出願と出願人が同一である2002年4月15日に出願された米国非仮出願第10/122,151号にも関連している。これらの出願も、参照として本出願に組み入れられる。
【０００２】
技術分野
本開示は、粒状物を含む液体、たとえば生物学的流体である検体を捕集、処理する装置および方法に関するものであり、粒状物を捕集し、顕微鏡用スライドあるいは他の表面に、観察に適した（たとえば、細胞学のプロトコールの使用に適した）検体由来の粒子（たとえば細胞）の均一な層を堆積させる工程を含む。
【背景技術】
【０００３】
背景技術
診断細胞学、特に、臨床病理分野において、細胞をはじめとする顕微鏡観察の対象物の検査結果にもとづいて、細胞学的解釈および診断を行う。スクリーニング処理や診断でどの

程度の精度が得られるか、また解釈を行うのに適した試料を検体から調製しうるか否かは、適切な検体および試料の調製にかかっている。この点で理想的な試料は、細胞が実質的に等間隔に並んだ単層の細胞であり、こうした理想的な試料であれば、細胞技術者、細胞病理学者、その他の医療の専門家であれば、そして細胞像をより明瞭な画像で見ることができる自動スクリーニング装置および診断装置によって、異常をより容易に、正確かつ再現性をもって特定することができる。免疫細胞化学や細胞画像解析のような新しい方法論は、安全かつ有効で、正確で、精度が高く、再現性があって、安価で、効率がよく、迅速かつ手軽な調製装置および調製方法を必要としている。

【０００４】

試料の細胞学的検査は、患者から細胞の試料を含む検体を採取するところから始まり、この過程は、通常、頚部の検体の場合のように特定領域の掻き取り、綿棒でのこすり取り、ブラシでの採取を行うことによって、また、体液の採取、たとえば、胸腔部、膀胱、脊柱からの体液の採取を行うことによって、さらには、細針を用いた吸引や細針による生検を行うことによって実施される。通常の手作業での細胞学的検体の調製では、採取した流体中の細胞を観察するために、直接、または、遠心分離に基づく処理によってガラス製の顕微鏡用スライドに移す。典型的な自動化された細胞学的検体の調製では、フィルター組立体（assembly）を懸濁液中に配置し、フィルター組立体によって、細胞をフィルターに分散させつつ捕捉する。その後、フィルターを取り外し、顕微鏡のスライドに接触させる。こうした試みのいずれにおいても、試料調製プロトコールでの制限要因となっているのは、固形物を、その固形物を担持している流体から適切なかたちで分離する過程であり、固形物をたやすく、かつ効率的に捕集、濃縮して、顕微鏡での検査に使用しやすい形状とする過程である。

【０００５】

現在、細胞学的検査に供する生物学的検体は、特別の容器を使用することによって採取されている。こうした容器には、大抵の場合、採取地点から細胞学的診断を行う検査施設までの搬送の間に細胞学的検体を保存するために、保存剤と、搬送用溶液とが入っている。また、体腔から、綿棒、スパチュラ、またはブラシを使用して採取された細胞学的検体の場合も、細胞をスライドまたは膜上に移して染色または検査を行うまでは、固定液（たとえばアルコールまたはアセトン固定液）の入った特別の容器中で保存される。検体容器としては、液体ベースの生物学的検体を容器中で直接処理して、容器自体に付随した捕集部位（粒状物質分離チャンバーを規定するフィルターハウジング）上に実質的に均一な細胞の層を得ることのできる容器が公知である。たとえば、Raouf A. Guirguisの米国特許第5,301,685号、米国特許第5,471,994号、米国特許第6,296,764号、および米国特許第6,309,362号を参照されたい。なお、これらは、いずれも、参照として本明細書に組み入れられる。

【０００６】

これらの特許で開示された濾過技術では、確かに、スライド上に細胞の単層を得るという意味では、かなり良い結果が実現されているものの、まだまだ改善の余地がある。さらに、これらの特許で開示された検体容器類では、特別な形状の穴あきカバーと、このカバー用のアダプターが必要とされ、このアダプターは、フィルターのハウジングに、ならびに液体を容器から吸引してフィルターを通過させるために使用する吸引装置（たとえば、シリンジまたは機械化された真空源）に嵌合するよう設計されている必要がある。さらに、フィルターを顕微鏡用スライドに押しつけて、捕集された細胞をスライドに転写するためにフィルターを取り出す際には、カバーおよび/またはカバーに付随するアダプターのフィルターと協調する各部品を分解せねばならない。この操作を自動化装置で行う場合には、こうした分解を行うための特別の取り扱い装置が必要となる。装置がこのように複雑であるため、実際の細胞学的検査を行う前に必要とされる処理の時間、材料、および労賃がかさむ。

【０００７】

一般に、これまでに液体ベースの検体を処理するために開発されてきた自動化装置では、

癌のスクリーニング、他の細胞学的な医療、分析、スクリーニング、および診断の手順において現在、そして今後にわたって見込まれる必要性の数々を満たすのに十分な一貫性、信頼性、迅速性、自動化度は実現されていない。本明細書で開示するバイアルを基本とした自動化処理システムは、こうした問題について、安全で洗練された有効な解決方法を提供する。

【発明の開示】

【０００８】

発明の概要開示

本明細書に開示する検体バイアルは、完結した処理用組立体、典型的には、液体ベースの検体をその内部で撹拌し、検体由来の細胞を均一な細胞層としてその上に捕集するフィルターを保持した処理用組立体を収納している。検体バイアルは、通常行われるように、液状の保存用溶液を予め梱包し、検体を集める目的で医療現場に送付されることを想定している。

【０００９】

処理用組立体は、単純で、安価で、脱着可能な結合手段によって、バイアルの簡易カバーに結合させておく。そのため、医療現場（医師の診察室、診療所、病院など）でカバーを取り外しても、処理用組立体がカバーから外れないので、医療従事者は、容器の内部に簡単にアクセスさせて生物学的検体をバイアルに入れることができる。検体をバイアルに入れたら、カバーを、処理用組立体に結合させたままバイアルにかぶせて、バイアルを密封する。密封したバイアルは、検査施設に送って処理を行うことができる。

【００１０】

バイアルを閉じたままバイアルを簡単な方法で操作すると、処理組立体はカバーから離れて、バイアル中にとどまり、その結果、その後カバーを取り外すと、自動化検査装置または手動の検査装置にアクセスすることが可能となる。好ましい態様では、カバー中央部に下向きの力を加えるだけで、処理組立体をカバーから離脱させることができる。上述の従来技術の検体バイアルとは異なり、本発明のバイアルは、カバーにそれ以上の相互作用を行う必要はなく、カバーは、カバー取外し簡易装置で取り外して廃棄し、汚染を避けることができる。処理組立体は、バイアルの内側に設けられたリブによって適正な位置に保持されるので、処理の間のアクセスが可能となる。この内蔵式バイアルおよび処理組立体により、痰、またはその他の各種検体、たとえば尿、脊椎穿刺液、胃の洗浄液、細針による吸引物、婦人科試料等に含まれる結核菌、または他の病原物質等のバイオハザードに操作者が曝されるのを最小限に抑える。

【００１１】

本明細書で開示する自動化検体処理装置を、「LBP」装置（液体ベースでの調製用（liquid-based preparation）装置）と称するものであり、この装置は、品質が高く、ばらつきの少ないスライドを製造できるよう設計されている。LBP装置は、また、細胞レベルでの形態学的、細胞化学的および/または分子的な変化を検出および/または定量を行う装置と組み合わせることもできる。

【００１２】

この2年間あまり、文献を再評価し、既存のデータを再分析することによって、最も一般的な癌であり、高い感受性および特異性を示す癌でもある肺癌を検出しうるような一連の分子診断用物質が特定されてきている。たとえば、本発明と譲受人を同一とする米国特許出願第10/095,297号および米国特許出願第10/095,298号（双方とも2002年3月12日出願）および米国特許出願第第10/241,753号（2002年9月12日出願）を参照のこと。こうした場合では、細胞を、癌の診断結果と対応するような変化のパターンを識別しうる抗体および/または核酸「プローブ」と反応させることができる。こうした分子システムは、上記のような腫瘍の異質性に合わせて微調整したアルゴリズムを利用することができる。

【００１３】

細胞レベルで分子の変化を識別する方法は、癌を早期の治癒しやすい段階で検出する方法の一つである。このような分子診断手段は、集団を基礎として癌の発症リスクをもつ個人

をスクリーニングする際の使用が正しいものとされるのに必要なだけの感度と特異性とをもって、早期の検出および診断に使用することができる。こうした分子診断手段は、腫瘍の特性を決定することによって、腫瘍の専門家が患者を層別化し、治療方法を患者に合わせて作成し、患者をモニターして、治療の効果と疾患の縮退、進行、または再発について評価するために使用することもできる。こうした検査が可能となることで、早期段階における疾患の治療に際しての、新規で、より効果的な治療方法の開発もまた促進される。

【００１４】

こうした分子診断は、コストと検査性能とのバランスがとれるように設計される。スクリーニング検査は、高い感受性と特異性とを示す必要があるものの、こうした検査は、リスクは有するが、疾患を裏付ける症状を通常は呈していない多数の個人を対象として行うことを通常意図しているので、コストは常に極めて重要な要因となる。この点に関しては、本発明のLBP装置は、分子診断手段と組み合わせることによって、個々人の身体に対して、ほとんど、またはまったく介入せずに癌の自動化された診断を行うことのできるシステムを開発することができる。または、本発明のLBP装置は、LBP装置で製造された個々のスライドの観察を医療の専門家が行う病理観察用のワークステーションと組み合わせることもできる。得られた診断システムは、自動化された装置であっても、手動の観察装置であっても、特定の目的に特化したソフトウェアとコンピュータ・オペレーティング・システムを基本とする統合データ管理システムとを組み合わせることによって、データの入力、情報の交換、検査施設と病院情報システムとのネットワークを管理することができる。

【００１５】

本発明のLBP装置では、複数の上述の新型検体バイアルが、各種の処理ステーションを通って逐次搬送されており、スライド上に固定された検体が作製される。その際、各スライドは、バーコードを付され、データ管理システムによって、バイアルおよび採取元の患者と関連づけられる。カセットから、新しいスライドが1回に1枚ずつ自動的に取り出され、このスライドは、検体の固定後に同じカセットに返却される。LBP装置は、複数のスライド用カセットを搭載することができ、前のカセットのスライドがすべて使用されたら、装置は、自動的に、次のカセットから新しいスライドを引き出す。スライド用カセットは、液体に浸漬することができ、かつカセットからスライドを取り出さなくても染色が可能であるような自動化された染色装置と組み合わせうる形状としておくのが好ましい。この点からすると、カセットには、液体の排出に使用しうるスロットを設け、かつ他のタイプのスライドホルダーを吊るす目的で染色装置に通常使用されているようなフックと協働するスロットまたは他の手段を設けておくことが好ましい。このスライド用カセットは、統合システムの一部を構成する自動化された診断装置および他の装置類とも組み合わせうる形状としておく。

【００１６】

検体バイアルは、手動で搬送手段に搭載することも可能ではあるものの、検体バイアルを自動的に搭載して処理を可能とし、処理が完了したら各検体バイアルを取り除くバイアル取り扱いシステムを必要に応じて使用すると、自動化の利点を十分に生かすことができる。こうした取り扱いシステムの一態様では、バイアルを、それぞれバイアルを41本まで保持することのできる特別の省スペースのトレーに、最初は、手動でバイアルを搭載する。LBP装置には、トレーを8枚まで搭載することができ、装置では、トレーからバイアルを1回に1本ずつ取り出し、処理済みの（再度封止した）バイアルをトレーに戻すことによって、それらのすべてを順次処理していく。トレーは、処理済みのバイアルを保存したり、捕集したりする際にも使用することができる。

【００１７】

各バイアルは、各バイアルごとのレセプタクル（receptacle）に収納されて、コンピュータによって制御されたコンベヤで、LBP装置を搬送される（本明細書に開示する態様では、コンベヤには、30個のレセプタクルが設けられている）。バイアルとレセプタクルとは楔止されているので、処理経路を適正な向きのまま移動し、それぞれのレセプタクルと独立に回転することはない。バイアルは、まず、（データ取得ステーションで）バーコード

リーダーを通過し、ここでバイアルのバーコードが読みとられ、その後、LBP装置の以降の処理ステーション、すなわち、キャップ廃棄操作を含むキャップ取外しステーション、一次混合または拡散ステーション、フィルター搭載ステーション、検体取得およびフィルター廃棄ステーション、細胞塗布ステーション、およびキャップ再装着ステーションを順次移動する。LBP装置は、検体をスライドに転写するために、新しい顕微鏡用スライドが検体取得ステーションに対して呈示されるスライド呈示ステーションも備えている。各ステーションは、コンベヤによって呈示されるバイアルとは独立に作動するが、コンベヤは、作動しているすべてのステーションが、それぞれの作業を終了するまでは前進しない。

【００１８】

バイアルキャップ取外しステーションは、バイアルからカバーのねじを緩めて外し、廃棄する回転把持手段を備えている。ただし、その前に、キャップ取外しヘッドは、カバーの中央を押して、バイアル内部の処理組立体をカバーから脱着させる。一次撹拌ステーションは、処理組立体を把持してわずかに持ち上げ、各検体に即した撹拌プロトコール（速度および時間）にしたがって移動（たとえば回転）させる拡張式のコレットを備えている。フィルター搭載ステーションは、処理組立体上部の粒状物質分離チェンバー（マニホルド）に、検体に対応した種類のフィルターを載置する。検体取得ステーションは、吸引ヘッドを備えており、この吸引ヘッドは、処理組立体の上方のフィルターを封止し、まず、処理組立体を動かして、液体ベースの検体中の粒状物質を徐々に再懸濁させる。次に、吸引ヘッドは、フィルターに陰圧をかけて液体ベースの検体をバイアルから吸引してフィルターを通過させ、単層の細胞がフィルター底面に残るようにする。その後、単層検体が新しいスライドに転写され、バイアルはキャップ再装着ステーションへと移動し、ここで、バイアルに金属箔の封止が施される。

【００１９】

フィルターシステムは改良されているので、極めて高品質の単層検体が確実に生成する。検体液体は、フィルターを通過して流れるとともに、フィルター前面を実質的に横切る方向にも流れる。具体的には、検体液体には、フィルター面を横ぎるような二次的な流れ成分がある。この二次的な流れは、半径方向外側に向かって流れるか、あるいは、実質的に半径方向の流れ成分を含むよう設計されており、その結果、相対的に弱い力で付着している粒状物質の塊を押し流すような剪断作用が生じ、フィルター前面に、分布がより均一の薄い層を形成することが可能となる。この点に鑑み、本発明のシステムでは、フィルター前面に隣接する領域から検体液体が流れこんで通過することのできる流出口が周囲に設けてある。

【００２０】

フィルター組立体は、ホルダーと、ホルダーに収納したフリットと、フリットの外面を覆い、フリットと接触するよう配置したメンブレンフィルターとを備えることが好ましい。フリットは、ホルダーの端部を超えて延在させることができる。メンブレンフィルターは、ホルダーに固定することができる。フリットのホルダーを超えて延在している側壁部分は、検体液体が通過しうる領域を形成することとなり、その結果、二次的な流れが形成される。ホルダーは、フリットの中央部がわずかに外向きに湾曲した形状として、検体転写工程でスライドに圧力を加えたときに、フリットの中央部が平坦となり、メンブレンフィルターがスライドとより均一に接触して、より効果的に転写されるようにする。

【００２１】

処理組立体の上端に位置するマニホルドは、フィルター組立体を、メンブレンフィルターの側が下向きとなるように収納する。マニホルドの底部壁は、（処理組立体の、下垂する吸引管部分と連通する）中央流入口から立ち上がる実質的に円錐の形状とするのが好ましい。フィルター組立体と円錐形状の底部壁は、マニホルドチャンバーを形成しており、このマニホルドチャンバーには、周囲にわずかな隙間が設けてある。この隙間は、スペーサとして機能する隆起部材または支柱が設けてあるので、周囲流出口を形成している。支柱の間には、流路が形成されており、検体液体は、この流路を通って、マニホルドチャンバーから流出することができる。

【００２２】
本明細書では、システムを構成する部品のいくつかについて、各種の好ましい材料や、それらを代替しうる材料について記載する。ただし、選択しうる材料は、具体的に記載された材料に限定されるものではなく、また、代替材料の選択は、（たとえば、使用者の要求やマーケティングの要請に応えるうえでも、）多くの要因、たとえば、官能性、成形時の精度、耐性、耐薬品性、保存性、コスト、入手容易性、および/または光学的透明性によって左右されると理解されたい。
【００２３】
特許請求の範囲に記載した本発明の最も基本的な局面では、本発明は、複数の粒状物質含有液体検体を各容器中で個別に処理する自動式の装置および方法に関する。容器は、処理経路に沿って順次搬送され、呈示される任意の容器中の検体流体を予備処理する予備処理装置に対して少なくとも呈示され、その後、 呈示された任意の容器から、その後の分析検査または評価に備えて予備処理済みの検体流体を採取する検体取得装置に対して呈示される。各装置は、各装置に容器が呈示されるのに応答して作動し、各装置それぞれの操作を個別に実施する。検体は、生体物質を含有していてもよい。
【００２４】
予備処理装置は、検体に作用して、検体流体の粒状成分を、たとえば混合によって分散させることができる。一方、検体取得装置は、粒状物質の試料を、たとえばフィルター上に捕集することができる。濾過の場合には、検体取得装置の上流のフィルター搭載ヘッドが、フィルターを、容器によって担持された粒状物質分離チャンバーに供給し、フィルター搭載ヘッドは、呈示される任意の容器に応答して、他の装置とは独立に作動する。フィルターに担持された試料は、スライドに転写することができる。
【００２５】
本発明の他の局面において、本発明の方法には、さらなる別の操作、たとえば、検体の予備処理を行う前に、容器からキャップを取り外す操作、および処理の完了後に、容器に再度キャップを装着する操作を含めてもよい。装置に関しても同様に、こうした操作を行うために、さらなる別のヘッド等の装置を含んでいてもよい。各操作は、各操作ステーションに容器が呈示されるのに応答して、独立に実施される。
【００２６】
開示するシステムおよび発明の好ましい態様を、発明を実施するための最良の形態も含めて以下に詳述する。これらは、例示の目的で示すものであって、説明に際しては、添付図面に言及する。
【００２７】
最良の形態の詳細な説明
本発明のバイアルを基本とする検体の取扱い・処理システムについての全般的な説明を開始するにあたっては、バイアルそれ自体の説明から開始せねばならない。このバイアルは、容器、カバー、およびバイアル中に配置された処理組立体（撹拌部材）から構成されている。
【００２８】
検体バイアル
図1、2a、および2bについて説明すると、バイアル10は、容器20、カバー30、および処理組立体40を備えている。処理組立体40は、撹拌をはじめとするいくつかの機能を実行すべく設計されており、この好ましい回転式の態様については、便宜上撹拌部材と称するものとする。容器20は、半透明プラスチック、好ましくはポリプロピレンから成形するのが望ましく、容器の長手方向軸線を取り囲むかたちで実質的に円筒形状の壁21を備え、この壁21が、円錐形状の底部壁22に接合されている。プラスチックとしては、ABSおよびポリシクロヘキシレンジメチレンテレフタレート、グリコール（イーストマン・コダック社（Eastman Kodak Co.）からEASTAR(登録商標)DN004の名称で市販）をかわりに使用することもできる。壁21の一部24を平坦とし、この平坦部の外面に、バイアルに入れた検体に関する情報を含む表示、たとえばバーコードのラベルを配置できるようにするのが好ましい。図

には平坦部分が一カ所のみ示されているものの、容器は、平坦部分のない形状とすることも、または、二カ所以上の平坦部分を備えた形状として、それぞれに表示を設けることもできる。または、表示は、壁21の曲面部に配置することもできる。平坦部分24の下端には、弓形のノッチ25が設けてあり、このノッチ25は、容器を架台に載せて各種の処理ステーションを移動させるLBP装置によって容器をハンドリングする際に作動して、容器を適正な向きに保持する。ノッチがLBP装置と適正に嵌合するかぎり、別の形状のノッチ（たとえば、V字形のノッチ）を使用することもできる。他の適当な嵌合用構造をかわりに使用することも可能である。

【００２９】

壁21からは、4本の長手方向リブ26が内向きに突出している。撹拌部材40がカバー30から離脱した際には（図10を参照のこと）、このリブ26の上端27が、撹拌部材40の支えとして機能する。容器20の頂部は開口部28となっており、標準的な右手方向の螺旋状ねじ29が形成され、このねじ29は、好ましくは、一回半分延在し、カバー30上の同様のねじと嵌合する。カバーと容器とを結合する形式としては、他の形式を使用することもでき、たとえば、差込式結合、スナップ嵌合の配置などを用いることができる。

【００３０】

カバー30は、プラスチック成形された市販の単純なねじ付きキャップ31と、キャップ内に保持された新規なライナー32を備えている。キャップ30は、ポリプロピレンから成形するのが好ましいものの、プラスチック材料としては、他にも、ABSおよびEASTAR(登録商標)DN004を使用することができる。キャップ31は、平坦で硬い頂部と、そこから張り出した、外面にぎざぎざのついたフランジを含み、このフランジの内面には、容器20のねじ29と嵌合する螺旋状のねじ33が設けられている。図4について説明すると、ライナー32は、プラスチック材料、好ましくはポリエチレンから成形されており、ライナーが簡単にキャップから外れることがないようキャップ31内のねじ33の奥にちょうど納まる寸法の実質的に平坦な基部34を備えている。図1からわかるように、ライナー基部34は、キャップ31と容器の壁21のリムとの間で、ガスケット型の封止材の役目を果たしている。

【００３１】

ライナー基部34は、環状突出部35形状の結合部材を備えており、この環状突出部は、やや円錐形状とするのが好ましく、中央軸線に対して約5°の角度で設けることが好ましい。すなわち、環状結合部材35の内径は、先端より、ライナー基部34に結合している基端で大きめとする。ライナー基部34は、中央環状ボス36も備えており、このボス36は、基部34からみて環状結合部材35より先まで突出し、後述するように撹拌部材40と相互に作用する。キャップとは別のライナーを、標準的なキャップと嵌合させて使用することが好ましいものの、カバーを1部品として一体に成形し、環状結合部材35および中央環状ボス36を含むものとすることもできる。カバーは、こうした1部品のカバー（または、上述したような2部品のカバー）ではなく、容器の壁21のリムの内側に沿って突出し、リムの内側との間で封止が生じるような栓型のシールとして作用する形状とすることもできる。

【００３２】

図1、3、および5について説明すると、撹拌部材40は、プラスチック、好ましくはポリプロピレンから成形され、中央が傾斜し、中央流入口42の設けられた円形の基部または底部壁41と、管の底部付近に2つの半径方向の両端に位置する吸引口44の設けられた中央に下垂する吸引管43と、外側に向かって延在する羽根45の形状とした分散用（撹拌用）部材とを備えている。撹拌部材40の上部は、基部41と、上方に立ち上がった環状壁47とによって規定された杯状の粒状物質分離チャンバーまたはマニホルド46を備えている。壁47の上端は傾斜させ、内縁48は、傾斜をきつめとして、後述するように、マニホルド46内にフィルター組立体Fを配置しやすい形状とするのが好ましい。撹拌部材に使用しうるプラスチック材料としては、他に、ABSおよびEASTAR(登録商標)DN004が挙げられる。

【００３３】

環状壁47は、撹拌部材40をキャップのライナー32に着脱可能に結合するための結合部材の役割を果たしているため、環状結合部材35にちょうど納まる寸法とする（図1を参照のこ

と）。具体的には、結合部材35と結合部材47とは、摩擦嵌めまたはプレス嵌めで結合されており、閉じたバイアルを通常のかたちで取り扱っても、さらに、（たとえば、生物学的検体を容器に入れる目的で）容器20からカバー30を取り外し、取り外したカバー30を通常のかたちで取り扱っても、撹拌部材がカバーから離れることはない。結合部材47は、結合部材35に対して、当初の直径方向の干渉が極めてわずか、好ましくは、約0.31 mmとなるような寸法とする。結合部材47の方が結合部材35より硬いので、撹拌部材をカバーに取り付ける際には、わずかな変形が、主に結合部材35の側に生じ、その結果、摩擦力が生じて撹拌部材がカバーに係合したままとなる。こうした摩擦による保持力に打ち勝つ外力をバイアルに加えると、撹拌部材40がカバー30から離脱し、重力によって、さらに容器20に落ちる（図10を参照のこと）。

【００３４】

外部から撹拌部材を離脱させるために加える力は、カバー30の中央部分に加えるのが好ましく（図10の矢印を参照のこと）、この力は、キャップ31とライナー32とを内向きに変形させる。図1に示すように、ライナー32の中央ボス36は、その先端が、撹拌部材の基部41にちょうど触れるかわずかに触れないくらいの寸法となっている。そのため、カバーの中央部をくぼませると、中央ボス36は、ライナー32の環状結合部材35より大きく変形し、撹拌部材40が押されて、結合部材35との係合関係が外れる。また、ライナー32が内向きに変形すると、結合部材35が外向きに広がり、撹拌部材を保持する力が低減し、撹拌部材が離脱しやすくなる。撹拌部材を離脱させるためにカバー30に加える力は、5～30ポンドの範囲、好ましくは約12ポンドとする必要がある。

【００３５】

撹拌部材40は、カバー30から離脱すると、リブ26の上端27で受け止められる。図10を参照のこと。このようにして、粒状物質分離チャンバー（マニホルド）46は、容器開口部付近で安定したかたちで支えられ、LBP処理ヘッドが容易にアクセスし、撹拌部材を操作することによって検体を直接容器中で処理することが可能となる。撹拌部材を安定的に支えるためには、少なくとも3本のリブ26が必要であるが、リブは4本設ける方が撹拌に際して粒状物質が液体中でよりよく分散するようであり、好ましい。医療現場において、撹拌部材が不注意にもカバーから離脱してしまった場合には、医師または補助者は、単に、撹拌部材をバイアル中に軽く置いて、検体中に撹拌部材が沈むようにすればよく、その後、普段と同様にして、カバーを回し締めすればよい。この過程は、困難ではない。というのも、バイアル中にリブが設けられているために撹拌部材を一方向にしか挿入できないからである。検体の入ったバイアルが一度閉じられると、撹拌部材は、処理の過程を通じてバイアル中に保持され、バイアルのキャップを締め直す際にもバイアル中に封止されている。

【００３６】

患者の検体には、ごく一部ではあるが、婦人科のパパニコロー塗抹検査や他の種類の検体のように、大きな細胞塊、人工物、および/または細胞や細胞以外の破片の含まれるものがある。こうした大型の混雑物には、捕集されてスライド上に載せられた場合に、診断対象である細胞の視認を困難とし、結果的に、スライドの試料についての解釈や診断の正確さを損なうものも含まれている。こうした混雑物の大半は診断上重要ではないので、一般的には、試料から取り除いておくことが望ましい。そのためには、撹拌部材の吸引管43の側面吸引口44を設けずに（図10aを参照のこと）、吸引管43の底部と、容器20の底部壁22中央に設けた小型の突起23との間の境界面で細かい制御を行うことが望ましい。この境界面は、効果的に計量バルブを形成しており、その形状（オリフィス）23aは、撹拌部材40が容器20のリブ26に受け止められる際にかたちづくられる（図10を参照のこと）。環状の流入オリフィス23aを適正な寸法としておくことで、大型混雑物が吸引管43に入ることを防止しつつ、診断上有用な可能性のある小型成分は通過させることができる。オリフィス23aに設けられているのは、細い通過セクションと小型の計量領域であるが、径が大きいために、詰まりが問題になることはない。環状オリフィス23aは、外径を0.105インチ程度、内径を0.071インチ程度とするのが好ましく、この場合には、通路の幅は、0.017インチ程度となる。オリフィスのこの寸法は、婦人科の検体について最適化したものである。

【００３７】
フィルターシステム
図6および8に、本発明のフィルター組立体Fの一態様を示す。図3および6に、本発明の（撹拌部材40中の）マニホルド46の一態様を示す。フィルターシステムは、フィルター組立体Fと、マニホルド46とを含む。
【００３８】
図6および8について説明すると、フィルター組立体Fは、フィルターのハウジングまたはホルダー200、多孔質のフリット202、および多孔質メンブレンフィルター205を含む構成となっている。図8に、これらの構成部分を、拡大図でより明瞭に示す。ホルダー200は、フリット202を納めるくぼみまたは凹部206、およびフリット202とホルダー200との間に規定されたチャンバー207を備えた杯形状または容器形状とすることができる。フリット202およびメンブレンフィルター205は、上掲のGuirguisの特許、すなわち米国特許第5,301,685号および米国特許第5,471,994号に開示された材料から製造することができる。なお、これらの開示については、参照として本発明に組み入れられる。
【００３９】
本フィルター組立体Fでは、メンブレンフィルター205、フリット202、およびホルダー200を一緒に組み立てて、ユニットとする。円筒形状のフリット202を、まず、ホルダー200内に配置する。次に、メンブレンフィルター205を、ホルダー200に、恒久的に固定、接着、結合、または融着する。図示した態様では、メンブレンフィルター205の外周または外延が、ホルダー200に融着されている。この点に関しては、ホルダー200の外周コーナー部に、斜角面または傾斜面208が形成されている。この傾斜面208は、通常の結合技術、たとえば、超音波溶接を使用することによってメンブレンフィルター205を付着することのできる、角度のついた表面となっている。ホルダー200とメンブレンフィルター205は、互いに融着する材料から形成する必要がある。双方をポリカーボネートから形成するのが好ましいが、ABS製のホルダーであれば、ポリカーボネート製のメンブレンフィルターとともに使用することができる。メンブレンフィルターが同一材料から形成されているのであれば、熱可塑性ポリエステルをホルダーに使用することも可能である。フリット202は、ポリエチレン製のものが好ましい。
【００４０】
図8について説明すると、ホルダー200は、円筒形とするのが好ましく、底部壁または基部210と、基部210から実質的にまっすぐ立ち上がってリム211aまで延在している円筒状の側壁211とを含む実質的に杯形状の胴部を備えている。側壁211には、半径方向内側に中央に向かって延在する環状の肩部212が設けられている。肩部212は、フリット202を正確に位置決めする受け部の役割を果たす。フリット202は、フリット背面の周囲部分が肩部212と当接した際に、フリットの外面またはリム211aが前面213にとってとるに足る（リム211aを超えて前面213がさらに延在する）ような寸法とする。
【００４１】
側壁211の内径は、フリット202を摩擦によって所定の位置に係合して保持するような寸法とすることができる。この点については、フリットの外径を、側壁211の内径と実質的に対応するものとして、機械的に、すなわち摩擦によってフリット202を所定の位置に保持することができる。しかし、メンブレンフィルター205がフリット202を覆っているので、フリットは、摩擦によってホルダーに保持しなくてもよい。すなわち、フリット202は、ホルダー中に余裕を持って納めてもよい。しかし、フリット202を摩擦によってホルダー200に載置すると、フリット202が所定の位置に保たれ、メンブレンフィルター205の付着を、離れた位置にて行うことが可能となる。また、フリット202を摩擦によってホルダー200に載置すると、ホルダー200とフリット202とを結合させて準組立体を製造し、この準組立体を保存しておいて、その後、メンブレンフィルター205を取り付けることができるので、フィルター組立体の大量生産をより単純かつ低コストで実施することが可能となる。
【００４２】
フリット202をホルダー200に載置した後、図6にわかりやすく示すように、メンブレンフ

ィルター205を、フリット外面213と、フリット側壁215の、ホルダー200を超えて延在する露出部214とに覆い被せ、傾斜面208に付着させる。フリットの露出した外部側壁部分214は、検体の液体が通過して流れることのできる環状の表面領域となっており、この部分を検体液体が通過することで、図7aに模式的に示すように、二方向の流路が形成される。

【００４３】

フィルター組立体Fには、コードを付して、特定の処理プロトコールで必要とされる可能性のある各種の孔径および孔密度（単位断面積あたりの孔の数）を記載することができる。フィルター組立体には、色でコードを付すことが好ましいが、機械による検出が可能であれば、任意のコード、たとえば、触知基部のセンサーによる認識が可能な小型ニップルのような識別用突起を付すこともできる。LBP装置には、色または他のコードを識別しうるセンサーを設け、適正なフィルターを確実に選ぶ。フィルター組立体には、LBP装置に挿入しやすいよう、紙製の支持体入りとすることもできる。

【００４４】

図8について再度説明すると、ホルダーの底部壁210には、中央開口部204が設けてあり、この開口部204を通して真空を引き、検体液体を吸引することができる。ホルダー200には、さらに、底部壁210からホルダー内部に向かって延在する中央突出部または突起216が設けてある。この中央突起216は、開口部204と同心的に配置しされ、フリットの内面218、底部壁210の内面219、側壁211の内側220によって規定されるチャンバ207の内部に位置している。突起216は、実質的に中空で、複数の側面開口部221を備えており、この側面開口部221によって、チャンバー207が減圧され、チャンバーを通過する実質的に対称な流れが創出される。メンブレンフィルター205とフリット202を通して吸引された検体液体は、チャンバー207を満たし、その後、側面開口部221と中央開口部204を通ってチャンバー207を出る。

【００４５】

突起216は、ホルダーの開口面に向かって延在する当接面217を備えている。この当接面217は、フリットの背面218と当接する形状を有する。具体的には、当接面217は、環状肩部212よりわずかに先に存在している。すなわち、当接面217は、環状肩部212のレベルよりわずかに上側または先に存在しているので、フリットをホルダーに装着すると、フリットの外面213が、わずかに外向きに湾曲することになる。たとえば、当接面217は、環状肩部212の高さより、約0.002インチ先まで延在させることができる。その結果、突起がフリット202の中央部を外向きに押し出して、フリット202の中央部がわずかに湾曲することとなり、このわずかな湾曲が存在しているために、メンブレンフィルター205の中央部がスライドと確実に接触することになる。押圧転写の間にスライドに加えられる圧力によって、フリットの前面213が平坦となり、メンブレンフィルター205がスライドと十分に接触し、捕集された粒状物質がスライドに効果的に転写され、堆積の欠損箇所が低減する。こうしたわずかに湾曲した形状が望ましい場合には、フリット202は、上述したように、摩擦によってホルダー200にしっかり納めることが好ましい。

【００４６】

フリットが湾曲形状をしているので、メンブレンフィルター205は、張りつめた状態でなくてもよい。このことにより、製造過程が簡素化され、コストが削減され、検品での棄却率も低減する。フィルターは、めだった皺さえなければ、有効に作動する。前述したように、フリット202は、わずかに変形可能とするのが好ましく、そうすると、吸引後にフリットのコンプライアンスによってフリットが変形してスライドに対して平らとなり、目的とする細胞や他の構成成分をフィルターからスライドに転写することが可能となる。こうしたことを可能にするためには、フリットは、8ポンドの力を加えると、0.0016インチ変形して、平らに押しつぶされうるような弾性を有している必要がある。良好なフリット材料としては、焼結ポリエチレンおよび焼結ポリエステルが挙げられる。フリット202は、孔径が通常約50 μm～70 μmの範囲の孔が空間的にランダムに配置された多孔質材料とすることができる。この材料の顕著な特性として、薄層のメンブレンフィルター205（通常は孔径約5 μm～8 μm）の材料と比べて、流れが妨害されにくいことが挙げられる。すな

わち、圧力降下は、メンブレンフィルター205を通過する場合と比べてフリット202ではるかに低い。したがって、フィルターを通過した流体は、フリットを自由に流下する。フリット202は、また、ランダムに配置された孔ではなく、多数の小内径（たとえば、50 μm～70 μm）の流路が平行に延在し、その内部を吸引された流体と粒状物質が通過する構造を有した材料から製造することもできる。こうした平行な流路の配置は、見かけ上流れの妨害が少ない内部流体通過性メジュームとして機能する。実際、検体捕集ステーションには、孔の有無にかかわらず、流れが適正な程度に妨害されにくく、変形/弾性特性を有する材料や素子であれば、任意のものを使用することができる。

【００４７】

検体液体を実質的に軸線方向、すなわち、メンブレンフィルターと垂直方向に流すと、特に、必要以上の時間にわたってメンブレンフィルターを通して真空を引いた場合には、図7bに模式的に示すように、粒状物質の層または塊が蓄積する可能性があることがわかっている。こうした状態は、流れが二方向に生じ、半径方向の二次的な流れ構成成分がある程度生じるGuirguisのデザインの場合であっても生じることがある。たとえば、Guirguisの米国特許第5,471,994号および米国特許第5,301,685号の図4および12を参照のこと。この形状によって形成される二次的な流れは、メンブレンフィルターを横断して押し流したり、剪断したりする効果を生じるには不十分なようである。Guirguisのさらに以前の特許、すなわち米国特許第5,137,031号には、漏斗または円錐形状のマニホルドが開示されている。この構成では、周囲に、二次的な半径方向外向きの流れは存在しない。フィルターそのものを通過して直接流れる流れ以外には流れが存在しないので、実質的な半径方向の流れの成分は存在していない。したがって、検体液体は、実質的にメンブレンフィルターに垂直な方向にのみ流れる。

【００４８】

図6について説明すると、撹拌部材40の頂部に位置するマニホルド46の縦壁47の内径は、フィルター組立体Fの外径、すなわちホルダーの側壁211の外径よりわずかに大きめの寸法としてあるので、図示するように、マニホルド46は、メンブレンフィルター205が下向きとなるようにフィルター組立体Fを受け止め、収納することができる。フィルター組立体Fは、マニホルド46に余裕をもって納めることができる。フィルター組立体Fをマニホルド46に納めると、メンブレンフィルター205の外周端が、底部壁41に受け止められる。底部壁41は、くぼみまたは凹部を備えた形状となっているので、フィルター組立体Fをマニホルド46に納めた際にマニホルドチャンバーMが形成される。このように、チャンバーMは、メンブレンフィルター205の外面と、底部壁41の上面41Sによって規定されている。

【００４９】

本発明の流れが二方向に生じる構成は、メンブレンフィルターの表面に粒状物質が堆積または蓄積するという問題を解決する。この構成では、粒状物質を脇に押し流し、堆積したり積層したりすることを防止するのに十分な剪断力または剪断作用が、メンブレンフィルターの前面を横切るように発生する。堆積または積層した粒状物質は、メンブレンフィルター205の孔が粒状物質で覆われるにしたがって吸引力が低減するので、堆積していくにしたがって下層に対する結合力が弱くなる。剪断力は、接線方向または実質的に半径方向の流れ成分を、メンブレンフィルター205の前面を横切るように、検体液体に対して付与することによって生成される。この流れ成分は、メンブレンフィルターの前面と実質的に平行、すなわち、層の堆積方向と垂直であり、粒状物質を、半径方向外向きに、メンブレンフィルターの前面から遠ざかる方向に押し流す。

【００５０】

二次的なまたは半径方向の流路を確保するために、マニホルド46は、メンブレンフィルター205の前面と底部壁41の上面41Sの間に形成されるマニホルドチャンバーMの周囲にわずかな空間または隙間G（図6を参照のこと）ができる形状とし、押し流された粒状物質が、メンブレンフィルターの前面から離れてマニホルドチャンバーMを出るようにする。隙間Gは、粒状物質が詰まることのないよう、十分な幅をとる。つまり、もし隙間が濾過を行っている粒状物質に対して狭すぎると、隙間Gが詰まり、二次的な流れが途絶えてしまうこ

とになる。隙間の最小寸法は、最終的には、粒状物質の粒径、検体液体の粘度、検体液体の温度によって決まる。隙間Gは、細胞粒状物質が詰まらないようにするうえでは、少なくとも0.004インチは必要がある。

【００５１】

図3および6について説明すると、マニホルド46の底部壁41には、流出ノズルを形成する隙間Gを形成するために、マニホルド46の周囲に、複数の互いに間隔をおいて配置された支柱または隆起リブ48aが設けてある。リブ48a間の空間49は、検体液体がチャンバーMから出る際の流路となる。図示した好ましい態様では、マニホルド46の内径は23.4 mmで、36本のリブ48aが10°の間隔をおいて配置されている。リブは、高さ0.150 mmで、図示するように、湾曲しつつ周囲の肩部に続いており、半径Rが0.63 mmである。本発明では、互いに間隔をおいて配置されたリブまたは支柱の形状として、他の形状も想定しており、このリブまたは支柱によって、フィルター組立体を底部壁41から厳密に離して配置して、厳密な流出領域を創出する。リブまたは支柱の数と太さに応じて、流出領域の合計面積は、流入領域と比較して、50%まで減らすことができる。

【００５２】

上記で言及したGuirguis型のフィルター構成では、半径方向外側に向かって移動する検体液体が失速することが観察された。本発明の流れが二方向に生じるフィルターシステムでは、検体液体が流下する実質的に円錐形状の浅い面を設けることによって、速度の低下を補う。この面は、メンブレンフィルター205と対向する実質的に円錐形状の分配用マニホルドチャンバーMを形成している。本発明のチャンバーMは、空間49経由での環状の半径方向出口0を備えており、この出口0は、中央流入口Iの最大面積にほぼ等しいか、それより狭い面積を有している。図9について説明すると、半径方向の環状の流路の「正面」領域は、円筒状で、任意の所定の半径R_1、R_x、Ry、...、R_2にて、メンブレンフィルター205の前面とマニホルドの円錐面41Sとによって規定されて（領域が定められて）いる。検体液体が外側に向かって移動するにつれて、半径が増大し、その一方で、マニホルドの高さは低減する。マニホルドチャンバーMは、高さH_1、H_x、H_y、...、H_2が、環状流路の正面領域がマニホルド流入口Iから外周流出口0まで実質的に一定に保たれるような割合で低減し、メンブレンフィルター205の正面に沿った半径方向流速が実質的にリニアとなるような形状とすることができる。

【００５３】

この点については、図9についてさらに説明すると、円形のマニホルド流入口Iの理論上の半径方向の最大流れ面積は、周囲の長さ（$2\pi R_1$）にマニホルドチャンバーの高さH_1を乗じたものとして定義することができる。この場合、$2\pi R_1 H_1$は、マニホルド流入口Iの最大周囲面積を定義する。マニホルド流出口0の最大周囲面積は、$2\pi R_2 H_2$として定義することができる。流出口の流れの面積が、流入口の流れの面積と同じである場合には、流入口の面積と流出口の面積は、下記のように表すことができる。

$$2\pi R_1 H_1 = 2\pi R_2 H_2$$

$$R_1 H_1 = R_2 H_2$$

この式を使用すると、高さ、たとえば、H_x、H_yを、流入口Iから流出口0までの所定の半径、たとえば、たとえば、R_x、R_yで定義することができる。流入口から流出口までの高さH_1、...、H_x,、...、H_y、...H_2をプロットしたとすると、得られる表面41Sは、直線的でなく局面となる。しかし、マニホルドの下面が有意に湾曲していると、直線的な表面41Sほどは効果的に機能しないことが観察されている。したがって、現時点で好ましい態様では、流入口から流出口まで延在する直線状または実質的あるいはほぼ直線状の（わずかに湾曲していてもよい）表面41Sを想定している。また、検体液体が効果的に流れるためには、最低限の高さH_2として約0.006インチの隙間が必要である。この要件にもとづいて、最低のR_1は、$0.006R_2/H_1$インチとして定義することができる。こうした形状とすると、検体液体がフィルターを通して吸引されるのにつれて、検体液体がメンブレンフィルター205の前面を横切って、メンブレンフィルターの前面と実質的に平行または、ほぼ平行な方向に移動し、所望の剪断作用が創出される。

【００５４】
経験的には、直線的な円錐面41Sに関しては、流出口Oの面積は、好ましくは、流入口Iの最大面積以下とする必要があり、すなわち、R_1H_1　R_2H_2とする必要がある。一例を挙げると、マニホルドは、以下の寸法（ここでの単位はすべてmm）、すなわち、R_1 = 1.24、H_1 = 1.32、R_2 = 10.00、H_2 = G = 0.15を有することができる。この場合、最大流入口面積は、3.27π mm^2となり、流出口面積は、3.00π mm^2となって、これは最大流入口面積よりわずかに少ないものの、最大流入口面積（1.64π mm^2）の50%として定義することのできる平均流入口面積よりは大きい。このように、流出口面積は、最大流入口面積と平均流入口面積の間となる。別の例では、マニホルドは、以下の寸法（単位は、すべてインチ）、すなわち、R_1 = 0.040、H_1 = 0.060、R_2 = 0.400、H_2 = 0.006を有することができる。この場合、最大流入口面積は、0.0048π in^2となり、これは、流出口面積と等しい。
【００５５】
まとめると、実質的に平坦なメンブレンフィルターと対向するマニホルドチャンバーMは、浅い漏斗状の形状とし、周囲に流出口を設けて、メンブレンフィルターの外面に沿った実質的に半径方向の流れを創出する必要がある。半径方向の流れは、相対的に弱い力で結合した粒状物質を洗い流し、または、押し流して、メンブレンフィルターの表面に、粒状物質の極めて薄い層、すなわち単層を残す。
【００５６】
LBP装置および方法
図11～57には、本発明のLBP装置の好ましい態様を示す。LBP装置は、観察、画像診断、または光学的分析を行うスライドを調製するための自動化機械である。LBP装置は、上述の流れが二方向に生じる濾過システム（図6、7a、9）を使用して、細胞の単層または薄層を捕集し、それらをスライドに転写する。
【００５７】
図11について説明すると、この図に図示した態様のLBP装置は、少なくとも6つの別々の処理ステーション、すなわち、データ取得ステーション（バーコードリーダー）230、キャップ取外しステーション400、一次撹拌ステーション500、フィルター載置ステーション600、検体取得ステーション700、およびキャップ再装着ステーション800に分かれている。これらの6つのステーションは、平行処理を行いうる構造となっており、すなわち、これらの6つのステーションは、いずれも、他のステーションと同時かつ独立して作動しうる。LBP装置は、これらとは別に、データ読み出しステーション、スライド呈示ステーション、スライド取り扱いステーション、およびカセット取り扱いステーションを備えており、これらはいずれも、統合システム900として設置することができる。LBP装置は、さらに、検体容器を各種の操作ステーションへと移動するための搬送機構240を備えている。LBP装置は、さらに、検体バイアルを搬送機構に自動的に搭載、脱搭載する自動搭載機構300も備えている。いずれのステーションも、コンピュータによって制御されている。図11aは、LBP装置の操作シーケンスを示す。この図は、オペレーティングソフトウェアを構成した際に最重要となる表である。
【００５８】
図12は、LBP装置の基本的な構成要素を示す。こうした構成要素としては、好ましくは押し出しアルミニウムから形成され、好ましくは移動しやすいようにキャスター（図示せず）上に載置されたフレーム260と、フレームによって支えられ、作動機構の主要部がその上に装着された機械加工アルミニウム製基板262とがある。また、基板の下には、いくつかの構成部品の動力源として圧縮空気を供給する圧縮器264；各種構成部品の真空源となる真空ポンプ（図示せず）；自動搭載機構300で使用されるバイアルトレーを支えるステンレススチール製の棚；ならびに電源供給・制御装置、および多岐にわたる機器を含む電気部品が配置されている。空気を動力源とする作動装置でなく、電気を動力源とする作動装置を使用する場合には、圧縮器は不要である。ユーザ・インタフェース、たとえば、タッチセンシティブなLCD表示部（図示せず）を、搬送機構240の左側に装着すると、技術者は、マシンにおける通常の自動化処理プロトコールを超えた作業を制御することも可能

となる。ユーザ・インタフェースに現れうるログイン画面（上側の図）およびナビゲーション画面（下側の図）の例を示す図25を参照のこと。利用者が、ユーザ・インタフェースと対話する際には、もちろん、他の画面も呈示される。

【００５９】

LBP装置の「低価格」版は、一度に処理する検体の数が限定された卓上式のモデルとすることができる。こうしたモデルでは、いくつかの構成要素、たとえば、フレーム260および自動搭載機構300を省きつつ、他の構成要素のスケール、たとえばフィルター載置ステーション600の容積を減らすことがことができる。外部の真空源および圧縮空気源を使用して当該装置を駆動し、他の構成要素（電源、制御装置、等）は、改変した機械の基板に隣接した、または当該機械上の1つ以上のモジュールに再配置すればよい。当業者であれば、こうした改変を実施する各種の方法を容易に思いつくはずである。

【００６０】

搬送機構

図11について説明すると、搬送機構240は、ステッパモーター（図示せず）で、高精度のスプロケット242、244の周囲に駆動されたエンドレスなリンクベルトコンベヤ242を備えている。このコンベヤは、ピン248によって連結された複数のレセプタクルまたは支持体246を備えており、このレセプタクルが、対応する数の検体バイアルを受け止める。図11に図示した態様では、1～30の番号を付した30個のレセプタクルを備えている。試料バイアルの寸法と、コンベヤの長さに応じて、LBP装置では、30個より少ない、または多いレセプタクルを、必要に応じて使用することができ、コンベヤは、すべての処理を一列のラインで完了するのに十分な長さを有している。

【００６１】

リンクベルトコンベヤのレセプタクル246は、軌道を形成する一対の誘導レール250によって、スプロケットの間に誘導されており、通常の位置補正システム（図示せず）を備えているので、レセプタクルは正確に位置決めされる。LBP装置は、各レセプタクルの位置を追跡し、かつそれらのレセプタクルを、通常の方法でステップ駆動または割出し駆動することができる。たとえば、LBP装置の各リンク上に、直動位置センサー、たとえば光学センサーまたはフォトインタラプタを設けて、この直動位置センサーによって、制御装置に位置を送り込んで支持体の位置を登録し、各支持体を、処理パス上の各処理ステーションで正確に割出し駆動することができる。正確な整列化や位置決めが期されるようにコンベヤを運転する方法は通常の技術なので、ここにこれ以上記載することはしない。

【００６２】

Z軸およびY軸方向に軌道を形成している誘導レール250は、レセプタクルの側面に機械加工されたスロットと係合している。たとえば、図29、33、37、および43を参照のこと。機械的軌道と駆動スプロケットは、外部から潤滑剤を加えなくても作動するように、自己潤滑性プラスチックから構成することができる。レセプタクル246には、それぞれ、窓247を設けて（図12を参照のこと）、検体容器のバーコードを、レーザで、すなわち光学的に走査できるようにする。コンベヤは、清浄しやすいようにPTFE7を含浸させたhard-coated-alminum(登録商標)とすることができる。リンクピン248は、精密に研削して硬化させることができる。リンクピンは、非回転リンク孔に、軸線方向に固定して位置させることができる。回転リンク孔は、潤滑剤をさらに追加しなくても作動しうる適当なベアリング材料を用いて装備することができる。操作者の安全のために、コンベヤの作動は、機械のカバーと連動式にしておくこともできる。（図示せず）。

【００６３】

レセプタクル246は、検体バイアルを特定の向きに受け入れ、または受け止めるような形状としてある。すなわち、検体バイアルとレセプタクルとは、バイアルが特定の向きにのみレセプタクルに納まるよう相補的な形状とし、つまり楔止する。たとえば、バイアルは、「D」字形として、平坦な側面を含むような形状とすることができ（図2a、2bを参照のこと）、レセプタクルも「D」字形として、平坦な側同士が並列するようにする。こうすると、バイアルは、レセプタクルに対して回転することがなくなる一方、レセプタクルに

対する縦方向の動きは制限されずに確保される。D字形以外にも、各バイアルに底部ノッチ25を設け（図2aを参照のこと）、レセプタクルに、ノッチ25と嵌合して楔止するペグまたはスタッド（図示せず）を設けることができる。図示したノッチおよびペグは、弓形であるが、相互に嵌合する他の形状（たとえば、V字形の形状）とすることもできる。

【００６４】

バイアルの搭載/取り出し機構

図12、13、および14は、バイアルの自動搭載/取り出し機構機構300を示す。縦方向（Y軸）の縦型スタンダード310の頂部に設けられた親ねじ（lead screw）モーター308によって駆動されるエレベータ・キャリッジ306には、枢動型ピック＆プレース・アーム304が、装着されている。このアーム304は、通常の電気または空気によって操作される顎型の把持手段312を備えており、この把持手段312は、検体バイアル10を三方向の自由度で移動させることができる。アームは、エレベータ・キャリッジ306のクレバス型ブラケット316に枢動可能に装着された横方向の親ねじモーター314によって水平面内を移動する。図示した顎型把持手段のかわりに、ピック＆プレース・アームには、図15に示すような、通常の空気によって操作される吸引ヘッド型の把持手段を設けてもよい。こうした把持手段は、シリコーンゴム製のベローズ318を備えており、このベローズ318は、カバーの上に載置して吸引ライン320を通して吸引すると、バイアルのカバー30に対してシールを形成する。把持手段は、機械的に操作するにせよ、空気で操作するにせよ、把持手段の操作は、当業者であれば理解しうるように、機械的にプログラムされた操作によって行う。

【００６５】

図17～20について説明すると、検体バイアル10は、機械の棚320に摺動して入る、特別に射出成形したプラスチック製のバイアルトレー330に保存する（図12を参照のこと）。混乱をさけるうえでは、図13～15に示すトレーは異なった種類（スタンピングした鋼製）であることを指摘しておかねばならないが、トレーを回転させる機構の操作は、その構成にかかわらず、同一である。プラスチック製のバイアルトレー330が好ましく、ポリプロピレンとするのが好ましい。「トレー」という用語は、本発明で使用する場合には、図示した態様に限られるものではなく、一般的には、平坦な別個の物体を、おおむね本明細書に記載するような方法で支え、移動させるようなものであれば、リムのあるものもないものも含め、任意の種類の支持体を包含するものと理解されたい。

【００６６】

各トレー330には、検体バイアル10を一方向にのみ受け止める寸法および形状とした円形の凹部332が41個設けてある。各凹部332の上端は、好ましくは、傾斜端333として、バイアルを滑らかに挿入できるようにしておく。凹部は、4本の同心の列が密集した配置とし、好ましくは、一番外側の列が16個の凹部、次の列が8個の凹部、3番目の列が、9個の凹部、最も内側の列が、8個の凹部となるように配置する。隣合った列のレセプタクルは、場所の節約上、互いにずらして配置する。2列目のレセプタクルは、4列目（最も内側）のレセプタクルと、半径方向に一致した位置に配置されている。最も外側の列のレセプタクルは、レセプタクル中央で測定して18°の間隔をおいて配置されている。他の列の各レセプタクルは、レセプタクル中央で測定して36°の間隔をおいて配置されている。もちろん、レセプタクルは、ピック＆プレース・アーム304がすべてのバイアルにアクセス可能であれば、さらなる他の並び方で配置してしてもよい。各レセプタクルは、独自に指定可能な位置を有しており、そのため、どのバイアルにも、随意に任意の順番でアクセスすることができる。

【００６７】

上述したように、処理を行う間に検体バイアルがどちらを向いているかは極めて重要であり、これらのトレーに保存されているバイアルが適正な向きに配置されていることで、ピック＆プレース・アーム304が、各バイアルをコンベヤのレセプタクル246の適正な位置に配置することが可能となる。そのため、各凹部332の底部には（図19を参照のこと）、固定された指標ペグ（indexing peg）334が設けてあり、このペグ334は、バイアルのノッチ25に嵌合するような寸法を有している。ペグ334は、たとえば接着剤で、凹部332の底部に

隣接してトレーに成形された溝335内に納められている。ペグのいくつかは説明の目的から図19に記載していない。

【００６８】

ペグ334は、トレー330のメジアン平面に対して特定の角度で配置して、トレーから取り出された各バイアルが搬送用レセプタクルに送達された際に、ノッチがレセプタクル中の嵌合相手のペグと、あるい嵌合相手のペグがノッチと整列するようにする。これらの各角度は、特定の凹部332中のバイアルにピック＆プレース・アーム304がアクセスする時点でのトレー330の位置と、バイアルをつまみ上げる地点からコンベヤのレセプタクル246にバイアルを載置する地点までのピック＆プレース・アームの回転角度とによって決まる。こうした角度の決定は、当業者の能力の範囲内であると考えられる。

【００６９】

トレー330には、3本の直立する誘導ポスト336が設けてあり、それぞれには、ばねを担持したボール338が配置されている。誘導ポスト336は、各棚302の上に設けられた誘導部（図示せず）と協働して、トレーを機械に挿入する際にトレーを誘導する役目を果たして、確実に適正な向きとなるようにする。誘導ポスト336は、保存に際してトレーを積み重ねる際の積み重ね用のポストの役目も果たし（図20を参照のこと）、ボール338は、上側のトレーの底部に設けられたくぼみ339（図19を参照のこと）と係合する。

【００７０】

トレー330は、大きな裾広がりのノッチ340を備えており、このノッチ340は、このトレーが棚302に挿入されるときには機械の方を向いている。ノッチ340の最奥部には、対向するキー溝342が設けられており、後述する浮動キーと係合するようになっている。キー溝は、好ましくは、ミリングした真鍮製のハブ挿入部343に形成されており、このハブ挿入部343は、トレーの上面のくぼみに、トレーの上面と面一となるように、ねじ止めされている。

【００７１】

図14、15、および15aについて説明すると、外側の回転スピンドル350の上部と下部が、ベアリング352、354で、それぞれ回転自在に軸支されている。外側のスピンドル350は、1回に1枚のみのトレーと係合して、そのトレーを回転させるので、ピック＆プレース・アーム304は、基板262に設けられた開口部266を通過し、任意の利用されていないトレーの定位置に位置あわせされたノッチ340を通過して下向きに移動することにより、バイアルにアクセスすることができる。図14は、トレーの定位置を破線で示し、ここで、トレーのノッチ340は位置あわせされており、外側スピンドル350を包持している。外側のスピンドル350は、コンピュータ制御された回転ステッピングモーター（stepper motor）356とタイミング歯車360、362と係合したタイミングベルト358によって、底部から、高精度で回転される。下向きの光学回転位置センサー363が、位置あわせされたトレーのノッチの上方に配置されており、この回転位置センサー363が、トレーがいつ、どのように定位置から回転したのかを検出し、そしてステッピングモーター356の回転を制御するためのフィードバックを提供する。

【００７２】

外側のスピンドル350の内部には、内側のスピンドル364が設けられ、この内側のスピンドル364には、各トレーに関して1対ずつ、8対の対向するキー365が設けられている。キー365は、外側のスピンドル350から、外側のスピンドルに設けられた対向するスロット366を通して突出している（スピンドルと、一番下のトレー2枚の中央部の断面図である図15aを参照のこと）。内側のスピンドル364は、内側の親ねじ372によって、外側のスピンドル350の内部を上下に移動する。親ねじ372は、タイミングベルト376およびタイミング歯車378、380を介して、親ねじステッピングモーター374によって回転される。内側のスピンドル364の頂部には、キー「定位置（home）」センサー382が設けられており（図15を参照のこと）、基準点を提供している。すなわち、機械の始動時には、内側のスピンドルがキー「定位置」センサー382まで戻り、その後、その位置からの内側のスピンドルの動きが参照される。

【００７３】
図15に示すように、キーの各組は、縦方向に均一間隔をおいて配置されている。この間隔またはピッチは、全数の搭載トレー330のキー溝342のピッチとは異なる。したがって、キーがどのキー溝と係合するかは、内側のスピンドルの上下方向の位置によって決まり、どの時点でも、係合しているのは1対のキー溝（トレー）だけである。図15aの拡大図では、一番下のトレー330-1のキー溝342は、キー365と係合しているが、下から二番目のトレー330-2のキー溝は、どのキーとも係合していない。内側のスピンドル364が、ピッチ差の1/8動くと、それまで係合していたトレーが外れて、すぐ隣のトレーが係合する。棚302によって規定されるトレースロットに1枚以上のトレーが不在であっても、搭載および取り出し機構の動作は影響をうけない。

【００７４】
ピック＆プレース・アーム304が、（コンピュータの制御装置によって決定された）特定のトレーにアクセスする場合には、親ねじモーター374によって、内側のスピンドルが適当な距離だけ移動され、適当なキーが、その特定のトレーのキー溝と係合する。次に、アーム304が特定の凹部332にアクセスできるよう、回転モーター356が、楔止されたトレーを適正な角位置まで回転させる。トレーが積層して配置され、積層されたトレーの裾広がりのノッチ340を通して把持手段312が特定のトレーにアクセスし、各トレーに凹部332が密集して配置されているので、LBP装置のコンパクトな基部に容易に組み込むことができ、極めてコンパクトで、容量が大きく、効率的なバイアル取り扱いシステムが実現されている。

【００７５】
図示した態様では、LBP装置は、それぞれ検体バイアル41本を保持するトレーを8枚まで収納することができる。この41本分の凹所のうちの1箇所を清浄用のバイアルのために確保し、このバイアルに清浄液を入れておいて、検体液と通常接触する装置の各部が清浄化されるようにすることができる。または、この41本目のバイアルには、較正（calibration）用の代表的な対照検体を入れておくこともできる。このように、LBP装置は、処理を行うべき検体の入ったバイアルを、少なくとも320本まで収納することができる。したがって、本装置は、長時間にわたって連続的に無人操作を行うことが可能であり、少なくとも8時間は連続無人操作を行うことができるので、検査施設の人員が通常は不在であるような、たとえば夜の時間帯であっても、検体の処理を行うことができる。

【００７６】
トレー330にバーコードを付すか、他のかたちで機械で読みとり可能な識別用データのラベルを付した場合には、指令を受けた場合に特定のトレーにアクセスすることができるような自動保存装置でトレーを使用することができる。トレーの識別データは、統合データ管理システムに入力して、トレーに保存したすべての検体バイアルの位置を容易に確認できるようにしておく。

【００７７】
トレーを利用した検体バイアルの保存に関しては、ライナー型のシステムをトレー330とともに使用することによって費用を低減することができる。たとえば、バイアルを、トレー330と合致させ、凹所332に容易に摺動して納まるような薄いシート状のライナー（図示せず）で保持して保存することができる。ライナーは、バイアルを最大限に搭載しても自立性が保たれるような堅さを有しており、積層が可能で、移動しやすいよう台車付きワゴンに収納することもできる。

【００７８】
データの受け入れと検体の管理
各検体バイアルと、各検体バイアルから製造された検体スライドについては、常時所在を確認しておくことがもちろん重要である。したがって、LBP装置は、通常、受け入れステーション102または他のコンピュータを介して、統合データ管理システム（DMS）104と通信している。図21には、検体バイアルの取り扱いと、LBP装置の操作に統合されるデータの流れを模式的に示す。LBP装置とDMSとの通信リンクは、直接的なピア・ツウ・ピア（pe

er-to-peer）の接続を使用するイーサネットや他のプロトコールを介して、または、サーバーを基本としたネットワークを介して構成することができる。

【００７９】

検体処理操作は、ラベルを付した検体バイアルから、データを、たとえば、データ入力端末または受け入れステーションに設けたバーコードリーダーを経由して、DMSに回収または移動するところから開始し、この過程は、直接接続することによっても、ネットワークを介して行うこともできる。検体追跡データは、たとえば、患者の氏名、検査の識別（ID）番号、患者についてのデータ、任意の特別な処理上の指示事項を含むことができる。たとえば、バーコードを付した検体バイアルは、当初は紙の申込用紙の様式、そしてその後はデータベース中の個別に割り当てた番号形式のIDによって、患者についての情報と関連づけることができる。好ましい態様では、バイアルのバーコードを含む患者と検査についての情報を、医療現場（たとえば、医師の診察室）で、ネットワークに繋いだDMSデータベースに入力することにより、紙の申し込み様式を完全に不要とすることができる。アキュメド・インターナショナル社（AccuMed International、Inc.）（現在のモレキュラー・ダイアグノスティック社（Molecular Diagnostics、Inc.）、すなわちMDI）に譲渡された米国特許第5,963,368号（本明細書に参照として組み入れられる）には、生物学的検体分析用のコンピュータ-制御機器（顕微鏡）に適用した類似の概念と、各分析で得られたデータを保存することが開示されている。この米国特許第5,963,368号は、液体ベースの細胞診断の分野モノジェン社（MonoGen、Inc.、この出願の所有者）に対して、非蛍光に基づく画像解析素子、方法、システムおよび/または機器と組み合わせて、あるいはそれらとともに使用するべく排他的に認可されている。モノジェンの市販の病理ワークステーションおよびデータ管理システムは、米国特許第5,963,368号に開示された概念を実現したものである。

【００８０】

各検体バイアルは、識別用（ID）の記号またはラベル（たとえば、バーコード）および/または保存された情報ラベルまたは記号、たとえば、ホログラムまたはメモリーチップまたは素子を備えている。本態様は、IDラベルを光学読みとり装置、たとえばバーコードリーダーで読みとり、この光学読みとり装置から情報をDMSに送って、同一または異なった場所、たとえば検査施設、医師の診察室、病院、または他の患者の看護に置かれた別々のワークステーションまたは機器の間で情報を共有することを念頭に置いている。図21aは、DMSを拡張し、検体データ/患者データをサーバーを通じて各種の検体処理装置および/またはコンピュータ化したワークステーションと関連づけて、完全に統合された検体の管理を実現した検査システムの全体を図示したものである。

【００８１】

別のバーコードリーダー230（図11を参照のこと）が、LBP機械自体に装着されおり、このバーコードリーダー230が、処理を行う前に、すべての検体バイアルを、各搬送用レセプタクル246に設けられたスリットを通して走査する。各搬送用レセプタクル246は、こうした通常の光学読みとり装置で読みとり可能な記号またはコード、たとえばバーコードを使用して追跡する。LBP装置で使用するバーコードリーダーは、任意の市販の型式、たとえば、キーエンス（Keyence）のBL-600のような、最低限、BCR対象コードとして、物流用の標準バーコード（Interleaved 2 of 5）、コード128c、またはEAN128を読みとることのできるものとすることができる。操作者を保護するうえでは、バーコードリーダーは、液密な格納容器に封止されているのが好ましい。検体バイアル/搬送用レセプタクルのIDを読みとった後、データを、ホストデータベースまたはワークステーションのDMSに送ると、ホストデータベースまたはローカルワークステーションは、LBP装置に、その個別の検体で実施すべき具体的な処理プロトコールを送り返してくる。

【００８２】

データ管理システム（DMS）の最も重要な機能としては、たとえば、以下のものがある。受け入れの間に患者と検体についてのデータを得、必要に応じて各装置にこのデータを提供して、処理パラメータを設定し、医療データをスライドの観察者に提供する。

検体およびスライドについての物証保管の継続性を維持し、データ保全を確実に行う。
データをコンパイルし、規制、法令順守、検査管理報告書として必要とされる様式を印刷する。
医学報告書を作成し、保護されたデジタル電子署名を使用してデータ保全を確実に行う。
機器について、「使用回ごとの」料金の請求書作成発送を管理する。
各処理に関して最適な処理プロトコールを蓄積し、検体の種類および/または利用者の要求にしたがって、装置に最適の処理プロトコールを供給する。
遠隔診断および修理を可能とし、利用者のマニュアルおよびトラブルシューティングの手引書を提供する。
図21bは、これらの作業を遂行する際に使用することのできるリレーショナル（relational）データベース表の例を示す。

【００８３】

DMSは、細胞診断処理の各種の段階で、紙を必要としないデータの流れを実現することができるので、有意な量の人員の時間および費用を節約し、転記ミスを減らし、正確さを向上し、紙の記録を保存するのに必要な空間を不要とすることができる。データの取得、保存、検索を自動化して管理することによって、検体に対する応答時間が有意に短縮され、各操作の効率が上がる。較正が自動的に実施され、機械的に照合確認されるので、潜在的な問題が早い段階で特定され、検体の質が向上する。また、多文化環境にある検査施設の場合には、世界規模での販売にむけて外国語に関して自在に支援を受けることができる。

【００８４】

DMSは、共通のユーザ・インタフェースを提供し、このユーザ・インタフェースは、連結された各検査装置およびワークステーションの操作についての詳細な情報を提供し、かつオンラインの利用者マニュアルや訓練補助プログラムを使用できるので、使用が容易となり、訓練が低減される。DMSは、備え付けのソフトウェア・インタフェースを通じて、患者や検体に関するすべての関連データの、利用者自身のLIS（または他のデータ管理システム）との交換を取り扱う。その上、離れた場所にある機器で診断を行うことができるので、中断のない最大限の操作を確実に行うことができる。ペーパーワークが減り、他の機器および既存のコンピュータネットワークとの相互互換性が高まり、他の中央病院または検査情報システムとの統合が可能となると、利用者の便益も有意に高まる。

【００８５】

通常の操作では、検査施設は、（1）健康管理の提供者から、申込用紙を、バーコードを予め付した検体バイアルとともに受取り、（2）検体に個別のID番号（受け入れ番号）を割り当て、（3）申込用紙の情報にもとづいて、具体的なLBP検査IDを入力して、使用する処理を具体的に指定する。図23は、技術者に呈示され、バイアルのバーコード、受け入れ番号、LBP処理コードが入力される受け入れ（データ入力）画面の例を示す。処理を行うために検体バイアルをLBP装置に搭載する際には、LBP装置は、自動的に検体バイアル上のバーコードを読みとり、バーコードの番号（106）をDMSに送り、DMSは、選択された検査と、作成すべきスライドの数についての処理パラメータを送り返す。LBP装置は、受取通知（108）を送り返し、検体を処理して、DMSを介して指示された1枚または2枚以上のスライドを作成する。LBP装置が、検体バイアルから濾過によって得られた材料を検体スライドに押圧転写する直前に、LBP装置は、検体試料を載置する予めバーコードを付しておいたスライドからバーコードを読みとる。LBP装置は、各スライドのバーコード（110）と、関連したバイアルのバーコードをDMSに送り、DMSは、患者データベースにスライドのバーコード番号を記録してデータベースをアップデートし、スライドのバーコード番号を正しいバイアル番号と関連づけ、LBP装置に処理命令信号（112）を送る。すると、LBP装置は、検体から得た細胞診断用試料を1枚以上のスライドに押圧転写し、オンボード・データのログを、次に処理を行う検体に備えさせる。図24に図示してあるのは、バイアル番号、スライド番号、および患者のデータを含む、この時点でDMSデータベースに関連づけられているデータ項目を示すDMSのメニュー画面の例である。DMSは、スライドのID番号と、関連するバイアルのID番号、患者のデータ、および処理プロトコールが列挙された印刷可能

な報告書を生成することができる。

【００８６】

最低でも、プロトコールの変数は、検体混合時間（撹拌速度および時間）およびフィルターの選択を含む。通常、初期撹拌速度は、500 rpm～3,000 rpmの範囲で50 rpmきざみで選択可能とする。撹拌間隔は、5～120秒の範囲で5秒ずつ選択可能とする。フィルター型の選択は、平均孔径を基準とし、選択した検査プロトコールに応じて、5ミクロン（赤色のハウジング）（たとえば、痰検体のような非婦人科検体の場合）としたり、または8ミクロン（白色のハウジング）（たとえば、婦人科検体の場合）としたりする。

【００８７】

LBP装置は、試料の入り交じったかたちでの運転（すなわち各種の検体の入ったバイアルが混在するかたちでの運転）を互換的に行うこともでき、さらに同種の検体ごとにバッチ処理を行う必要がない。検体の処理に際しては、少なくとも100種の異なった処理プロトコールを実施することができ、こうした処理プロトコールは、DMS内に、利用者がアクセス可能なかたちで存在している。予め定義しておいた手順コード（検査ID）、たとえば下記のようなコードを使用して、操作者の入力を簡略化し、どのプロトコールを使用するのかを特定することができる。

1 乳房嚢胞、左
2 乳房嚢胞、右
3 気管支のブラッシング液
4 気管支洗浄液
5 気管支肺胞洗浄液
6 脳脊髄液
7 結腸のブラッシング液/洗浄液
8 食道のブラッシング液/洗浄液
9 胃のブラッシング液/洗浄液
10 歯肉（頬側）の掻き取り液
11 婦人科のパパニコロー塗抹検査検体
12 小腸ブラッシング液/洗浄液
13 乳頭分泌液、左
14 乳頭分泌液、右
15 卵巣嚢胞、左
16 卵巣嚢胞、右
17 膜液
18 腹水
19 胸水
20 直腸ブラッシング液/洗浄液
21 痰（誘導）
22 痰（自発）
23 尿（導尿）
24 尿（随時尿）

【００８８】

各検体は、新しいフィルターで処理して、相互汚染の可能性を防止する。本態様では、2種以上の異なった型のフィルターのいずれかを特定して使用することができるので、多岐にわたる選択肢の検査を行うことができる（本装置は、8本のフィルターチューブを備えているので、8種までの異なった型のフィルターを使用することが可能である）。各種の検体ごとの処理パラメータは、前もって遠隔操作で決定しておいて、鍵となる識別子として検体バイアルのバーコードを使用することにより、双方向通信リンクを通じて処理装置に通信することができる。LBP装置は、デフォルトの（DMSに予め搭載しておいた）処理プロトコールを使用することも、DMSに利用者が加えることのできる検査施設で生成した処理プロトコールを使用することもできる。

【００８９】
バーコードリーダー230の地点、あるいはそのすぐ下流に、充填量が過剰なバイアルを検出する装置（図示せず）を設けて、各半透明バイアルに過剰量の流体が入っていないかどうかを検出することもできる。充填量過剰バイアルを開いて処理すると、生物学的流体がこぼれたり、射出したりして危険なことがある。したがって、充填量過剰バイアルが検出された場合には、DMSにその旨の通知がなされ、そのバイアルについての全LBP処理プロトコールがキャンセルされ、充填量過剰バイアルの蓋は開かれぬまま、処理経路をまわることが可能となる。あるいは、充填量過剰状態を、バイアル搭載機構300によってバイアルが搭載されるコンベヤホルダー246で検出することもできる。充填量過剰バイアルがこの地点で検出された場合には、DMSにその旨の通知がなされ、搭載機構は、たたちに、充填量過剰バイアルをそのトレー330に戻すよう指示される。
【００９０】
各バイアルのコンベヤへの搭載時に検出された他の異常に対処する際も、同様のアプローチをとることができる。たとえば、センサー（図示せず）を使用して、バイアル上のバーコードが読めない場合や、ホルダー246内でのバイアルの位置が適正でない場合を検知することができる。そうした状態が検出された場合には、DMSにその旨の通知がなされ、搭載機構は、ただちに、充填量過剰バイアルをそのトレー330に戻すよう指示される。
【００９１】
図22は、DMSを稼働する際に使用することのできる、汎用コンピュータシステムまたはワークステーション270の構成部品を示すブロック図である。コンピュータシステム270は、通常、中央処理装置（CPU）272とシステムメモリー274とを備えている。システムメモリー274は、通常、オペレーティングシステム276、BIOSのドライバー278、および応用プログラム271、たとえば、DMSを含む。また、コンピュータシステム270は、入力装置273、たとえば、マウス、キーボード、マイク、ジョイスティック、光学読みとり装置またはバーコードリーダーなどと、出力装置、たとえばプリンター275Pおよび表示画面275Mを含むものとすることもできる。
【００９２】
コンピュータシステムまたはワークステーションは、電子ネットワーク280、たとえばコンピュータネットワークに接続することができる。コンピュータネットワーク280は、公的ネットワーク、たとえばインターネットまたはメトロポリタンネットワーク（Metropolitan Area Network、MAN）、または他の私的ネットワーク、たとえば会社の構内ネットワーク（Local Area Network、LAN）または広域ネットワーク（Wide Area Network、WAN）、または仮想専用網とすることができる。この点に鑑み、コンピュータシステム270は、電子ネットワーク280との通信に使用しうる通信インターフェース277、たとえばイーサネット、USB、またはファイアワイヤを含むものとすることができる。他のコンピュータシステム279、たとえば、リモート・ホスト・データベース、他種のワークステーション、たとえば自動分析装置、および病院、検査施設、または他の医療機関のコンピュータまたはデータベース（たとえば、LIS）も、電子ネットワーク280につなぐことができる。他のLBP装置、および別のタイプの検体処理装置（たとえば、自動スライド染色装置およびカバーガラス載置装置）279aも、ネットワークを介して相互に、そしてDMSと接続することが可能である。
【００９３】
当業者であれば、上述のシステムが、電子ネットワークに接続された汎用コンピュータシステムの代表的な構成部品を含むものであることに気づくはずである。LBP装置およびその処理に際しては、他の多くの同様の構成も使用することができる。さらに、本明細書に開示するコンピュータシステムおよびネットワークは、当業者であれば、本明細書に記載した方法、システム、およびソフトウェアを実施し、かつ本発明を実施するうえで必要とされるコンピュータデータおよび電子シグナルを提供するために、プログラミングし、構成することができることを理解されたい。
【００９４】

また、当業者であれば、本明細書に記載した「コンピュータ」によって実現された発明が、コンピュータ自体ではない構成部品も含みうるものであり、本発明に記載した機能の1種以上を実現するために使用することのできるインターネット機器およびプログラム可能制御装置（PLC）のような装置も含みうることを理解できるはずである。また、「電子」ネットワークは、本発明の処理現場間を接続する通信ネットワーク一般を称するべく使用しているが、当業者であれば、光学技術または他の同等の技術を使用することによってこうしたネットワークを実現しうることが理解できるはずである。当業者であれば、別のシステムの構成やデータ構造を用いることによって本発明の機能を実現しうることも理解できるはずである。こうした構成およびデータ構造は、すべて本発明の範囲内であると理解されたい。こうした文脈では、本発明が、ネットワークを通じて電子データを送付する際に使用される公知のセキュリティ手段および情報処理手段も利用するものであることについても理解されたい。したがって、公的ネットワークおよび私的なネットワークの双方を通じて電子データを送る際に使用される暗号化、認証、検証、圧縮をはじめとするセキュリティ手段および情報処理手段も、等量者には周知の技術を使用することによって、必要に応じて提供される。

【００９５】

キャップ取外しステーション

本発明のバイアルを基本とするLBP装置およびシステムが有する利点の一つとしては、操作者が、潜在的なバイオハザード物質を含む可能性のある検体と接触する可能性が低減している点があげられる。図26～31について説明すると、LBP装置は、まず、バイアル中の撹拌部材40をカバー30から自動的に離脱させ、次に、カバーを取り外して廃棄するキャップ取外し機構400を備えており、こうした過程は、いずれも、操作者が介入することなく行われる。カバー30の取り外し後に、撹拌部材がバイアルのリブ26上に受け止められている状態を図示した図26を参照されたい。

【００９６】

搬送用レセプタクル246に入ったままキャップ取外しステーションに到着した閉鎖状態の検体バイアル10は、キャップ取外しヘッド402と遭遇し、このキャップ取外しヘッド402は、検体バイアルのカバー30まで降下する。図27および28を参照のこと。キャップ取外しヘッド402は、テーパーのついた脚部404を4本を備えており、この4本の脚部404が、テーパーのついた把持用の凹所を形成しており、この凹所は、ヘッド402が降下するにしたがってカバー30が徐々に締めつけられるような間隔および寸法を有する、たがね状の内側エッジ406を備えている。脚部がカバーにしっかりと係合したところで、中央スピンドルまたはプランジャ408が降下してカバー30と接触すると、プランジャによってカバーに下向きの力が加えられ、上述したように撹拌部材40がカバー30からはずれて、バイアル中でリブ26に落ちる。次に、プランジャを後退させ、キャップ取外しヘッド402を反時計回り（図28）に回して、カバー30のねじをゆるめて容器20から取り外す。その後、キャップ取外しヘッドと、ヘッドの把持部材内の取り外したカバーは、図29および11に破線410で示した位置まで横方向に移動し、プランジャ408が再度下降して、今度はカバー30を射出し、カバー30は、キャップ取外しヘッドの下方に配置された廃棄物シュートまたは貯蔵所に落ちる（図示せず）。または、移動可能な廃棄物シュートをキャップ取外しヘッドの下方に移動して、射出されたカバーを受け止め、キャップ取外しヘッドの横方向の移動を不要とすることもできる。相互汚染の可能性を排除するため、カバーは再使用しない。

【００９７】

プランジャ408は、キャップ取外しヘッドの頂部のL字形のブラケット415に装着された空気圧シリンダー412によって駆動され、この空気圧シリンダー412は、カバーに約30ポンド以下の力を加えることができる。シリンダー412の動作を停止させると、コイルばね413が、プランジャをその後退位置まで戻す。ヘッド402は、約10ポンド-フィート以下のキャップ取外しトルクを、把持用の脚部を介して加えることができ、このトルクは、カバーを緩めるのに十分である。把持用脚部は自己賦勢型として、カバーとの精密な心合わせや、カバーの形状のわずかな変形によって、把持に支障をきたすことのないようにすることがで

きる。
【００９８】
キャップ取外し機構は、装着フレーム414を備えており、この装着フレーム414は、レール418上処理経路を横方向に褶動するブロック416上に支持されている。Y軸ステッピングモーター420と親ねじ422は、横方向の動きを行う。キャップ取外しヘッド402は、軸受ブロック424内に回転可能に装着されている。軸受ブロック424は、装着フレーム414上を縦方向に褶動可能なC形フレーム426に固定されている。C形フレーム426、すなわちキャップ取外しヘッド402の縦方向の動きは、Z軸ステッピングモーター428および親ねじ430によって生じる。親ねじ430は、カバー30のねじが緩められるのにしたがって、カバー30の上向きの動きに応従することができる。しかし、ステッピングモーター428は、キャップ取外しの過程では、ヘッド402が、緩められつつあるカバーとほぼ同じ速度であってカバーより速くはない速度で上昇するよう作動させることが好ましい。キャップ取外しヘッド402は、キャップ取外しモーター432によって、ギヤ減速ユニット433、タイミングベルト434、およびタイミング滑車436、438を介して回転可能に駆動される。
【００９９】
上述したキャップ取外しヘッドは、容器とカバーが通常の「押してから回す」差込み方式で結合されているバイアルでも作動する。プランジャ408によって加えられる下向きの力は、結合の内部回転防止ロックを緩めるのに十分であり、把持手段は、カバーを回転させて取り外すことができる。取り外す際に回転を必要としないカバー、たとえば、スナップ・オン式のカバーを有するバイアルの場合は、カバーの結合形式に応じた、設計の異なるキャップ取外しヘッドが必要となる。
【０１００】
カバーを付されたバイアルに必要な外力を加えて撹拌部材をカバーから離脱させるにあたっては、上述のプランジャ408のかわりとなるものを、キャップ取外しステーションまたはその上流で用いることもできる。たとえば、カム、レバーアームなどの可動機械要素を接触させて、カバーを下向きに押圧することができる。または、唐突な上向きの外力をバイアルに加えて、結合部材35および47の間の摩擦による保持力を超えるような加速力を得て、撹拌部材をカバーとの係合状態から効果的に引き離すこともできる。唐突な外力による離脱は、たとえば、閉じたバイアルを急激に下向きに移動させて、容器20の底部を、硬めの表面に軽く打ちつけることによって、たとえば、機械的および/または空気によって、閉じたバイアルを、その後の処理工程の間バイアルを保持することになる搬送用支持体246に押し込んだり、または、バイアルを、シュートを通して支持体内まで、撹拌部材を離脱させるのに十分な距離だけ落としこんだりすることによって行うことができる。バイアルに対して唐突な上向きの力加える別の方法としては、容器20の底部を、打撃部材で打つ方法が挙げられる。この方法は、たとえば、容器20を架台に載せ、容器の底部を打撃部材で瞬間的に叩くことによって、たとえば、バイアルの支持体246に設けた開口部を通して、空気および/または機械的手段によって容器の底部を叩くことによって実施することができる。こうした機構や、こうした作業を実施するうえで適当な他の自動化機構を設計することは、当業者の理解の範囲内である。
【０１０１】
予備処理（一次撹拌）ステーション
キャップ取り外しの完了後、検体容器は、搬送機構によって、予備処理が行われるステーションまで割出し駆動される。予備処理ステーションは、予備処理作業、たとえば、容器および容器に入った検体が検体取得ステーションに移動する前に、容器内で検体を分散させておく作業が行われる位置である。予備処理ステーションでは、通常、分散作業を行う。好ましい態様では、機械的混合手段によって分散作業が行われ、この混合装置は、検体容器内で一定速度で一定時間回転する。この例では、混合手段は、大型の粒状物質と微細な粒状物質、たとえばヒトの細胞を、液体ベースの検体内で、検体を均一化することによって分散させる。あるいは、検体は、細胞以下の大きさのの物体、たとえば、結晶または他の高次構造を有する分子を含む場合もある。こうした場合には、機械的撹拌を行わなく

ても、予備処理ステーションで検体に化学物質を導入して、たとえば、特定の結晶構造を溶解させて、分子を化学的過程によって液体ベースの検体全体に分散させることができる。この例では、予備化学処理ステーションにおいて、分散剤が予備処理ヘッドを通して導入される。

【０１０２】

図示した好ましい態様では、予備処理は一次撹拌ステーション500で行われ、一次撹拌ステーション500では、所定の、または指示された撹拌プロトコールを使用して、容器中で、必要に応じて撹拌部材40を使用して、所定の速度（rpm）にて所定の時間にわたって検体を撹拌する。撹拌プロトコールは、上述したように、主に検体に応じて決定され、通常、粘膜材料および/または検体液体中の他の粒状物質を解離して分散することを意図している。

【０１０３】

図32～35について説明すると、一次撹拌ステーション500は、拡径可能な鋼製のコレット形状の撹拌ヘッド502を備えている。このコレットは、軸503の下端に形成されたおり、6本の等間隔に配置されたスリット506によって規定された6本の可撓性の指状部材504に分かれる。軸503は、軸受ブロック508内で回転可能に保持されており、軸受ブロック508は、装着フレーム512上を縦方向に摺動可能なC形フレーム510に固定されている。C形フレーム510の縦方向の動き、すなわち、撹拌ヘッド502の縦方向の動きは、Z軸ステッピングモーター514と親ねじ516とによって駆動されている。撹拌ヘッド502は、撹拌モーター518によって、タイミングベルト520およびタイミング滑車522、524を用いて回転可能に駆動される。

【０１０４】

コレット指状部材504の内面は、コレットの下端に向かって均一に内向きに傾斜している。中央のプランジャ526は、ブラケット530の頂部に設けられた空気シリンダー528によって上下方向に可動であり、プランジャ526が下降して、傾斜のついた指状部材と遭遇すると、プランジャ526が指状部材504を外向きに拡げる。その結果、プランジャ526の下降時には、撹拌ヘッド（collet）502の下端の直径が拡大する。この端部は、コレットの非拡径時に、撹拌部材40の頂部の環状壁47の内側に緩く、しかし近接して嵌るようなサイズとしてある。プランジャ526が下降すると、指状部材504が外側に拡がって、マニホルドM内で壁47の内側に楔止され、撹拌部材としっかり係合する。

【０１０５】

作動時には、撹拌ヘッド502をまず降下させて、コレットがマニホルドM内まで入るようにする。図33および34のモーターとブラケットの破線は、下降時の位置を示す。次に、プランジャ526が下降して、撹拌ヘッドを撹拌部材に固定する。次に、ステッピングモーター514を作動させて、撹拌ヘッドとヘッドに接続した撹拌部材40をわずかに上昇させる。この上下方向の動きは、ごくわずか、たとえば、0.050インチで十分であり、この操作により、撹拌部材をリブ26から自在として、撹拌の間に容器とぶつかることを避ける。次に、DC撹拌モーター518を、検体に固有の撹拌プロトコールにしたがって作動させる。撹拌速度は変化させることができ、通常、約500 rpm～約3,000 rpmの範囲とする。撹拌時間は、約5秒～約90秒の間で変化させることができる。撹拌部材の基部または底部壁41が水切りとして作用して、撹拌部材に沿って容器の壁に向かって上昇する液体を押し戻し、容器から液体が溢れ出るのを防止する。コレットからプランジャ526を後退させると、撹拌部材40がコレット502から解放されるので、検体容器は、次のステーションに移動可能となる。

【０１０６】

拡径するコレット502ではなく、縮径するコレットを使用することも可能である。この場合、コレットの指状部材は環状壁47の外側に嵌り、指状部材を取り囲むスリーブが下降することによって指状部材が絞られて、壁部が締め付けられる。

【０１０７】

フィルター載置ステーション

フィルター載置ステーション600では、撹拌部材40の頂部の解放したマニホルドMに、適当

なフィルター組立体F（図5を参照のこと）が搭載される。フィルター組立体は、異なったフィルター形状のものを使用することができ、それを自動的に機械で認識する。たとえば、一組のフィルター組立体を赤色とし（５μｍ）、別の一組を白色として（８μｍ）、それぞれ異なった濾過特性を有するものとし、色センサーが前面に位置しているのがどの型のフィルターなのかを検出して、適正なフィルターが搭載されるようにする。フィルター組立体は、複数のフィルターチューブを備えたマガジンから、押し込み手段によって供給される。

【０１０８】

図36～40は、フィルター載置ステーションの構造と操作を示す。図37および40について説明すると、フィルター供給ヘッド610には、フィルターマガジンが、スピンドル614上でステッピングモーター616によって回転可能な旋回台612として設けられている。上下方向に延在するポスト611が、旋回台を主に支えている。旋回台612は、頂部支持板618をを備えており、この頂部支持板618の外周の近くには8個の穴620が等間隔に配置され、各穴620は、スロット622で、板618の縁を貫いて開いている。スピンドル614上の底部誘導板624にも同様の穴が設けられており、この穴は、頂部支持板の穴およびスロットと同心に配置されている。

【０１０９】

穴620と、下方の同心に配置された穴によって、8本の上下方向に延在する鋼製のフィルターチューブ626が支持され、各フィルターチューブ626に設けられた上部支持肩部628が、頂部支持板618に受け止められている。各フィルターチューブ626には、全長にわたって延在するスロット630が設けられ、フィルターチューブ626の下端部分は、スロット634によって、4本のばね状の指状部材632に分かれている。指状部材632の下端部分のすぐ上は、内向きに湾曲しており、湾曲形状の内側肩部636が形成され、フィルター組立体Fは、この内側肩部636に受け止められている。フィルターチューブの寸法は、積み重ねられた全フィルター組立体Fがチューブから抜け落ちることのないように、肩部636でフィルター組立体を保持することができ、しかも、積み重ねられたフィルター組立体が下向きに押された場合には変形して、フィルター組立体に損傷を加えることなくフィルター組立体を通過させることのできるようなものとする。すなわち、指状部材632は、ばね状の絞り部を形成している。

【０１１０】

図39は、フィルターマガジン612の位置を、処理経路ならびに隣接した処理ステーション、すなわち、左側の一次撹拌ステーション500および右側の検体取得ステーション700との関係で示す。これらは、いずれも、誘導レール250によって規定される処理経路の片側に位置している。処理経路の反対側で、フィルターマガジン612と対向する位置には、押し込みアーム640を支持して駆動する組立体が配置されている。この組立体は、ステッピングモーター（図示せず）によって駆動されるZ軸方向の親ねじ644を支持する支持ポスト642を備え、このステッピングモーター（図示せず）が、押し込みアーム640を搬送するシャトル646を移動させる。底部誘導板624と対向する位置に配置されたフィルター検出手段650が、検体容器の方を向いた（すなわち検体容器の直上の）フィルターチューブ内での一番下のフィルター組立体Fの通過（落下）をモニターしている。センサー650は、フィルターチューブが空となった場合も検出する。第二のセンサー651が、フィルターの種類をモニターする。

【０１１１】

フィルター組立体は、各チューブ内で、メンブレンフィルターの側（傾斜端部の側）が下向きとなるように、同種のものを適正な向きで積み重ねる。たとえば、各チューブに54個のフィルター組立体を収納し、マガジンに総計で432個のフィルター組立体を搭載することができる。54個のフィルター組立体は、積み重ねた状態で予め包装しておくことができ、フィルターチューブに、包装状態のまま、包装材のタブがスロット630から突出するように挿入しておいて、タブを外向きに引っ張ることによって包装を解くことができる。または、同種のフィルター組立体を、幾何形状によってフィルター組立体の向きを認識する

ことのできる振動供給装置に投入して適正な向きに揃えてから、フィルター組立体をチューブに供給することもできる。こうした供給装置の数台を、フィルター組立体の各種について1台ずつ使用することができる。

【０１１２】

運転時には、押し込みアーム640が、図38に破線で示したシャトルの輪郭によって示される定位置（頂部）に位置した状態で、フィルターマガジン612が、ステッピングモーター616によって、センサー650が、センサー650前方のフィルターチューブ中に所定のタイプのフィルター組立体の存在を検出するまで回転される。その後、シャトル646が下向きに移動し、その際には、押し込みアーム640もスロット630内を移動して、チューブ内の積み重ねられたフィルター組立体を、一番下のフィルター組立体が、チューブから、撹拌部材40のマニホルドMに落ちるまで下向きに押す。フィルターの落下が検出されたら、シャトル646は、押し込アーム640とともに前進を停止する。別の構成では、重量センサーを使用して、積み重ねられたフィルター組立体の重量をモニターし、重量変化によって、フィルター組立体が、積み重ねられたフィルター組立体から落下した時点およびフィルターチューブが空になった時点を検出する。

【０１１３】

マガジン612で8本のフィルターチューブ626が使用されていることにより、バイアル自動搭載装置300のトレーに収納された全検体を無人処理することが可能となる。上述したような型式の卓上式のモデルの場合には、処理経路の上方の固定した位置に支持された1本のフィルターチューブによって、同種のフィルターを必要とする処理検体にフィルターが供給されることになる。

【０１１４】

検体取得および細胞堆積ステーション

図41について説明すると、検体取得ステーション700は、吸引ヘッド702を備えており、この吸引ヘッド702は、降下して撹拌部材40の上側部分と係合する。フィルター組立体Fを通して検体を減圧する前に、吸引ヘッドが、撹拌部材40を把持し、わずかに引き上げ、一次撹拌ステーションよりは低速で回転させて（通常、5秒間隔で、500 rpm以下）、検体液体で中で粒状物質を再度懸濁させる。この再撹拌モーターは、マクソン（Maxon）の24ボルトDC衛星歯車減速型とすることができる。次に、吸引ライン750を通して吸引を行い、検体液体を、容器20から吸引管43を経て粒状物質分離チャンバー（マニホルド）46まで吸引し、さらにフィルター組立体Fを通過させて、単層、すなわち薄層の均一に堆積した細胞が上述のフィルターの底面に残るようにする。検体液体を吸引する間も撹拌部材をゆっくり回転することも可能である。

【０１１５】

図6には、吸引ヘッドが、どのように、撹拌部材のマニホルドの環状壁47と、その内部に収納されたフィルター組立体Fと協働するかが示されている。吸引ヘッドの外側部分704が、壁47を包み込み、この外側部分704は、壁47の外側に対して封止を行うOリング760を備えている。吸引ヘッドの内側部分706は、フィルターホルダー200の上側に対して封止を行う2本の同心のOリング762、764を備えている。開口部750から加えられた吸引力によって、中央開口部204の周囲とフィルターホルダー200内に真空状態が創出され、この真空状態によって、液体がマニホルド46内に吸引され、さらにフィルター202を通して吸引される。吸引ヘッドの内側部分と外側部分との間には、Oリング766が配置されている。

【０１１６】

図42について説明すると、検体の吸引が完了したら、吸引ヘッド702を上昇させる。同時に、吸引ヘッドの内側部分706が、吸引ヘッドの上方に装着した空気シリンダー（図示せず）の作用よって伸張する。吸引ヘッド702が上昇するにしたがって、外側部分704は撹拌部材40から離脱するが、Oリング762および764の間の環状空間に吸引ライン752を通して真空を引くことによって、フィルター組立体Fは、内側部分706上に保持される。したがって、吸引ヘッド702によって、フィルター組立体Fが撹拌部材から取り除かれ、吸引ヘッド702は、さらに、吸引ライン750を経て、フィルターを通して軽い吸引力を加え続けて、フィ

ルター上の細胞物質水分を所望の程度に制御することもできる。

【０１１７】

次に、吸引ヘッド702は、縦軸のまわりを90°枢動することによって横方向に移動して搬送コンベヤから離れ、図46に示す細胞転写位置「P」まで移動し、フィルター組立体Fを、スライド呈示ステーション900のスライドカセットから供給された顕微鏡用のスライドSの上に位置させる。吸引ヘッド702のこの枢動運動は、図11および39でも看取することができる。次に、吸引ヘッド702の内側部分706が下向きに移動して、フィルターをスライドSに4～8ポンドの範囲の突き固め力で、押しつけて、細胞の単層をスライドに転写する。図42の細線は、この吸引ヘッド702の位置の変化と、フィルターのスライドSとの接触を示す。吸引ヘッド702は、枢動可能に装着するのではなく、吸引ヘッド702がスライドSの呈示される転写位置、たとえば処理経路の上方まで、直進運動で前進して後退するよう装着することもできる。

【０１１８】

図43～46について説明すると、吸引ヘッド702は、ブーム716に回転可能に装着されており、ブーム716は、タイミングベルト720を介して吸引ヘッド702を回転させる再撹拌モーター718も担持している。ブーム716は、スライド722上の縦軸721のまわりを枢動可能に支持されており、このスライド722は、Z軸ステッピングモーター726と親ねじ728とによって、フレーム支持部材724に沿って上下方向に可動である。したがって、モーター726は、吸引ヘッド全体を上下方向に移動させる。ブーム716の枢動は、歯車列（図示せず）によって操作されるステッピングモーター717によっている。吸引ヘッドの内側部分706の上下方向の動きは、吸引ヘッドの上方でL字型ブラケット719に装着した空気シリンダーと戻しばね（図示せず）によって操作され、この機構は、キャップ取外しヘッド402のプランジャ408を動かす際に使用した配置412、413、415（図29を参照のこと）と実質的に同一である。

【０１１９】

フレーム支持部材724は、搬送路を横断する方向に可動となるよう、スライド730上に装着されている。Y軸ステッピングモーター732と親ねじ734とが、この動きを可能としている。スライドへの転写が終了したら、吸引ヘッドをZ軸のモーターで上昇させると、Y軸ステッピングモーター732が、組立体全体を、図43に破線で示す位置「X」まで前進させる。次に、吸引ヘッドが枢動して、搬送路を横切ってもとの向きに戻る（図46の「S」の位置）。次に、Y軸のステッピングモーター732が、組立体全体を、もとの位置（図43の実線）に引き戻す。吸引ヘッド702が（図43では右側）に移動するのにしたがって、保持されたままとなっていたフィルター組立体Fが、上端が解放した使用済みフィルター（廃棄）チューブ738の端部736によって、吸引ヘッドから「剥が」される（図11および39も参照のこと）。その結果、吸引ヘッド702は、新たなフィルター組立体と自由に係合しうる状態となる。

【０１２０】

吸引ヘッド702と連通している真空源は、わずかな真空、たとえば、3インチ～10インチHgの範囲の（制御装置で調節可能な）真空を吸引ライン750を経由で引いて検体液体を吸引し、検体液体をフィルター組立体Fに通過させる。フィルター組立体を吸引ヘッド702に保持するために、これとは別に制御した真空を、吸引ライン752を経て引くが、この真空は20インチHg程度と、真空度がさらに高い。

【０１２１】

顕微鏡用のスライド上に高品質の検体を形成しうるか否かは、所定濃度（すなわち、単位面積あたりの細胞の数）の単層の細胞をスライドと接触するフィルター表面に堆積できるかどうかに臨界的に依存しており、その成否は、さらに、吸引速度および/または吸引された流体の容積に臨界的に依存している。フィルター表面上の細胞の濃度は、検体液体に懸濁していた固形物によってブロッキングされたフィルターの孔の数に応じて決まるので、フィルターの最大開口状態からの流量減少率が、フィルターのブロッキング率またはフィルター上の堆積量と相関していることになる。生体検体は、その性質上、固形粒子濃度が、処理中にも可変であり、この点についても考慮する必要がある。また、他の処理操作

のためにも、即時（real time）を基本とし、濾過した材料の総量を特定しておくことが重要である。

【０１２２】

したがって、検体取得ステーションは、流量および/または吸引容積をモニターすることによって、液体吸引用の真空適用時間を制御する堆積制御システムをさらに備えている。モニターした流量または吸引容積は、真空の切断および/または吸引ヘッドの後退の信号を発するために使用することができる、この信号は、メンブレンフィルターの表面に捕集された細胞の所定濃度と相関している。所定容積の流体が吸引されるまでに、所定の濃度係数が達成されない場合にも、システムは、後退信号を発することができる。

【０１２３】

こうした目的には、各種の堆積制御システムまたはモジュールを使用することができる。図47に、こうしたシステムの一つを模式的に示す。このシステムは、液柱にそって配置したデジタル水面検出装置の形態の計測装置を備えている。この「バブル・フロー」システムは、センサーとして、液柱の長さ方向に沿って配置した複数のLED発光体と対応する数の光センサー、たとえばオムロンのセンサーEE-SPX613 GaAs赤外LEDを使用することができる。他の任意の種類のセンサーを使用することもできる。あるいは、LEDセンサー、たとえば上述のオムロンのセンサーは、ガラスチューブのちょうど端部に配置した場合には、対応する発光体なしで使用することができる。チューブ内の液体のメニスカスの先端が、チューブを通過する光を回折し、上昇中のメニスカスの先端がセンサーに到達すると、センサーは、シフトした光のパターンを検出する。

【０１２４】

液柱は、上下方向に延在する透明のチューブまたはシリンダー770、たとえば、パイレックス（Pyrex）ガラス製で直径9 mm、肉厚1 mmのチューブの内部に形成される。吸引された検体流体は、シリンダーの頂部と接続された真空源772によって、検体容器から、メンブレンフィルターを通して吸い上げられ、吸引ライン750と三方弁778を経て、ガラスシリンダー770に入る。複数のセンサー774は、シリンダー770に沿って等間隔に、好ましくは、容積で1.5 mlの間隔をおいて配置されており、制御装置またはマイクロプロセッサ776と接続されている。

【０１２５】

運転時には、正常な状態では、センサー中継ライン（sensor relay line）は、チューブ770に流体が入っていない状態で「低」である。真空によって、フィルターを通してのチューブへの流体の吸引がはじまり、制御装置が、吸引作業の開始を記録する。流体が最初のセンサーに達すると、最初のセンサーのリレーラインが「高」となる。制御装置が、流体が最初のセンサーに達するのに要した時間を記録し、この値は、流体がほぼ自由に流れる状態と、検査での流体の相対粘度を示唆する。チューブに次の1.5 mlの流体が吸引されると、二番目のセンサーのリレーラインが「高」となる。最初の1.5 mlの流体に要した時間間隔（最初のセンサーと二番目のセンサーの時間間隔）を制御装置で記録し、この値を、基準基本時間とする。さらに1.5 mlの流体がシステムに吸引され（そのことが、以降のセンサーによって検出され）るごとに、その増加分の基本時間が計算される。増加分の基本時間が、当初の（基準）基本時間に対して経験的に得られている率（たとえば、120%）に達したら、制御装置が、細胞の捕集が完了したことを指示し、停止信号が送られ、好ましくは検体容器のマニホルドから吸引ヘッド702が後退する。上述の経験的に得られた値は、プロトコールによって可変であり、検体試料の細胞充実度（cellurality）を制御する。

【０１２６】

流体が自由に流れる状態の最良の近似は、流体が最初のセンサー774に到達するのに要する時間が、現実的に最低となる場合に得られる。この状態は、最初のセンサーを、図47aに模式的に示すように、吸引ヘッド自体に組み込むことによって実現することができる。この態様では、吸引ヘッドの内側部分706に、発光体774aと、対向するセンサー774bとが設けてあり、このセンサー774bが、フィルター組立体Fに極めて近い位置で液柱の先端を

検出する。タイミングベルト720（図示せず）と係合した歯775の設けられた外側部分704は、内側部分706の周囲を回転することができるので（間に配置されたベアリング773に注意のこと）、吸引を行う前に撹拌部材（図示せず）を回転させて検体を撹拌することができる。

【０１２７】

検体吸引操作の間、制御装置は、累積吸引容積、すなわち合計吸引容積を記録する。基準流量と比較して所定の流量減少幅まで達する前に、累積容積が所定レベルに達してしまった場合にも、制御装置は停止信号を発し、また、発せられた停止信号が、所望の流量減少が達せられた結果としてではなく、液体吸引最大限度量に達したために発せられたものである旨を表示するフラグを発する。フラグ発行状態で形成されたスライドは、細胞量が不足した状態となりがちである。制御装置は、スライドへの押圧転写を行い、なおかつ、DMSに対して、細胞量不足状態が存在する可能性が相当程度存在することを報告する。したがって、フラグが発行された状態が存在する場合には、制御装置は、シリンダー770中の液体を排出して、2回目の吸引を開始する旨の信号を発行する。シリンダーは、試料採取の各回ごとに、液体の全量を排出する。

【０１２８】

図48について説明すると、堆積制御システムには、空気抜き弁を設けて、吸引サイクルが完了したら、制御装置776によって発せされた停止信号が、空気抜き弁を開いて、真空供給ラインを大気に開放して、シリンダー770中に残っている液体を廃液容器に排出させることができる。シリンダー770は、陰圧に保つことが可能である。この段階で、システムは、次のサイクルの準備が完了している。具体的には、システムは、吸引ラインに一方780が大気に開放した二方電磁弁V-3を設けることができる。シリンダー770の底部は、2つの電磁弁V-2、V-4を備えた弁マニホルド782に接続されている。電磁弁は、真空システムで使用するために設計されたLFシリーズ、二方弁LFVA 2450110H、ヴァイトン（viton）シール、24ボルト、および三方弁、LFRX 0500300B、ヴァイトンシール、24ボルトとすることができる。二方弁V-4は、検体液体をバブルフローシリンダー770、または、真空バイパスに通すことができる。二方弁V-2は、フィルター脱水用真空源を制御することができる。図49は、バルブのロジックを示す。

【０１２９】

堆積制御システムは、デジタルのセンサー774のかわりにアナログの液面計を使用することもできる。アナログの液面計は、吸引した液体の静電容量を検知する。その違いは、シリンダー770中の液体の容積と充填速度を検知する方法のみの違いである。この場合、2つの間隔をおいて配置した電極を使用し、すなわち、一方の電極を、シリンダー770の外周をとりまくように配置し、もう一方の電極を、シリンダーの中央部の下方に、吸引した液体とは誘電体で分離して配置する。電極に、高周波数、たとえば、10 kHzの低電圧電流を印加する。このシステムの静電容量を、アナログで回路の静電容量を示すブリッジ回路で測定する。カラムに流体が充填されるにしたがって、回路の静電容量が上昇する。このシステムでは、直接静電容量で10倍の差を容易に得ることができる。静電容量は、即時を基本として示され、サンプリングシステムの制御を行うのに十分な頻度で試料とすることができる。この配置でも、最初の2つと同じく、コンピュータまたはマイクロプロセッサとバブルフロー技術を使用して、即時に流量と合計流体容積を計測する。こうした構成に用いる所定の容積増加分は、約0.1 ml～5.0 mlの範囲、好ましくは約1.0～2.0 mlの範囲とすることができる。

【０１３０】

別のシステムでは、チューブを通過する流体の動きを測定するのに、超音波インジケータを使用することができる。この超音波システムは、移動中の液体を通しての超音波の伝搬を利用する。この点では、この3つめのシステムは、液体吸引チューブ（吸引ライン750）の両側にクランプ止めされ、フィルター組立体Fの先端で作動する超音波発生器と超音波検出器を使用する。このシステムは、チューブ内の流体の流れをデジタルに表示し、チューブを通して吸引された流体の合計容積を、流れの間隔を計算することによって算出する

。このシステムでは、流速を測定するにあたって、超音波発生源から検出器までの位相変位を測定する。

【０１３１】

吸引された流体の量を計測し、検体吸引時間を制御する別の方法としては、検体バイアルの重量変化を検出する方法もある。この方法は、吸引対象検体の入ったバイアルの重量または質量を高精度で測定するセンサーを使用することによって実施することができる。バイアルの重量または質量を繰り返し高頻度で測定して、バイアルの重量または質量の変化率を正確に判定する。検体の吸引は、重量または質量の変化率が、当初の変化率より所定量または所定率低減した時点で完了させる。重量センサーは、たとえば、各搬送用レセプタクル246の内部に配置したロードセルとすることも、コンベヤの検体取得ヘッド地点の下方に設けられ、上昇して、上方の容器と係合する単一のロードセルとすることもできる。いずれの場合でも、検体取得ヘッドは、吸引の間にわずかに上昇させて容器を脱装填し、ロードセルが、容器と容器内に残っている検体の合計重量のみを測定できるようにする。

【０１３２】

検体の取得は、（真空を使用して）吸引することによって実施することが好ましいものの、容器の頂部を封止する適当なヘッドを通して容器20に圧力を加え、検体液体に正の空気圧を加えることによって、検体液体をチューブ43とフィルター組立体を通して上昇させることによって検体を取得することもできる。上述の流体の容積制御スキームおよび機構は、こうした加圧による検体取得システムでも、有効に用いることができるはずである。

【０１３３】

細胞濃度は、流れの制御のカットオフ値を定義することによって、低度から高度までの細胞濃度より選択することができる。細胞充実度を低度とするには、通常、上述の基準値120%に対してカットオフ値を80%とすることができ、細胞充実度を高度とするには、カットオフ値を、基準値の60%に設定することができる。このカットオフ値は、5%きざみで設定することができる。検体あたりのスライドの数は、1枚～3枚とすることができる。デフォルトのプロトコールのいくつかは、以下の通りである。

婦人科検体（GYN）：1,000 RPMで撹拌。30秒の間隔をおく。8 μmのフィルター。60% - 高度の細胞充実度。スライド1枚。

尿：1,000 RPM で撹拌。20秒の間隔をおく。5 μmのフィルター。70% - 中度の細胞充実度。スライド1枚。

肺の痰：3,000 RPMで撹拌。120秒の間隔をおく。5 μmのフィルター。80% - 高度の細胞充実度。スライド2枚。

【０１３４】

キャップ再装着ステーション

検体処理サイクルを完了したら、撹拌部材を容器中に残したまま、検体容器を再封止する。ロールの形態で入手が可能な、ポリプロピレンでコーティングした薄いアルミニウム箔を使用して、新たなキャップを形成することが好ましい。箔を、検体容器の開放端を横切るように引き出し、約365°Fの封止温度にて、約3秒間3ポンドの封止力をかけて容器に熱で接着し、ロールから切り離す。もちろん、バイアルの材料と適合性で、安全かつ信頼性の高い封止を行うことができるのであれば、他の任意の再キャップ材料を使用することが可能である。たとえば、熱可塑性樹脂接着剤で裏打ちした箔を使用することもできるし、裏面に粘着剤を塗布した箔を使用すれば、封止に際して熱が不要となり、また、プラスチックの封止材を超音波によって容器に接着することもできる。無人運転を可能とするうえでは、封止材の新しいロールをキャップ再装着機構に装填する自動装填器を設けておくことができる。ピールオフ・タブを有する予め打ち抜いておいた閉鎖手段をロールにマウントして、キャップ再装着機構に供給する場合には、ロールからキャップを切り取る工程を省略することができる。

【０１３５】

図50および52について説明すると、キャップ再装着機構800は、機械の基板に固定された

側面支持板802を備えている。この側面支持板は、スロット814、816と2枚の側面板818、820とが設けられた主フレーム810を備えている。駆動巻き上げ機822が側面板818、820に支承されている。ブラケット826に装着された箔前進モーター824が、巻き上げ機を駆動する。主フレーム810には、圧力ローラー828が枢動可能に装着されており、この加圧ローラー828が、巻き上げ機に、ばね830の作用で弾力的に係合している。巻き上げ機822と加圧ローラー828の間には、箔が通過する喉部が規定されており、この巻き上げ機822と加圧ローラー828は、弾性表面を備えているので、箔が把持され、きちんと供給される。喉部は、ハンドル832で手動で開くことができるので、箔の端部を、スロット814をまず通過させてから、喉部に供給することができる。支持板802によって担持されるスピンドル804が、箔の交換ロールを支持している。

【０１３６】

図51は、喉部を通過する箔の経路834を示す。L字型のカッター836の肘部は、主フレーム810の後ろ側に対して枢動する。単動で空気式のカッター駆動用シリンダー838の一端が、ブラケット840に装着されており、シリンダーの他端は、カッター836の上側脚部842に接続している。カッターの下側脚部は、ブレード844を備えており、このブレード844は、通常、箔の経路の喉部の下流側の上方に載置されており、上側脚部842と支持板802との間に張られたばね845によって、この位置に保持されている。

【０１３７】

後方ポスト850が、主フレーム810に向かって延在するアーム852を枢動可能に支持している。アーム852は、加熱した圧盤（platen）854と、喉部に向かって延在する歯を2本備えた箔誘導フォーク856とを担持しており、この2本の歯は、間隔を置いて配置されているので、圧盤854がその間を通過することができる。アーム852は、ばね858によって、図51に示す休息位置まで上昇したまま保持されている。キャップ再装着操作の間は、単動空気式シリンダー860が、アーム852を下方に引っ張って、圧盤854と誘導フォーク856を下降させている。圧盤854の下方の搬送用レセプタクル（図示せず）に入った容器20の位置に留意のこと。

【０１３８】

操作時には、箔前進モーターが、巻き上げ機822を回転させて、測定された長さの箔を、カッターブレード844を経てフォーク856、そしてさらに図51に破線で示す位置まで供給する。光電管862が、箔の先端を検知し、モーターに停止の信号を送る。次に、シリンダー838が作動して箔を切断し、シリンダー860も作動して、アーム852を封止位置まで下方に引っ張る。切断された所定長さの箔は、圧盤854と容器20との間に挟まれ、容器が封止される。約3秒後に、シリンダー860が停止し、アーム852が上昇して、もとの休息位置に戻る。封止に先だって、切断した箔を圧盤上の所定位置に保持するにあたっては、必要に応じて、陰圧を利用することもできる（図示せず）。

【０１３９】

キャップ再装着機構によって装着される箔キャップは、ほぼ矩形の形状である。箔キャップの各頂点は、バイアルの縁からさらに延在することとなり、トレー330に返却されるキャップ再装着済みのバイアルとぶつかる可能性がある。したがって、各箔キャップの縁と頂点を、容器の側面に沿って折り下げる箔折りリング870（図51の細線参照）を設けることが好ましい。箔折りリング870は、キャップ再装着機構のすぐ下流側の搬送位置、すなわち図51の「FF」の位置に対して作動するように搭載することが好ましく、キャップ再装着機構自体、たとえば、主フレーム810に装着して、シリンダー860を作動させると、ある容器に箔キャップが装着され、それと同時に、一つ前の（下流側の）容器の箔キャップの縁と頂点が折り下げられるようにすることもできる。また、箔折りリングまたは同等の箔折り機構は、キャップ再装着機構のさらに下流に、キャップ再装着機構とは独立に搭載することも可能である。

【０１４０】

箔折りリング870は、容器20のねじ部の外径よりわずかの大きめの内径を有する金属製のリングである。リング870は、アーム（図示せず）に装着されており、このアームは、作

動時に下降して、リング870を、容器の上端よりもさらに下降させる。リングが容器の周囲を取り囲むと、箔キャップの張り出し部分872が、リングによって、容器の側面に沿って折り下げられる。箔を折り下げた後にリングが上昇しても、板ばね（図示せず）に取り付けられ、リング870の中央に位置するピン（図示せず）によって、容器は、搬送レセプタクル中の所定の位置に保持される。この板ばねは、リングを保持するアームに取り付けられているので、アームとリングが完全に後退するまで、箔キャップの中央がピンによって弾力的に押さえられる。

【０１４１】

処理済み容器に付された箔による封止は、注射器またはピペットで容易に穿刺して、追加の液体検体試料を得ることができる。しかし、この封止は耐性が極めて高く、荒っぽい取り扱いにも耐え、周囲圧力が低い条件、たとえば、40,000フィートもの高さで航行中の航空機中でも、漏れが防止される。また、箔による封止という外観は、未処理のバイアルのカバーとは一目で見分けがつき、不慣れな操作者であっても間違える余地がない。不用意に箔による封止を穿刺してしまう潜在的な可能性を防止するには、再封止した容器に、目立つ色の未使用のねじ込み式カバーで蓋をすることもできる。

【０１４２】

スライドの取り扱いと呈示

LBP装置は、標準的な25 mm x 75 mm x 1 mm、すなわち1 x 3 x 0.040インチのスライドを収納することのできる30および40枚用のプラスチック製のスライドマガジン（カセット）を使用することができる。メートル法およびインチ基準のスライドは、互換的に使用することができる。図52～55は、LBP装置での使用に適したスライド40枚用のカセットCを示す。このスライドカセットは、いくつかの点で、米国特許第5,690,892号（参照として本明細書に組み入れられる）に開示されたカセットと類似しているが、他の装置、たとえば、自動染色装置、自動画像解析装置、病理ワークステーションでの使用にも特に適合させてあるので、こうした装置で使用する際に、スライドを取り出して、別のマガジンに装填しなおさなくてもすむ。カセットには、機械で読みとり可能な表示、たとえばバーコードまたは埋設したマイクロチップが設けてあるので、このカセット情報を、DMSによって、カセット内のスライド上のバーコードと関連づけて、任意のカセットと、そのカセットに入っている任意のスライドについての位置と状態を、検査システムで追跡することができる。カセットは、保存時に場所をとらず、取り出しやすいように、積み重ね可能となっている。

【０１４３】

具体的には、スライドカセットは、プラスチックから成形され、ほぼ矩形の形状を有しており、開放した前面902、背部壁904、頂部壁906、底部壁908、側壁910を備えている。頂部壁906には、バーコード化された情報909が表示されている。誘導フランジ912が、各側壁から外に向かって横方向に延在している。背部壁904には、矩形の中央開口部914が設けられ、この中央開口部914を、スライド・シャトルが通過して（後述）、1回に1枚ずつ、スライドを取り出して戻すことができる。中央開口部の周囲に設けられた内向きに突出する凸部916が、カセットにスライドが挿入された際にスライドが当接する停止部材として機能する。カセットの材料として好ましいものは、ABSプラスチックであり、場合によっては、ポリウレタン、熱可塑性ポリエステル、ポリプロピレンとすることもできる。開放した前面は、別の同様のカセットの背面を受け止める寸法となっているので、積み重ねが可能である。

【０１４４】

スライドは、カセットの両側に設けられた棚918で支持されている。例示した態様では、41組の左側および右側の棚が設けられており、各組（一番上の一組を除く）が、棚の間の空間に延在する1枚のスライドを支持している。図53の詳細な図について説明すると、各棚（一番上と一番上の棚を除く）には、スライドが載置される頂面側の隆起した縁920と、下面側のビームばね922を備えており、このビームばね922は、スライドを挟んで、スライドをその直下の頂面側の縁との間で摩擦によって拘束するための力を加える。この構成

によって、たとえカセットが正面側を下にして保持された場合でも、スライドがカセットからずり落ちることが防止され、しかも、各スライドを、後述のスライド呈示装置によって、スライドにマウントした検体をブロックしたり、擦り傷をつけたり、損傷したりすることなく、カセットから取り出して、また戻すことが可能となる。各棚918には、スライドをカセットに挿入する間にスライドを誘導する導入斜面924も設けてある。各棚918（ばね922を含む）は、カセットと一体に成形し、背部壁904と側壁910の双方に固着することが好ましい。しかし、棚の間には、別途形成したばね、プラスチック、または金属を挿入することもできる。

【０１４５】

各側壁には、染色浴から取り出した後に、染色液がカセットから排出される複数の排出口926が設けられている。各側の一番端の（一番上と一番下の）排出口923は、カセットを、ある染色浴から別の染色浴へと移動する際の染色装置の吊り下げ組立体とも協働する。染色作業の間は、カセットは、通常横向きとなっており、上側となった側の一番端の2つの排出口で吊り下げられている。カセット全体がプラスチックから構成されているので、カセットは、酸浴をはじめとする各種の染色浴の組成と適合性である。

【０１４６】

図54について説明すると、背部壁904には、2列の穴927が設けられ、この2列の穴927は、一体に成形された2本の歯車用ラック928を形成している。この2本の歯車用ラック928は、ピニオン歯車936（下記を参照のこと）と係合して、カセットを長手方向に移動するので、スライド・シャトルによる各スライドへのアクセスが可能となっている。2本の間隔をおいて平行に配置されたラックと2個のピニオン歯車が設けられているので、ラックが1本とピニオン歯車が1個の場合と比べて、動きが滑らかになり、正確な位置決めが可能となる。背部壁には、カセットの位置を検出するための40個のスロット929の列も一体に成形されており、このスロット929は、背部壁を貫通し、スライドの位置と対応しているので、各スライドを光学的に検出することが可能となっている。また、背部壁904には、40個の非貫通凹所925（これらの凹所は、背部壁を貫通していない）の列も形成されているので、歯車用ラック928による駆動時に、カセットの位置を正確に検出することができる。

【０１４７】

成形されたカセットは、スライドを収納した状態で、封止したビニールに梱包して供給することが清浄な状態を保つうえで好ましい。したがって、このカセットは、輸送に適しており、比較的低コストであり、廃棄可能であるとともに再使用も可能である。このカセットは、また、収納力が高く、積み重ねが可能であるので、検体試料を高密度で保管することができる。

【０１４８】

スライドの充填されたスライドカセットは、フィルター搭載ステーション600と検体取得ステーション700との背後に位置する高架供給トラック930（図11を参照のこと）経由で手動で、LBP装置に装填される。カセットをシステムに導入する際には、ラッチでの係止は不要である。LBP装置には、一度に10個までの未処理のカセットを装填することができるが、方向は一方向のみである。カセットには、どちらが上かを示す表示を付すことができ、逆の向きや上下逆に装填された場合には、そのカセットは搭載しない。カセットは、図11に示すように、開放された前面が右向きとなるように装填し、その際には、鉛直方向のレール932の間に、先頭のカセットが来るようにする。

【０１４９】

先端カセットは、検体の押圧転写のために新たなカセットを取り出すたびに、少しずつ下降する。この動作は、カセットC（図54を参照のこと）の背面に設けられたラック928と係合するピニオン歯車936を駆動するステッピングモーター（図示せず）によってなされる。カセット中の全スライドの処理を終えたら、カセットは、取り出しトラック940まで一挙に下降し、ステッピングモーター/親ねじ押し込み手段938が、カセットを、右方向に、取り出しトラック940へと移動させ、カセットを後退させる。次に、供給トラック930上の次のカセットが、モーター/親ねじ押し込み手段（図示せず）によって鉛直方向のレール9

32の間の正面位置まで前進させられ、カセットは、ここで、ピニオン歯車936と係合して、最初の（一番下の）スライドが抽出位置に来るまで下降する。供給トラックは、それぞれ、定位置センサーと、カセット満杯センサーを備えるものとすることができ、定位置センサーは、オムロン（Omron）の内蔵式のシャッター型とし、カセット満杯センサーは、キーエンス（Keyence）の光ファイバーとすることができる。

【０１５０】

図11、56、および57は、スライド呈示システムを示す。このシステムでは、スライド・シャトル供給システム960、たとえばAMパート番号5000-1を使用して、カセットからX軸に沿ってスライドを1回に1枚ずつ引き出し、Y軸ハンドラー上に載置する。Y軸ハンドラーは、スライドを呈示（押圧転写）位置まで移動させる。上掲の米国特許第5,690,892号には、病理ワークステーション（顕微鏡）で使用される、これと類似したスライドカセットとシャトルの配置が開示されている。Y軸ハンドラー962は、従動子966、967に固定されたスライド圧盤964を備えている。ハンドラーは、ステッピングモーター970とレール968に沿って誘導される親ねじ972とによって駆動される。スライドは、図56に示すように、固定肩部974と、ばねで反時計回り方向に賦勢された枢動アーム978の下方で（ばね976に対して）圧盤上に保持される。

【０１５１】

ハンドラー962が左に向かって移動すると、アーム978が、調整式の止め980を移動させて外し、スライドの上方で回転する。Y軸の全長（図57に「T」で表示）を褶動して移動すると、スライドの中央が、押圧転写位置「P」に来る（図56のスライドとハンドラーの破線の位置に注意のこと）。押圧転写位置への移動中に、スライド上のバーコード番号が、バーコードリーダー982によって読みとられ、ホストデータベースへと送られる。押圧転写位置に達したら、軸721を囲む弧「A」に沿って枢動してきた吸引ヘッド702によってフィルター組立体Fが降下し、上述したようにスライドと接触し、検体を、スライド上に堆積（押圧転写）する。押圧転写サイクルの間を通じて、フィルターへの真空の適用を継続し、試料の水分過剰と、意図しないしたたりを防止する。

【０１５２】

押圧転写の後、スライドは右方向に移動して戻り、固定液分注ヘッド984の下で休止する。ここで、ソレノイドで駆動したポンプ（図示せず）、たとえばLee LPL X 050AA、（24V、20マイクロリットル/パルス～12マイクロリットル/パルス（最大で2パルス/秒））によって、固定液を検体に適用する。固定液の総量は、ソレノイドサイクル数によって決定すればよい。この固定液の分注容積は、20マイクロリットル単位でプログラムすることができる。固定液は、0.030インチのオリフィスを備えた分注サファイアジェットノズルに、可撓性の接続を行うことができる。液体は、貯槽からポンプに重力で供給すればよい。貯槽は、タンクとすることができ、オペレーティングシステムと接続した「低水量」センサーを設けることができる。2つ以上の固定液分注器を用いて、処理プロトコールに応じて決定される別の固定液を用いることもできる。

【０１５３】

検体が固定されたら、完成したスライドは、右側まで完全に戻り、スライドは、スライドシャトル機構によって、カセットのもとの位置に戻される。カセットの処理がすべて終わったら、上述したように、カセット全体が、排出トラック940に放出される。

【０１５４】

完結した検査システム

本発明のLBP装置は、検体を装置への搭載前に前処理しておく必要がなく、スライド作製過程の全工程を自動化することができる。さらに、本装置では、操作者は、検体容器を開く必要が一切なく、この点は、操作者の安全という観点から重要な特徴である。本LBP装置は、粘膜を含有する婦人科および非婦人科検体をはじめとするあらゆる種類の検体から、一体に組み込んだ、高速で剪断力が高く、粘膜を解離しうるような撹拌ステーションを使用することによって、高い品質の細胞診用スライドを自動的に作製することができる。また、二方向流路のフィルターシステムが組み込んであるので、細胞の分離の程度、細胞

の濃度、細胞の分散が最適化され、抗原、DNA、形態学的特徴が最適化され、そのため、その後の検査成績が向上する。それぞれ40枚以下のスライドを収納することのできるスライドカセットは、その後の検査用処理装置で使用することができるので、スライドをさらに処理する際に、スライドを別のラックに移すという労働集約的な作業を行わなくてもすむ。患者についてのデータ、検体、バイアル、カセット、スライドは、DMSソフトウェアのインターフェースを通じて利用者のネットワークから自動的にLISに移すことができる。

【０１５５】

本発明のLBP装置は、8時間の無人操作時間を行うことができる。したがって、操作者が、職場を離れる前に再装填を行えば、交替勤務制でない検査施設でも、人件費や装置のコストを余分に支払うことなく、1日あたり2交代分の処理量を実現することができる。本発明のLBP装置はは、年間処理量がスライド160,000枚を超え、検査1回あたりのコストも、現在の最先端のLBPシステムより、有意に低い。

【０１５６】

本LBP装置は、現在および将来の分子診断検査、たとえば、定量的DNA分析、マーカーやプローブを利用する検査に備えて検体を処理する能力も備えている。装置に組み込まれた特性としては、複数の固定液分注装置を用いて、特別な分子診断検査で必要とされる所定以外の固定液も使用することができる点も挙げられる。

【０１５７】

たとえば図21aに図示した完結した検査システムは、病理学的再検討用のステーションを含むものであり、この病理学的再検討ステーションは、専門家が検体のスライドを再検討して、細胞診の場合については署名して送り出す、コンピュータ支援顕微鏡観察作業ステーションである。検査システムのすべての構成部分と同じく、この病理学的再検討ステーションは、患者のデータや検体の処理についての情報に迅速にアクセスできるよう、DMSとともにネットワークを構成しており、したがって、システム上の他のすべての装置とともにネットワークを構成している。病理学的再検討ステーションは、スライドカセットを受け取ると自動的に搭載し、検体スライドの検討を行う。コンピュータ化され、完全に自動化された画像分析装置が、DNAの定量的分析と分子診断検査を行い、その際には、操作指示を受取り、その結果を検体バーコードを介して、一体化されたDMSを使用して報告する。たとえば、アキュメド（AccuMed）/MDI、米国特許第5,963,368号、米国特許第6,091,842号、および米国特許第6、148,096号を参照されたい。なお、これらは、いずれも、参照として本明細書に組み入れられる。

【０１５８】

本検査システムは、たとえば、DMSによって制御され、本発明のLBP装置と同じスライドカセットを利用するスライド自動染色装置および自動カバーガラス載置装置（および/または自動染色/カバーガラス載置装置の組み合わせ）も含む。処理済みのスライドを収納したカセットは、スライドを一度取り外してから別のラックに搭載しなおさなくても、直接、これらの追加の装置で使用することができる。

【０１５９】

このように、検査システムを構成する各処理や各分析装置が相互に接続され、高度に自動化されているので、高品質かつ高処理量の検体の処理および分析を比較的低コストにて実施することが可能となる。

【０１６０】

産業上の利用の可能性

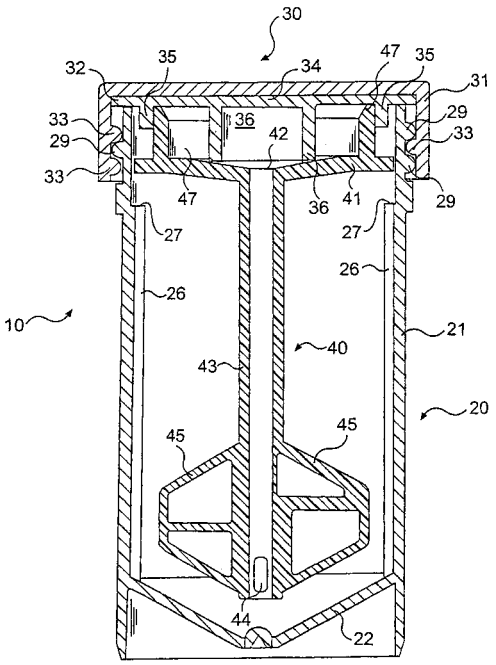
以上では、液体ベースの細胞検体を捕集し、取り扱い、処理する際に使用することのできる、安全で、有効で、正確で、精度が高く、再現性があり、安価で、効率が良く、迅速かつ簡便なバイアルを基本とするシステムおよび装置を開示してきた。こうした開示によって、完結した細胞診断検査システムにおいて、検体と情報とが完全に一体化した管理を行うことが可能となる。

【図面の簡単な説明】

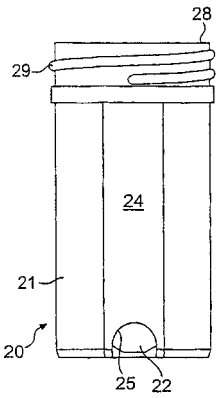
【０１６１】
【図１】LBP装置とともに使用する検体バイアルの縦断面図であり、カバーと結合された処理組立体（撹拌部材）がバイアル中に収納されている状態を示す。
【図２Ａ】バイアルの容器部分の正面図である。
【図２Ｂ】撹拌部材を取り外した状態での容器の上面図である。
【図３】撹拌部材の上面図である。
【図４】カバーと嵌合するライナーの底面図である。
【図５】撹拌部材、およびこの撹拌部材とともに使用するのに適したフィルター組立体の拡大縦断面図である。
【図６】撹拌部材の上側部分の縦断面図であり、フィルター組立体を粒状物質分離チャンバーの所定位置に載置した状態を示す。
【図７Ａ】図6に示した構成の部分模式図であり、液体、および液体から分離する粒状物質の流れを示す。
【図７Ｂ】図7aと同様の図であり、従来技術のフィルターシステムでの液体の流れを示す。
【図８】フィルター組立体の拡大断面図である。
【図９】流体マニホルドの寸法形状を示す模式図である。
【図１０】図1と同様の検体バイアルの、撹拌部材からカバーを取り外した状態での縦断面図である。
【図１０Ａ】図10と同様の部分縦断面図であり、撹拌部材の改変例を示す。
【図１１】LBP装置の上面図である。
【図１１Ａ】LBP装置の操作順序を示す模式図である。
【図１２】LBP装置の前面斜視図であり、見やすいように、一部を取り除いてある。
【図１３】LBP装置の背面斜視図であり、自動搭載/取り出し機構を示す。
【図１４】自動搭載/取り出し機構の上面図である。
【図１５】自動搭載/取り出し機構の正面図である。
【図１５Ａ】図14の線15a-15aに沿って見たときの詳細な断面図である。
【図１６】自動搭載/取り出し機構の把持手段の別の態様の正面図である。
【図１７】自動搭載/取り出し機構に使用する検体バイアルトレーの斜視図である。
【図１８】図17の円18部分の拡大詳細図である。
【図１９】図17の検体バイアルトレーの底面斜視図である。
【図２０】検体バイアルトレー3枚を積み重ねた状態の斜視図である。
【図２１】検体バイアルの取り扱いとデータのフローを示すブロック図である。
【図２１Ａ】LBP装置が組み込まれた検査システムの全体を示す図である。
【図２１Ｂ】リレーショナルデータベースの表である。
【図２２】コンピュータまたはワークステーションを示すブロック図である。
【図２３】コンピュータ画面の模写図である。
【図２４】別のコンピュータ画面の模写図である。
【図２５】2台のコンピュータ画面の模写図である。
【図２６】キャップを取り外した検体バイアルの縦断面図である。
【図２７】LBP装置のキャップ取外しヘッドと係合されたの検体バイアルの部分断面正面図である。
【図２８】図27の線28-28に沿って見たときのキャップ取外しヘッドの上面図である。
【図２９】LBP装置キャップ取外しステーションの側面図である。
【図３０】図29の線30-30に沿って見たときの断面図である。
【図３１】図29のキャップ取外しステーションの上面図である。
【図３２】一次撹拌ヘッドを係合させた状態の、検体容器の縦断面図である。
【図３３】LBP装置の一次撹拌ステーションの側面図である。
【図３４】一次撹拌ステーションの正面図である。
【図３５】一次撹拌ステーションの上面図である。

【図３６】フィルターを搭載する間の検体容器縦断面図である。
【図３７】LBP装置のフィルター搭載ステーションのマガジン部分の側面図である。
【図３８】フィルター搭載ステーションの押し込み手段部分の正面図である。
【図３９】フィルター搭載ステーションの押し込み手段部分の上面図である。
【図４０】フィルター搭載ステーションのマガジン部分の上面図である。
【図４１】検体を取得する間の検体容器の縦断面図である。
【図４２】スライドに検体を移す間の検体容器の縦断面図である。
【図４３】LBP装置の検体取得ステーションの側面図である。
【図４４】検体取得ステーションの下側部分の正面図である。
【図４５】図43の線45-45に沿って見たときの取得ステーションの部分断面上面図である。
【図４６】検体取得ステーションの上面図である。
【図４７】検体取得ステーションで使用する泡流量計の模式図である。
【図４７Ａ】図47の流量計の改変例の模式図である。
【図４８】検体取得ステーションで使用される真空システムの模式図である。
【図４９】図48の真空システムの操作図である。
【図５０】LBP装置のキャップ再装着ステーションの前面斜視図である。
【図５１】キャップ再装着ステーションの側面図である。
【図５２】LBP装置で使用されるスライドカセットの前面斜視図である。
【図５３】図52のスライドカセットの詳細な斜視図である。
【図５４】スライドカセットの背面斜視図である。
【図５５】スライドカセット側面図である。
【図５６】LBP装置のスライド呈示システムの上面図である。
【図５７】スライド呈示システムの側面図である。

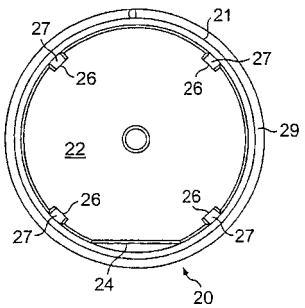
【図１】



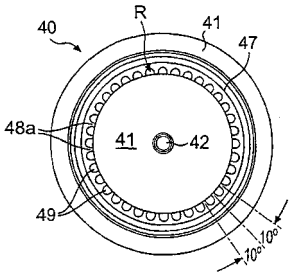
【図２Ａ】



【図２Ｂ】



【図３】



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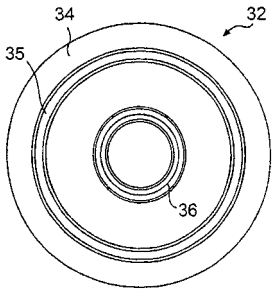

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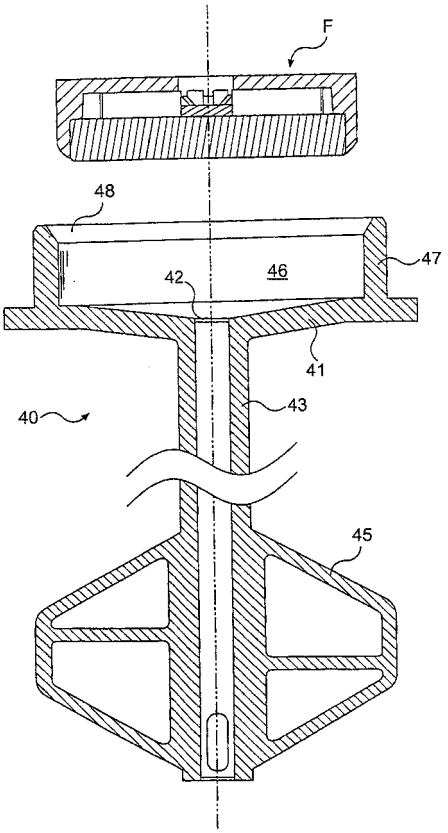

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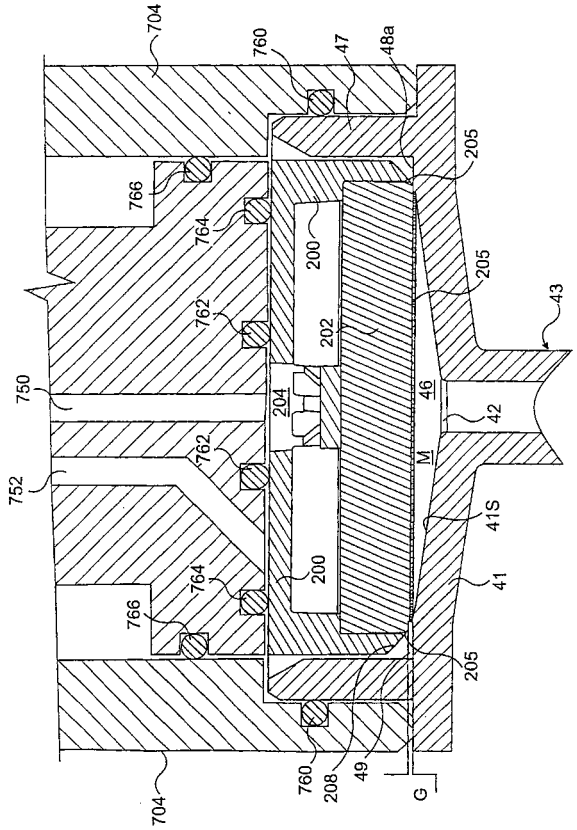

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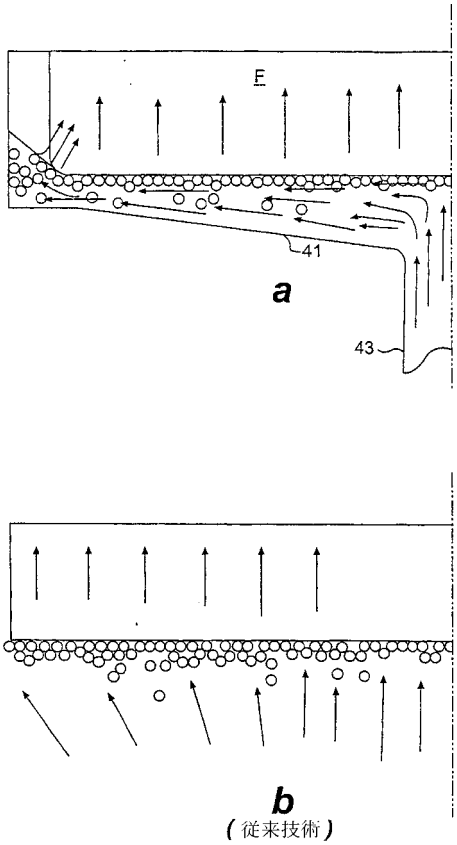
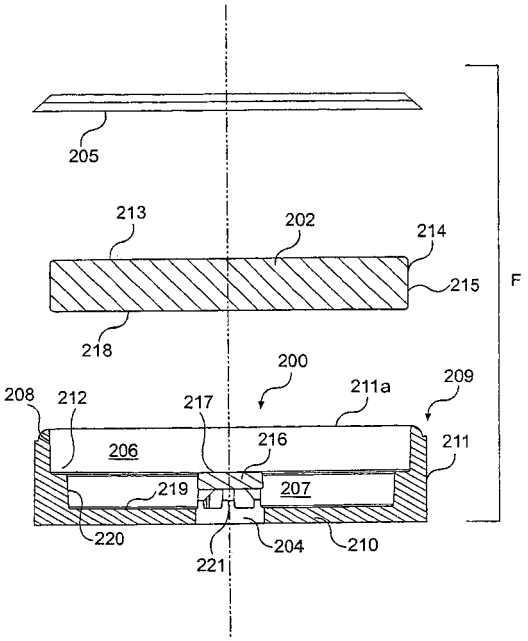


（従来技術）

【図８】



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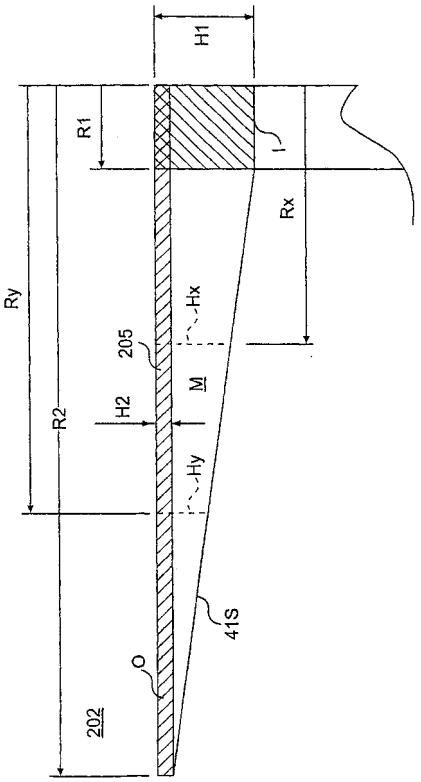

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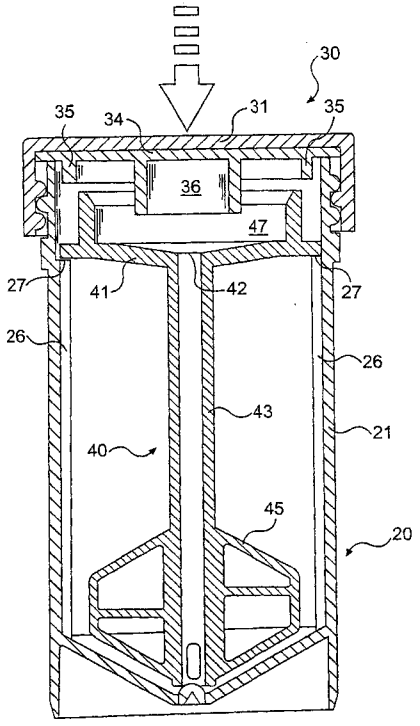

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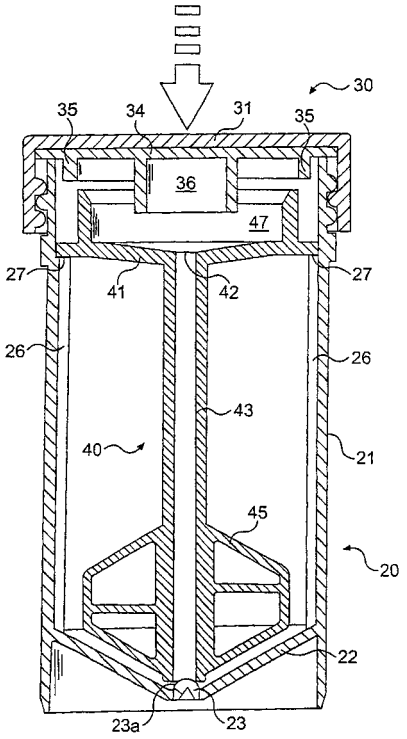

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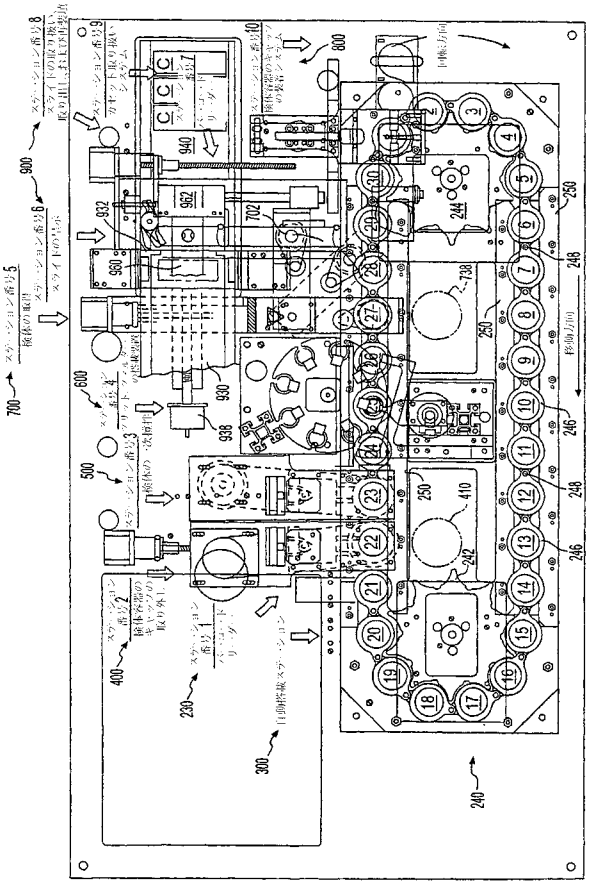

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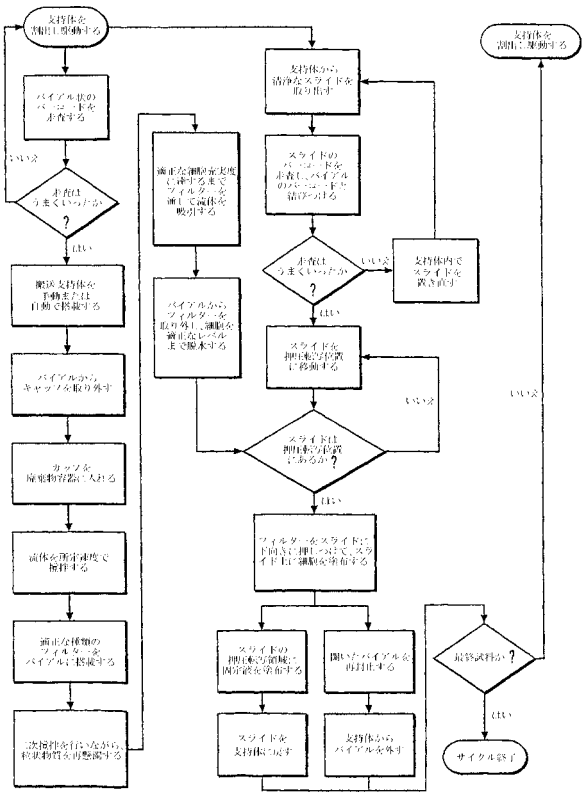

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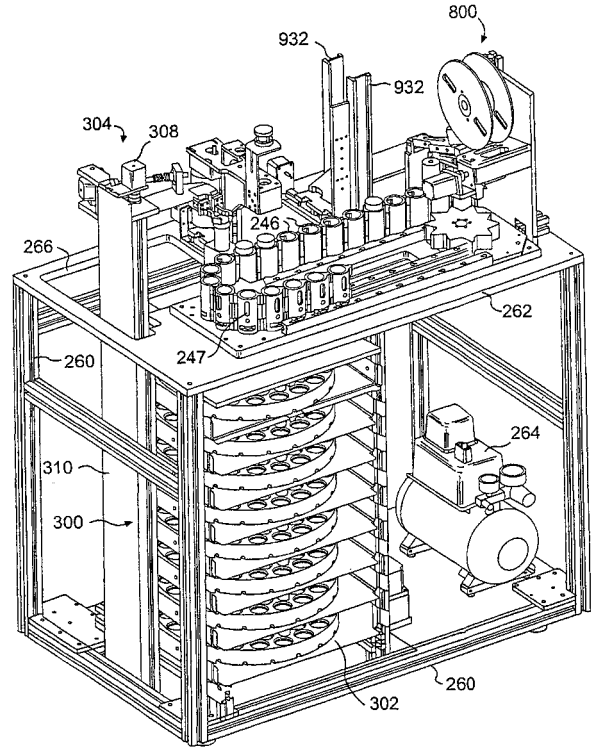

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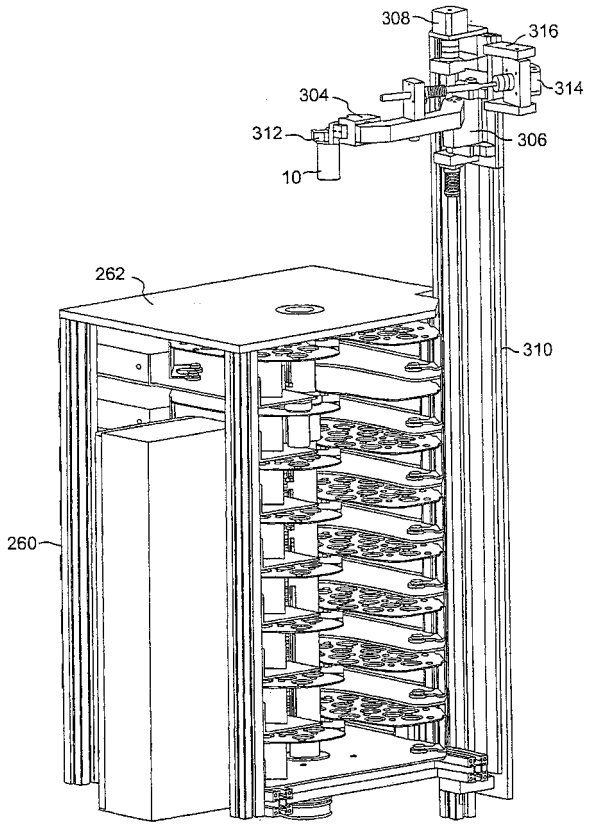

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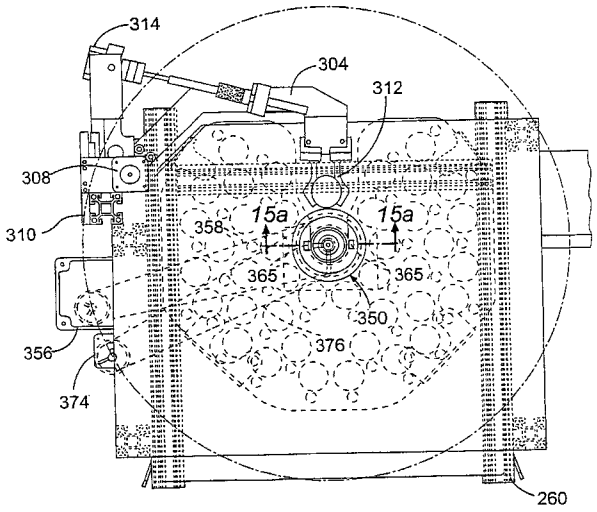

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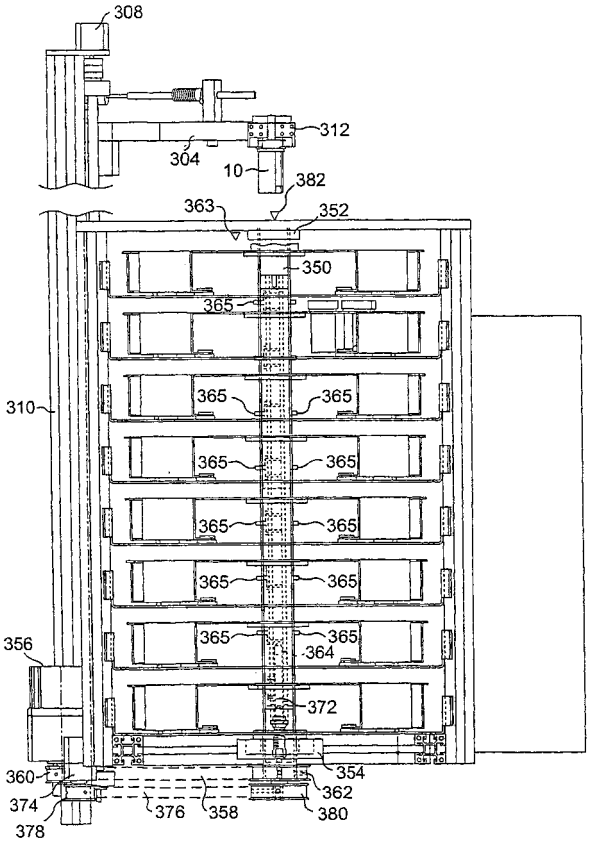

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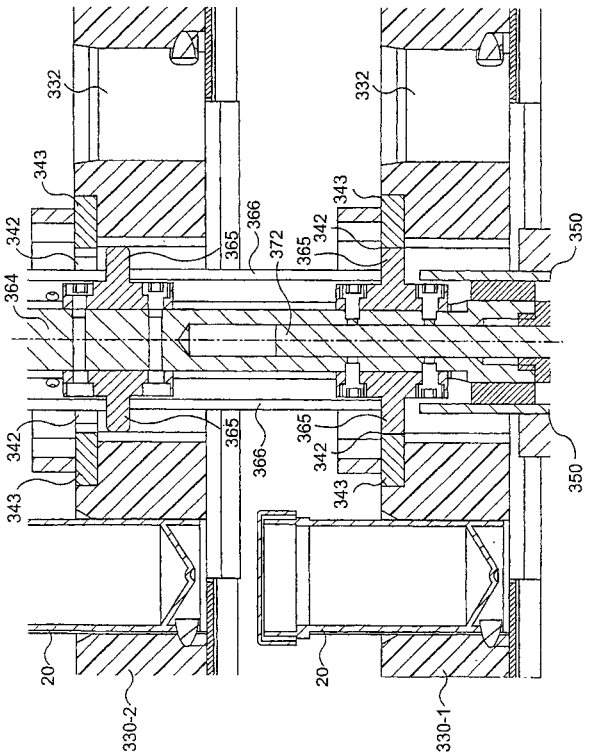

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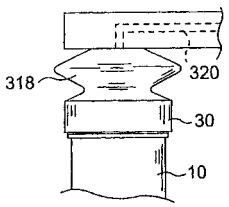

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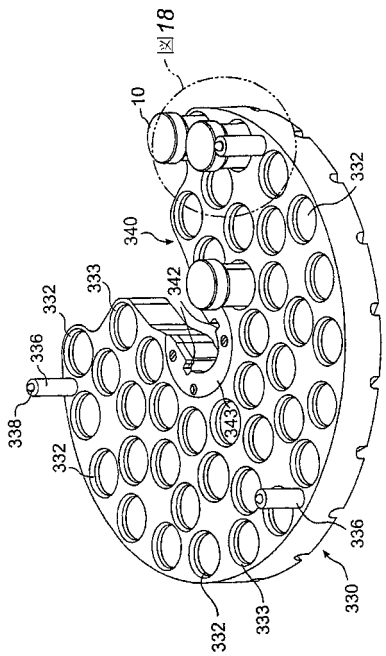

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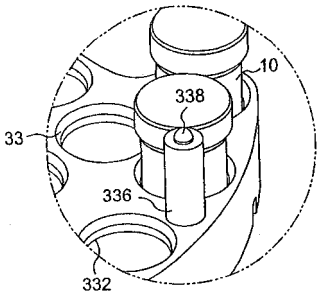

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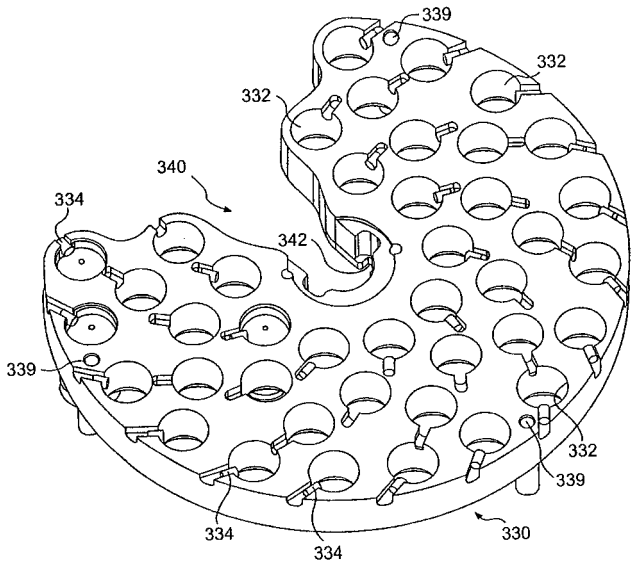

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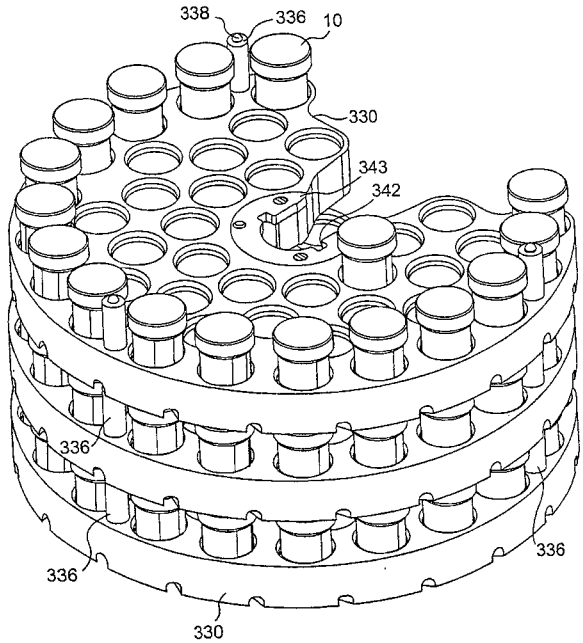

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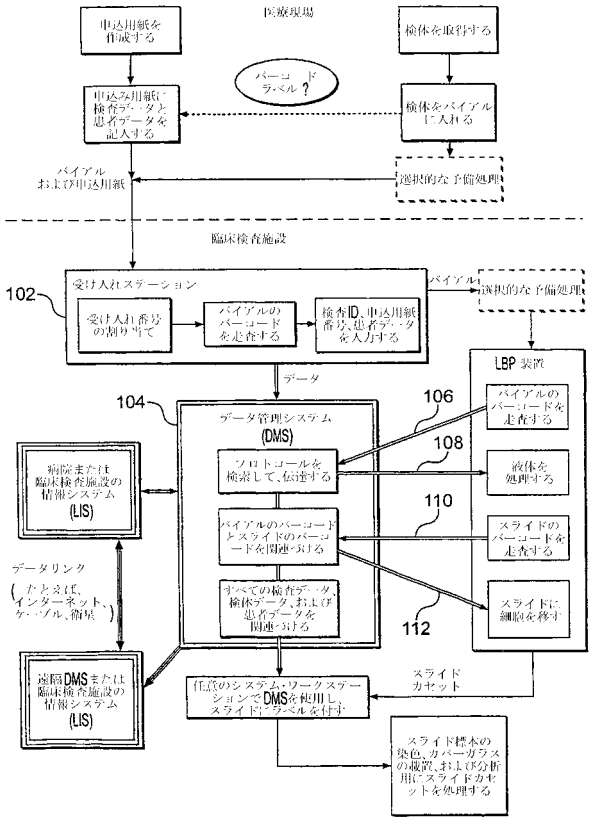

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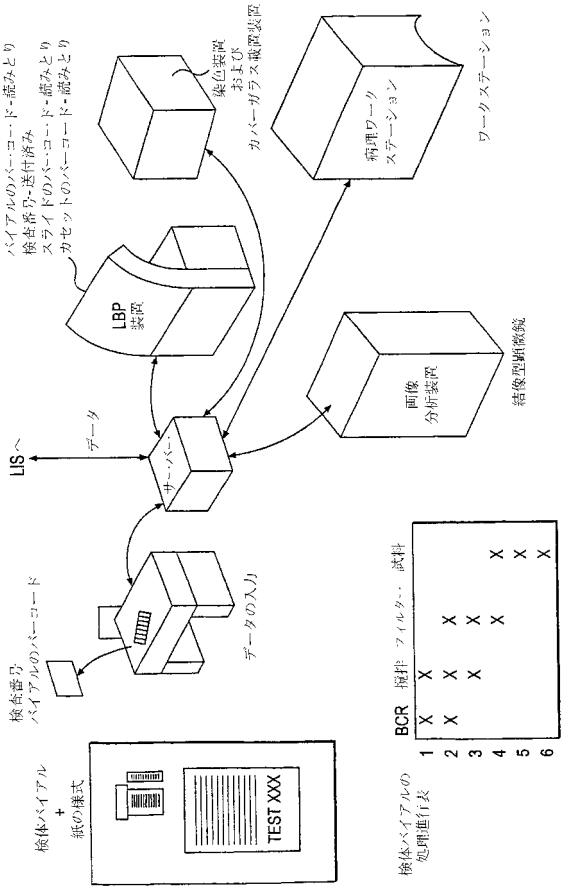

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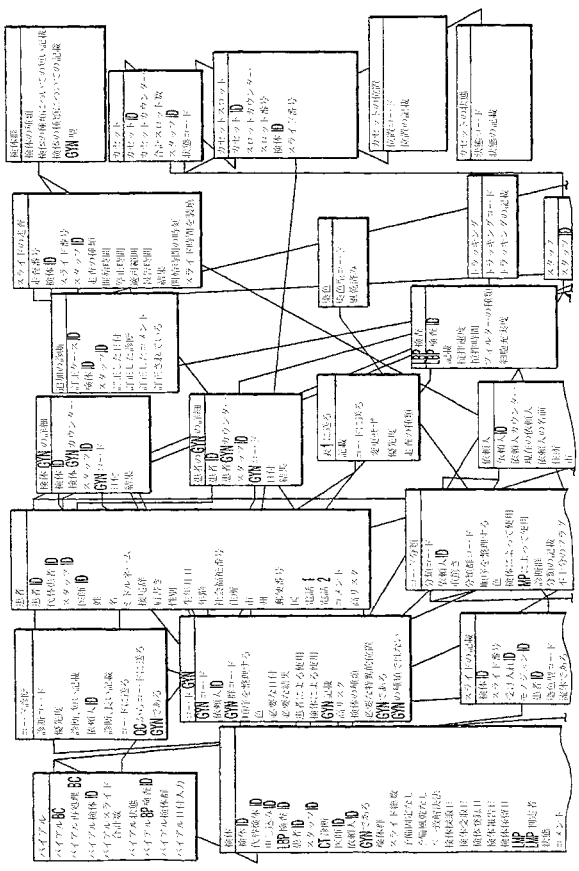

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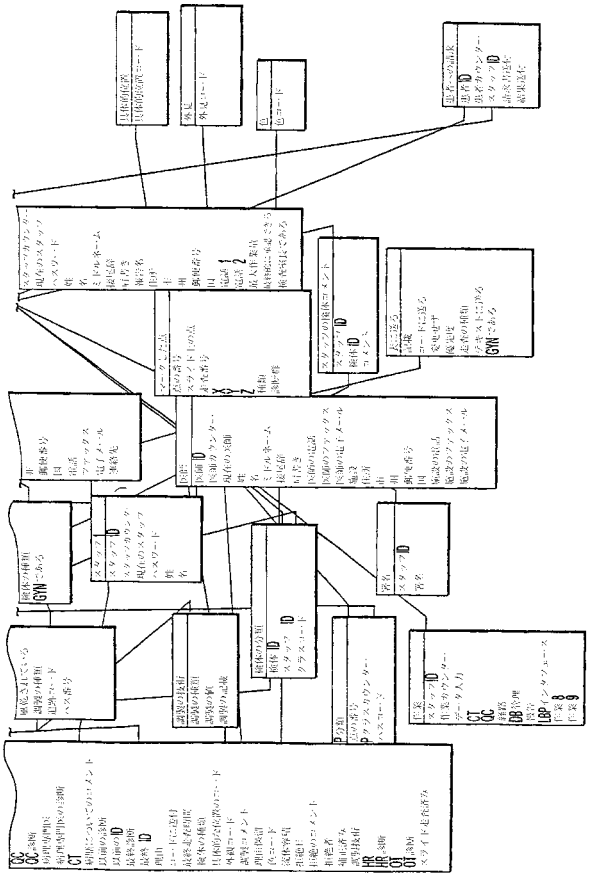

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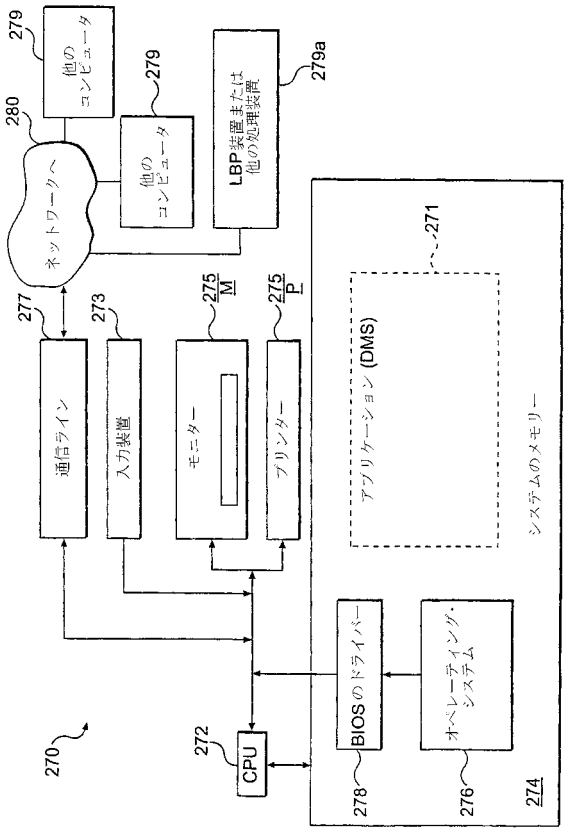

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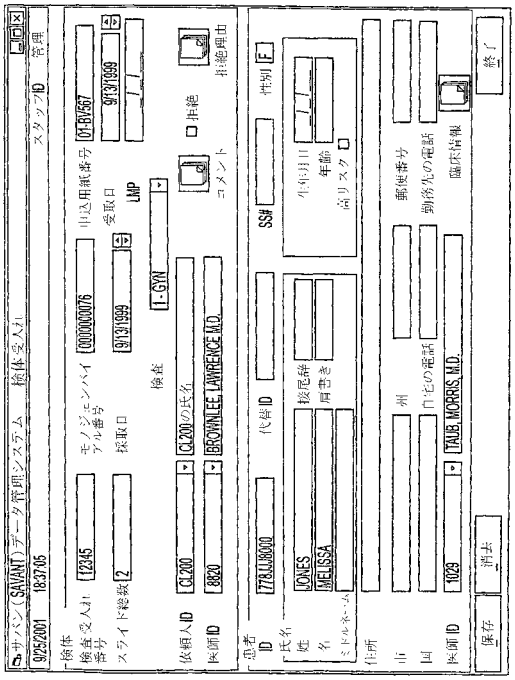

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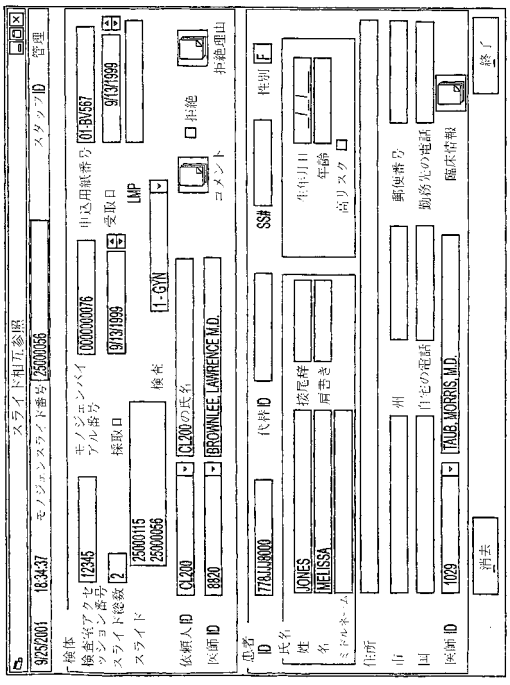

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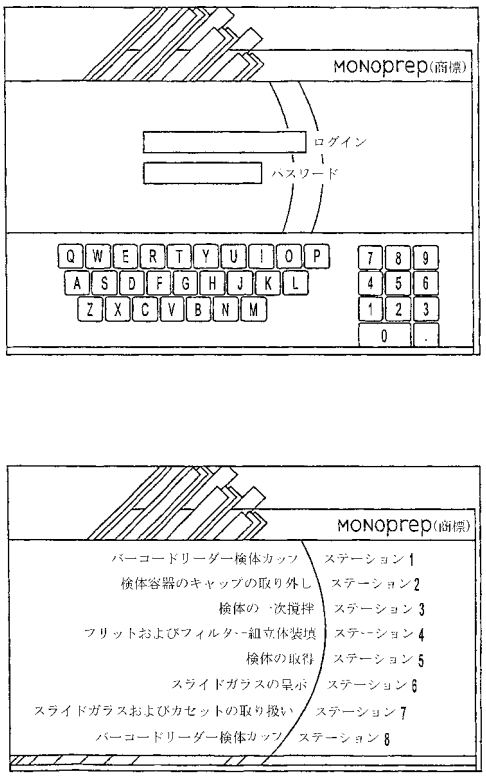

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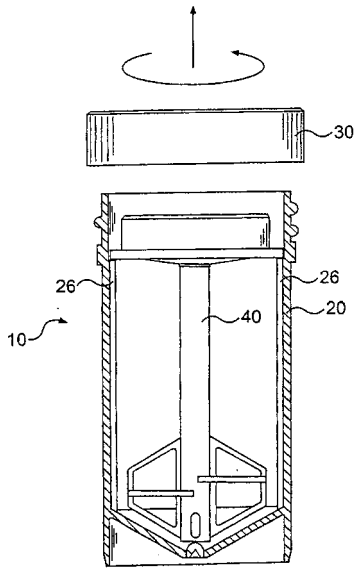

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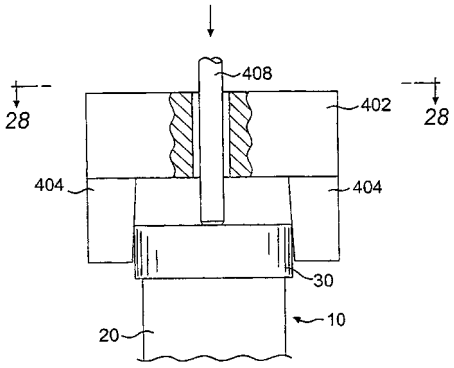

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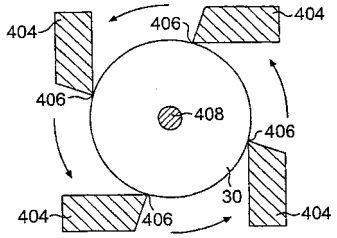

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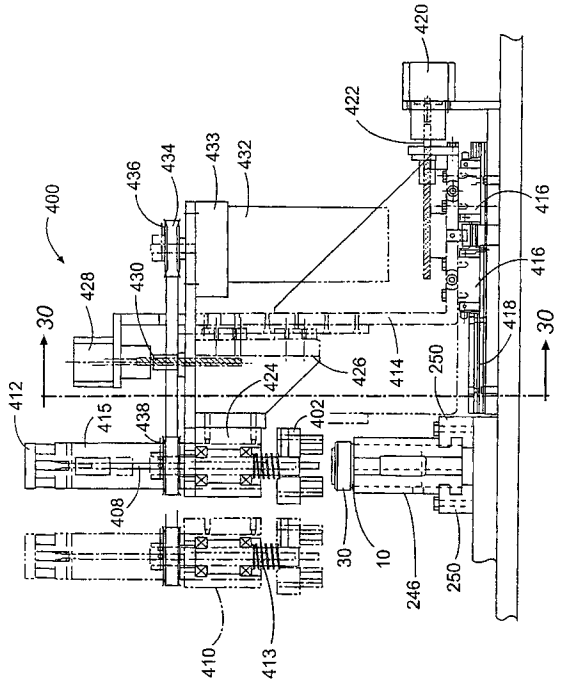

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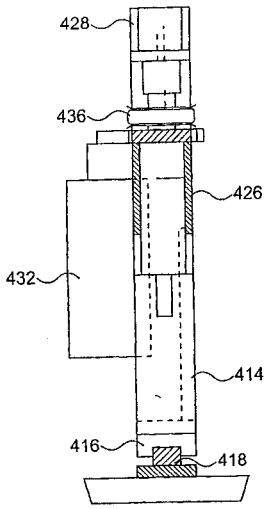

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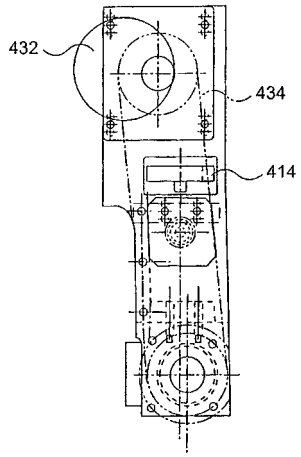

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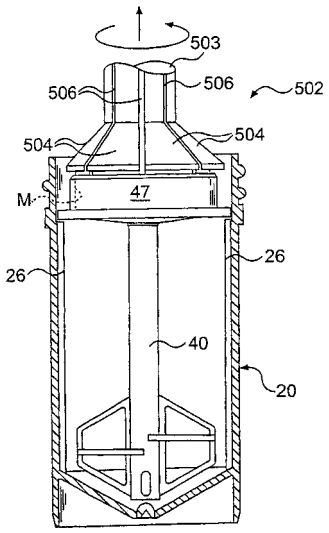

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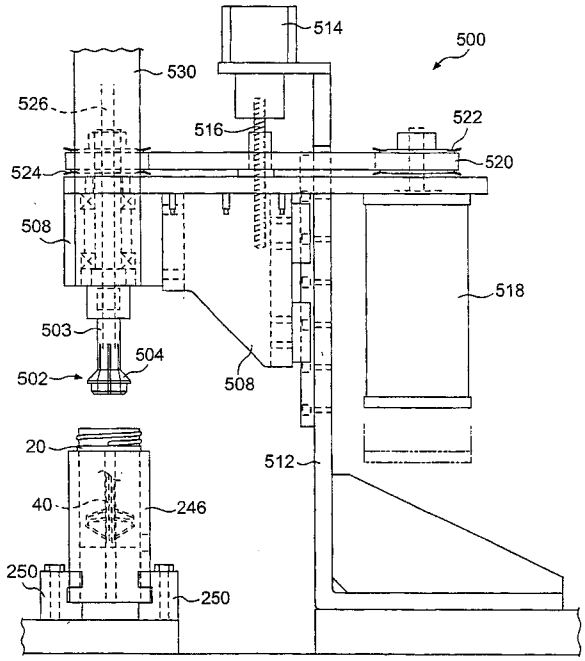

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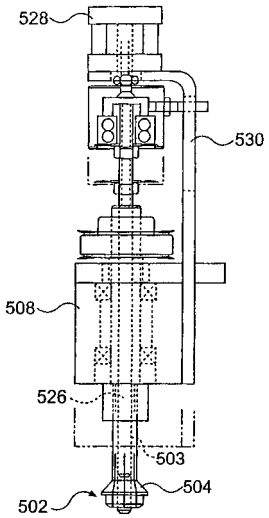

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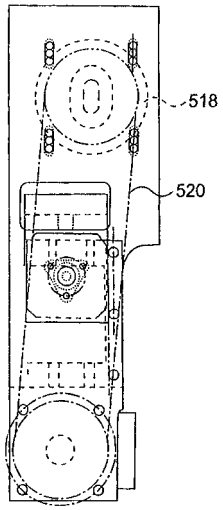

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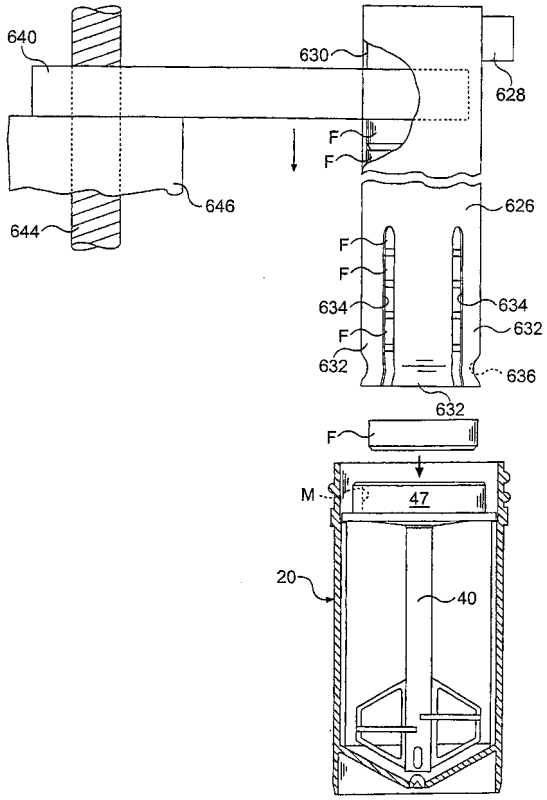

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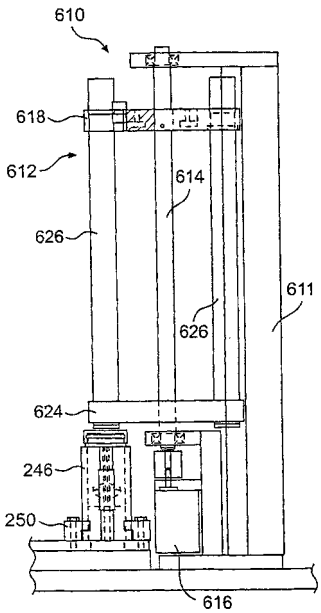

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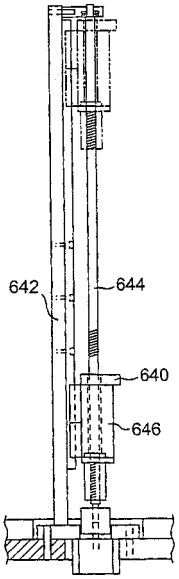

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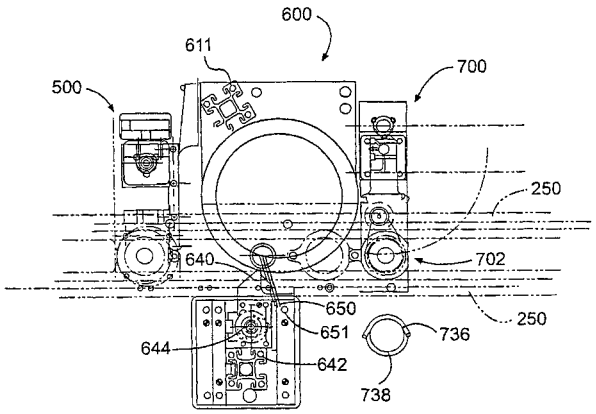

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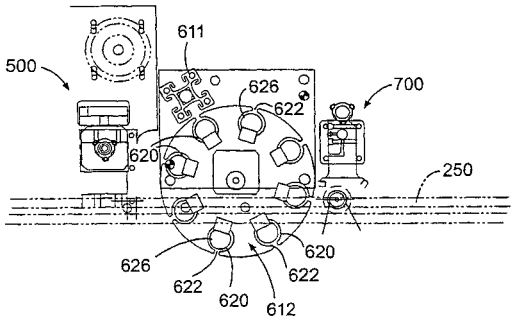

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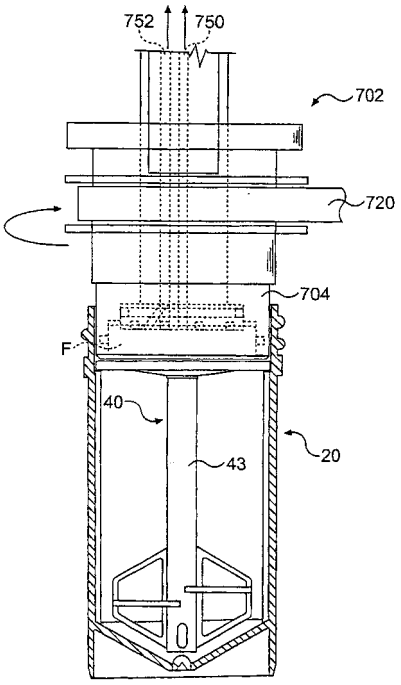

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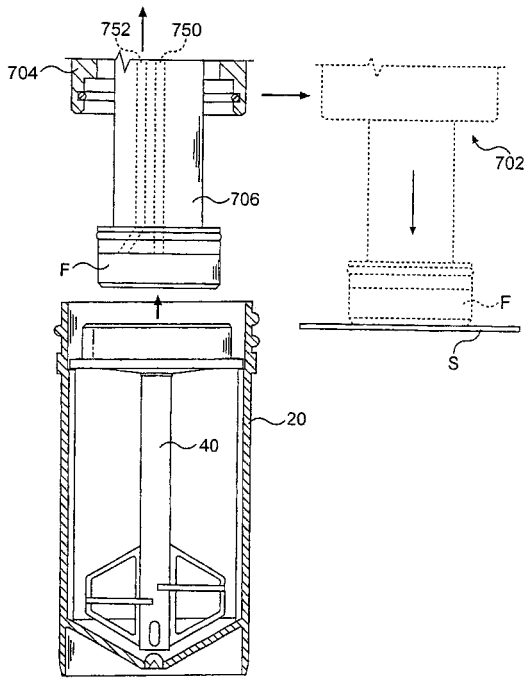

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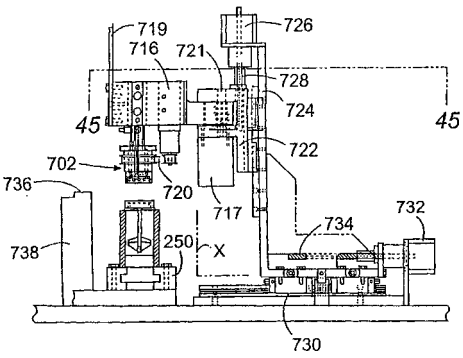

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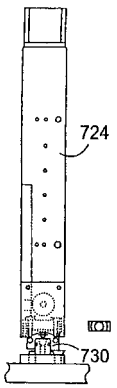

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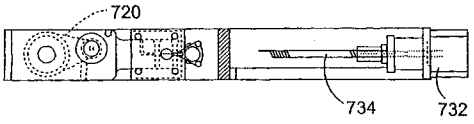

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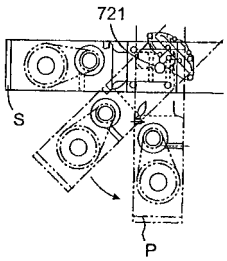

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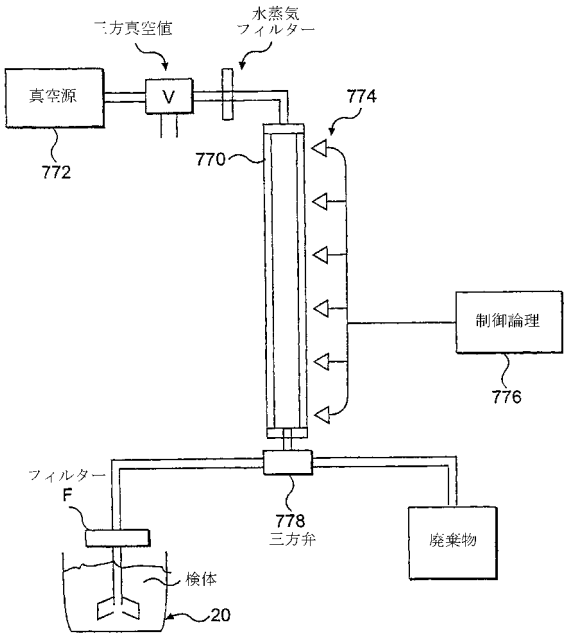

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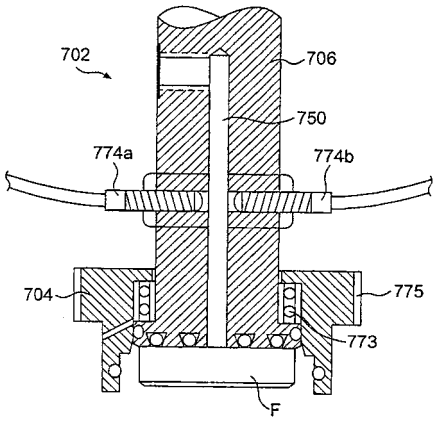

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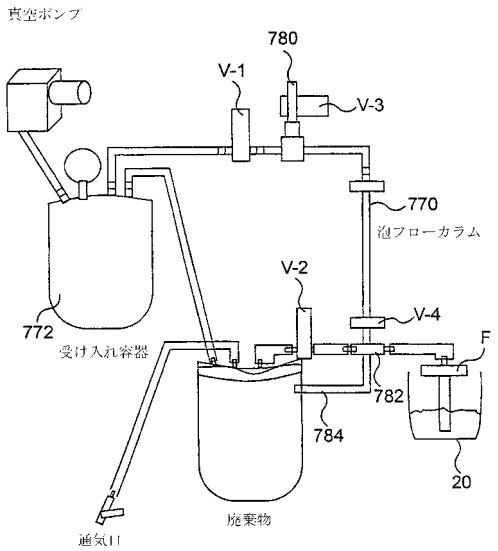


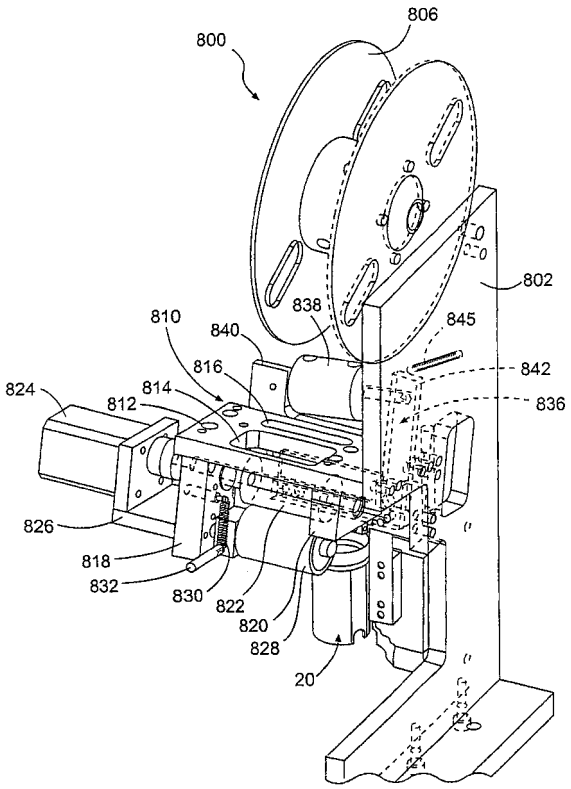
【図４９】

流量センサーの操作

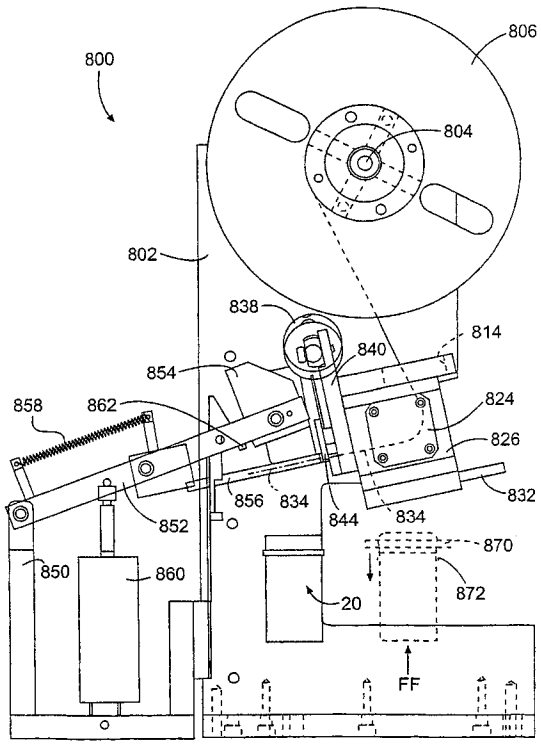
操作の順序

	V-1	V-2	V-3	V-4
#1				
測定プル	オン	オフ	オフ	オフ
#2				
タンピング押圧転写 (Tamp Print)	オフ	オン	オフ	オフ
#3				
パージ	オフ	オフ	オン	オン

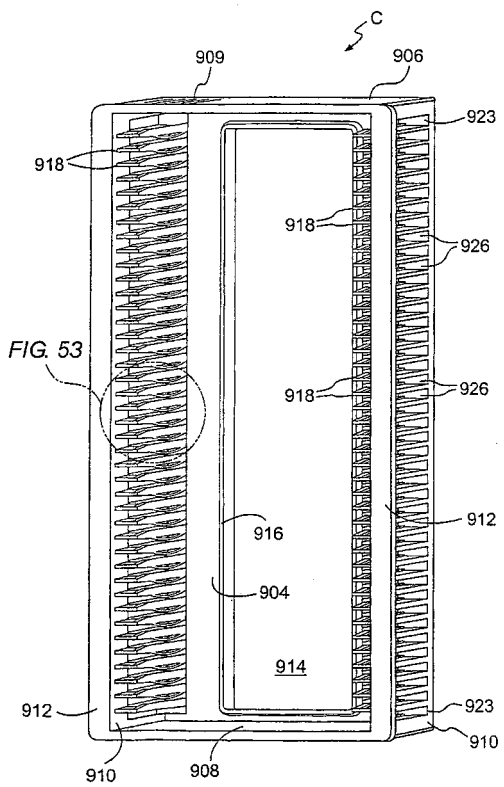
【図５０】



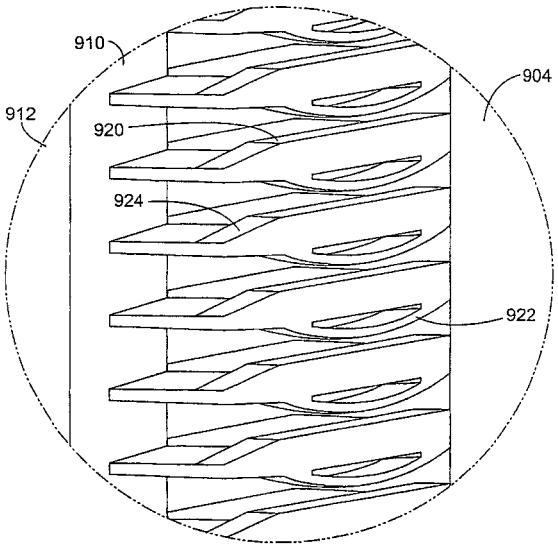
【図５１】



【図５２】



【図５３】



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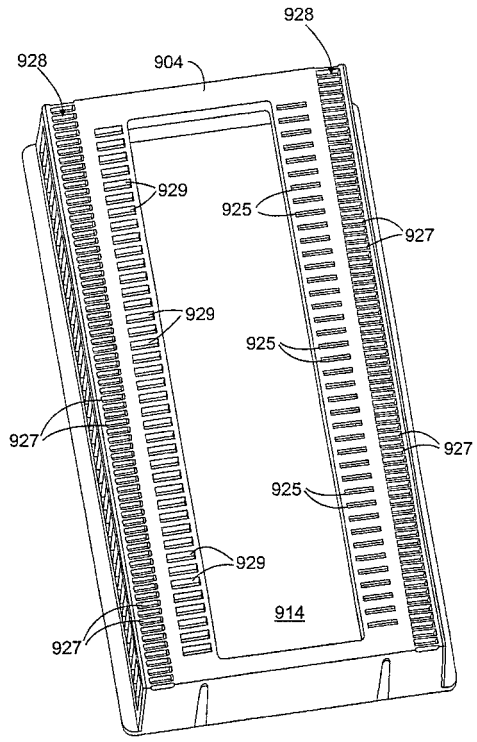

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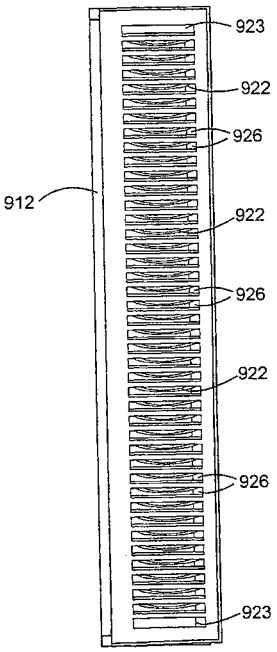

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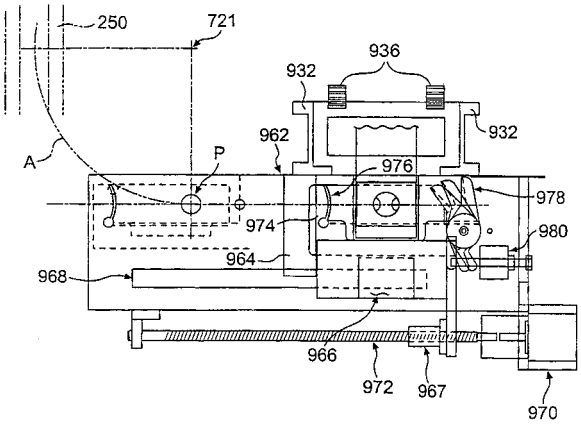

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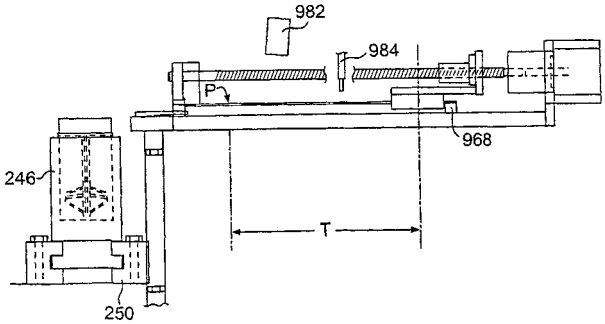

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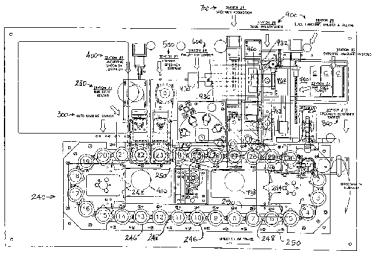
(54) Title: AUTOMATED SYSTEM AND METHOD FOR PROCESSING MULTIPLE LIQUID-BASED SPECIMENS



(57) Abstract: An automated system and method for individually processing multiple specimens of particulate matter-containing liquid in respective containers. The containers are transported seriatim along a processing path to present them to, at least, a preprocessing apparatus (e.g., a mixing head), and then to a specimen acquisition apparatus, which removes preprocessed specimen fluid from the container for subsequent analytical testing or evaluation. Each apparatus is actuated in response to presentation of a container thereto so as to carry out its respective operation independently. An exemplary system can include, in sequential order, stations for container loading and unloading, container uncapping and cap disposal, specimen mixing, filter loading, specimen acquisition (e.g., by aspiration, and then slide printing), filter disposal, and container resealing. The system is capable of unattended operation for many hours at a time, and can interface with an integrated data management system to provide fully integrated specimen and information management in a complete diagnostic laboratory system.

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AUTOMATED SYSTEM AND METHOD FOR PROCESSING MULTIPLE LIQUID-BASED SPECIMENS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of commonly owned U.S. provisional application Nos. 60/330,092, filed October 19, 2001, 60/372,080, filed April 15, 2002, and 60/373,658, filed April 19, 2002, all of which are incorporated herein by reference. This application also is related to commonly owned U.S. non-provisional application No. 10/122,151, filed April 15, 2002, which is also incorporated herein by reference.

TECHNICAL FIELD

The present disclosure is directed to apparatus and methods for collecting and processing specimens of particulate matter-containing liquid, e.g., biological fluid, including collecting and depositing onto a microscope slide or other surface a uniform layer of particulates therefrom (e.g., cells) suitable for examination (e.g., use in cytology protocols).

BACKGROUND ART

Diagnostic cytology, particularly in the area of clinical pathology, bases cytological interpretations and diagnoses on examination of cells and other microscopic objects. The accuracy of the screening process and diagnosis, and the preparation of optimally interpretable samples from specimens typically depends upon adequate specimen and sample preparation. In this regard the ideal sample would consist of a monolayer of substantially evenly spaced cells, which enables cytotechnologists, cytopathologists, other medical professionals, and automated screening and diagnostic equipment to view or image the cells more clearly so that abnormalities can be identified more readily, more accurately and more reproducibly. Newer methodologies such as immunocytochemistry and cytometric image analysis require preparation apparatus and methods that are safe, effective, accurate, precise, reproducible, inexpensive, efficient, fast and convenient.

Cytological examination of a sample begins with obtaining specimens including a sample of cells from the patient, which can typically be done by scraping, swabbing or brushing an area, as in the case of cervical specimens, or by collecting body fluids, such as those obtained from the chest cavity, bladder, or spinal column, or by fine needle aspiration or fine needle biopsy. In a conventional manual cytological preparation, the cells in the fluid are then transferred directly or by centrifugation-based processing steps

onto a glass microscope slide for viewing. In a typical automated cytological preparation, a filter assembly is placed in the liquid suspension and the filter assembly both disperses the cells and captures the cells on the filter. The filter is then removed and placed in contact with a microscope slide. In all of these endeavors, a limiting factor in the sample preparation protocol is adequately separating solid matter from its fluid carrier, and in easily and efficiently collecting and concentrating the solid matter in a form readily accessible to examination under a microscope.

Currently, biological specimens are collected for cytological examinations using special containers. These containers usually contain a preservative and transport solution for preserving the cytology specimen during shipment from the collection site to the diagnostic cytology laboratory. Further, cytology specimens collected from the body cavities using a swab, spatula or brush are also preserved in special containers with fixatives (e.g., alcohol or acetone fixatives) prior to transferring cells onto the slide or membrane for staining or examination. Specimen containers are known that allow a liquid-based biological specimen to be processed directly in the container so as to obtain a substantially uniform layer of cells on a collection site (in a filter housing defining a particulate matter separation chamber) that is associated with the container itself. See, for example, U.S. patent Nos. 5,301,685; 5,471,994; 6,296,764; and 6,309,362, of Raouf A. Guirguis, all of which are incorporated herein by reference.

The filtration techniques taught in these patents in practice have yielded fairly good results in terms of obtaining close to a monolayer of cells on slides, but there is room for improvement. Further, the types of specimen containers disclosed in these patents require specially configured apertured covers and adapters therefor that are designed to mate with the filter housing, and with suction equipment (e.g., a syringe or a mechanized vacuum source) used to aspirate liquid from the container and draw it through the filter. In addition, extraction of the filter so that it can be pressed against a microscope slide to transfer collected cells to the slide requires disassembly of the cooperating parts of the cover and/or adapters associated therewith. If the processing is done by automated equipment, special handling devices are required to carry out such disassembly. All of this complexity adds time, and material and labor cost to the processing required prior to the actual cytology examination.

In general, automated equipment thus far developed for processing liquid-based specimens have not performed with sufficient consistency, reliability, speed and automation to satisfy current and projected needs in cancer screening and other cytology-

based medical, analytical, screening and diagnostic procedures. The vial-based automated processing system disclosed herein provides a safe, elegant and effective solution to these problems.

SUMMARY DISCLOSURE OF THE INVENTION

The specimen vial disclosed herein houses a complete processing assembly, typically one for mixing the liquid-based specimen therein and for holding a filter on which a uniform layer of cells can be collected from the specimen. It is expected that the specimen vial would be prepackaged with a liquid preservative solution, as is commonplace, and sent to the point-of-care site for specimen collection.

The processing assembly is coupled to a simple cover for the vial by means of a simple and inexpensive releasable coupling. When the cover is removed at the point-of-care site (physician's office, clinic, hospital, etc.), the processing assembly remains with the cover to allow medical personnel easy access to the container interior for insertion of a biological specimen into the vial. The cover, along with the attached processing assembly, is then replaced to seal the vial. The vial may then be sent to a laboratory for processing.

When the vial is manipulated in a simple way while still closed, the processing assembly detaches from the cover and remains in the vial for access by automated or manual laboratory equipment when the cover is subsequently removed. In a preferred embodiment, a downward force on the center of the cover is all that is required to detach the processing assembly from the cover. In contrast with the prior art specimen vials discussed above, the vial of the present invention requires no further interaction with the cover, which can be removed by a simple uncapping device and is discarded to avoid contamination. Ribs inside the vial support the processing assembly in the proper position for access during processing. This self-contained vial and processing assembly arrangement minimizes human operator exposure to biohazards, such as tuberculosis or other pathogens in sputum or in other specimens types, such as urine, spinal tap fluid, gastric washings, fine-needle aspirates, and gynecological samples.

The automated specimen processing apparatus disclosed herein is referred to as the "LBP" device (for liquid-based preparation), and is designed to produce slides of high quality and consistency. The LBP device also can be interfaced with a device for detecting and/or quantifying multiple morphologic, cytochemical, and/or molecular changes at the cellular level.

During the past two years or so, a review of the literature and reanalysis of existing data have led to the identification of a panel of molecular diagnostic reagents that are

capable of detecting and characterizing lung cancer, which is the most common cancer, with high sensitivity and specificity. See, for instance, commonly owned U.S. patent application Nos. 10/095,297 and 10/095,298, both filed March 12, 2002, and No. 10/241,753, filed September 12, 2002. Here, the cells can be reacted with antibodies and or nucleic-acid "probes" that identify a pattern of changes that is consistent with a diagnosis of cancer. The molecular system can utilize algorithms fine tuned for that tumor heterogeneity.

Identifying molecular changes at the cellular level is one of the ways cancer can be detected early and at a more curable stage. Such molecular diagnostic devices can be used for early detection and diagnosis with the necessary sensitivity and specificity to justify their use as population-based screens for individuals who are at-risk for developing cancer. Such a molecular diagnostic device also can be used to characterize the tumor, thereby permitting the oncologist to stratify his/her patients, to customize therapy, and to monitor patients in order to assess therapeutic efficacy and disease regression, progression or recurrence. The availability of such tests will also foster the development of new and more effective therapeutic approaches for the treatment of early stage disease.

Such molecular diagnostics are designed to balance cost and test performance. While screening tests must exhibit high sensitivity and specificity, cost is always a critical factor, as the tests are typically directed to performing on a large number of individuals who, while at-risk, do not typically have symptomatic evidence of the disease. In this respect, the present LBP device can be interfaced with a molecular diagnostic device to develop a system for automatically diagnosing cancer, with a minimum or no human intervention. Alternatively, the present LBP device can be interfaced with a pathology work station, where medical professionals can observe individual slides prepared by the LBP device. The resulting diagnosing system, regardless whether an automated device or a manual observation device is interfaced, can be interfaced with an integrated data management system based on specialized software and a computer operating system to manage data entry and exchange of information, and network with the laboratory and hospital information systems.

The present LBP device transports multiple specimen vials of the novel type mentioned above sequentially through various processing stations and produces fixed specimens on slides, each slide being bar-coded and linked through a data management system to the vial and the patient from which it came. Fresh slides are automatically removed one at a time from a cassette, and each is returned to the same cassette after a

specimen is fixed thereon. Multiple slide cassettes can be loaded into the LBP device, and the device will automatically draw fresh slides from the next cassette after all of the slides of the preceding one have been used. The slide cassettes preferably are configured for liquid immersion and interfacing with automated staining equipment that will stain the specimens without having to remove the slides from the cassette. In this regard the cassettes preferably have slots that allow for liquid drainage, and slots or other means that cooperate with the hooks normally used in the staining equipment to suspend other types of slide holders. The same slide cassettes are also configured to interface with automated diagnostic equipment and other devices that are part of an integrated system.

While specimen vials can be loaded into the transport manually, the full benefits of automation can be realized by using an optional vial handling system that automatically loads specimen vials for processing, and removes each one after its processing is complete. In one example of such a handling system the vials initially are loaded manually into special space-saving trays that hold up to forty-one vials each. Up to eight trays can be loaded into the LBP device, and the device will process all of them sequentially, removing one at a time from a tray and returning processed (and resealed) vials to a tray. The trays also can be used for storing and retrieving processed vials.

Each vial is transported through the LBP device on a computer-controlled conveyor, in its own receptacle. (In the example disclosed the conveyor has thirty receptacles.) The vials and the receptacles are keyed so that the vials proceed along the processing path in the proper orientation, and cannot rotate independently of its respective receptacle. They first pass a bar code reader (at a data acquisition station), where the vial bar code is read, and then proceed stepwise through the following processing stations of the LBP device: an uncapping station including a cap disposal operation; a primary mixing or dispersal station; a filter loading station; a specimen acquisition and filter disposal station; a cell deposition station; and a re-capping station. There is also a slide presentation station, at which a fresh microscope slide is presented to the specimen acquisition station for transfer of the specimen to the slide. Each of the stations operates independently on the vial presented to it by the conveyor, but the conveyor will not advance until all of the operating stations have completed their respective tasks.

The vial uncapping station has a rotary gripper that unscrews the cover from the vial, and discards it. Before doing so, however, the uncapping head presses on the center of the cover to detach the internal processing assembly from the cover. The primary mixing station has an expanding collet that grips the processing assembly, lifts it slightly

and moves (e.g., spins) it in accordance with a specimen-specific stirring protocol (speed and duration). The filter loading station dispenses a specimen-specific filter type into a particulate matter separation chamber (manifold) at the top of the processing assembly. The specimen acquisition station has a suction head that seals to the filter at the top of the processing assembly and first moves the processing assembly slowly to re-suspend particulate matter in the liquid-based specimen. Then the suction head draws a vacuum on the filter to aspirate the liquid-based specimen from the vial and past the filter, leaving a monolayer of cells on the bottom surface of the filter. Thereafter the monolayer specimen is transferred to a fresh slide, and the vial moves to the re-capping station, where a foil seal is applied to the vial.

An improved filter system ensures that the highest quality monolayer specimens are produced. Specimen liquid flows through the filter as well as substantially across the front surface of the filter. Specifically, the specimen liquid is made to have a secondary flow component across the filter surface. The secondary flow is designed to flow radially outwardly or have a substantial radial component, which creates a shearing action that flushes or washes clusters of relatively weakly adhering particulates so that a more uniformly distributed and thinner layer can be formed on the front surface of the filter. In this respect, the present system includes a peripheral outlet through which specimen liquid can flow from the area adjacent the front surface of the filter.

The filter assembly preferably has a holder, a frit seated in the holder, and a membrane filter positioned over and in contact with the outer surface of the frit. The frit can extend beyond the end of the holder. The membrane filter can be attached to the holder. The sidewall portion extending beyond the holder forms an area through which the specimen liquid can flow, creating a secondary flow. The holder can be configured so that the frit is slightly bowed outwardly at the center so that when pressure is applied to a slide during the specimen transferring step, the central portion of the frit flattens to more evenly contact the membrane filter to the slide for more effective transfer.

The manifold at the upper end of the processing assembly seats the filter assembly with the membrane filter side facing down. The manifold preferably has a substantially conically configured bottom wall that rises from the central inlet (which communicates with the depending suction tube portion of the processing assembly). The filter assembly and the conically configured bottom wall form a manifold chamber that has a slight gap at its periphery, forming a peripheral outlet, by virtue of raised members or standoffs that act

as spacers. The standoffs can have channels between them through which the specimen liquid can flow out of the manifold chamber.

Various preferred materials and possible alternatives are specified herein for several components of the system. It is to be understood that material choices are not limited to the specific materials mentioned, and that the choice of an alternate material is governed by many factors, among them functionality, molding accuracy, durability, chemical resistance, shelf life, cost, availability, and/or optical clarity (e.g., to address user requirements or marketing issues).

In its most basic aspect the invention claimed herein is directed to an automated method and automated apparatus for individually processing multiple specimens of particulate matter-containing liquid in respective containers. The containers are transported seriatim along a processing path to present them to, at least, a preprocessing apparatus adapted to preprocess the specimen fluid in any container presented to it, and then to a specimen acquisition apparatus adapted to remove preprocessed specimen fluid from any container presented to it for subsequent analytical testing or evaluation. Each apparatus is actuated in response to presentation of a container thereto so as to carry out its respective operation independently. The specimens may contain biological material.

The preprocessing apparatus may act on the specimen to disperse particulate components of the specimen fluid, e.g., by mixing, while the specimen acquisition apparatus may collect a sample of the particulates, e.g., on a filter. In the case of filtration, a filter loading head upstream of the specimen acquisition apparatus dispenses a filter into a container-borne particulate matter separation chamber, the filter loading head operating independently of the other apparatus in response to any container presented thereto. The filter-borne sample may be transferred to a slide.

According to other aspects of the invention, the method may involve additional operations, including container uncapping prior to specimen preprocessing, and recapping of containers after processing is complete. The apparatus similarly may include additional heads or other devices for performing these operations. Each operation is carried out independently in response to presentation of container to the respective operating station.

BRIEF DESCRIPTION OF THE DRAWING FIGURES

Preferred embodiments of the disclosed system and the invention, including the best mode for carrying out the invention, are described in detail below, purely by way of example, with reference to the accompanying drawing, in which:

Fig. 1 is a vertical sectional view through a specimen vial for use with the LBP device, showing the processing assembly (stirrer) in the vial coupled to the cover;

Fig. 2a is a front elevational view of the container portion of the vial;

Fig. 2b is a top plan view of the container, shown with the stirrer removed;

Fig. 3 is a top plan view of the stirrer;

Fig. 4 is a bottom plan view of the liner that fits within the cover;

Fig. 5 is an exploded vertical sectional view of the stirrer and a filter assembly adapted for use in the stirrer;

Fig. 6 is a vertical sectional view of the upper portion of the stirrer, showing the filter assembly in place in the particulate matter separation chamber;

Fig. 7a is a partial schematic view of the arrangement depicted in Fig. 6, showing the flow of liquid and particulate matter separated therefrom;

Fig. 7b is a view similar to Fig. 7a, showing liquid flow in a prior art filter system;

Fig. 8 is an exploded, cross-sectional view of the filter assembly;

Fig. 9 is a schematic illustration of the dimensional configuration of the flow manifold;

Fig. 10 is a vertical sectional view of the specimen vial similar to Fig. 1, but showing the stirrer detached from the cover;

Fig. 10a is a partial vertical sectional view similar to Fig. 10, showing a modification of the stirrer;

Fig. 11 is a top plan view of the LBP device;

Fig. 11a is a schematic diagram of the operating sequence of the LBP device;

Fig. 12 is a front perspective view of the LBP device, with certain parts removed for clarity;

Fig. 13 is a rear perspective view of a portion of the LBP device, showing the auto loader/unloader mechanism;

Fig. 14 is a top plan view of the auto loader/unloader mechanism;

Fig. 15 is a front elevational view of the auto loader/unloader mechanism;

Fig. 15a is a detail sectional view taken along line 15a-15a in Fig. 14;

Fig. 16 is an elevational view of an alternative embodiment of a gripper for the auto loader/unloader mechanism;

Fig. 17 is a perspective view of a specimen vial tray used in the auto loader/unloader mechanism;

Fig. 18 is an enlarged detail view taken at encircling line 18 in Fig. 17;

Fig. 19 is a bottom perspective view of the specimen vial tray of Fig. 17;

Fig. 20 is a perspective view of three stacked specimen vial trays;

Fig. 21 is a block diagram showing specimen vial handling and data flow;

Fig. 21a is a pictorial diagram showing an overall laboratory system incorporating the LBP device;

Fig. 21b is a relational database table;

Fig. 22 is a block diagram showing a computer or work station;

Fig. 23 is a facsimile of a computer screen;

Fig. 24 is a facsimile of another computer screen;

Fig. 25 is a facsimile of two computer screens;

Fig. 26 is a vertical sectional view of a specimen vial being uncapped;

Fig. 27 is a front elevational view, partly in section, of a specimen vial engaged by the uncapping head of the LBP device;

Fig. 28 is a top plan view of the uncapping head, taken along line 28-28 in Fig. 27;

Fig. 29 is a side elevational view of the uncapping station of the LBP device;

Fig. 30 is a sectional view taken along line 30-30 in Fig. 29;

Fig. 31 is a top plan view of the uncapping station of Fig. 29;

Fig. 32 is a vertical sectional view of a specimen container showing engagement by the primary stirring head;

Fig. 33 is a side elevational view of the primary stirring station of the LBP device;

Fig. 34 is a front elevational view of the primary stirring station;

Fig. 35 is a top plan view of the primary stirring station;

Fig. 36 is a vertical sectional view of a specimen container during filter loading;

Fig. 37 is a side elevational view of the magazine portion of the filter loading station of the LBP device;

Fig. 38 is a front elevational view of the pusher portion of the filter loading station;

Fig. 39 is a top plan view of the pusher portion of the filter loading station;

Fig. 40 is a top plan view of the magazine portion of the filter loading station;

Fig. 41 is a vertical sectional view of a specimen container during specimen acquisition;

Fig. 42 is a vertical sectional view of a specimen container during specimen transfer to a slide;

Fig. 43 is a side elevational view of the specimen acquisition station of the LBP device;

Fig. 44 is a front elevational view of the lower portion of the specimen acquisition station;

Fig. 45 is a top plan view of the specimen acquisition station, partly in section, taken along line 45-45 in Fig. 43;

Fig. 46 is a top plan view of the specimen acquisition station;

Fig. 47 is a schematic of a bubble flow meter used in the specimen acquisition station;

Fig. 47a is a schematic of a modification of the flow meter of Fig. 47;

Fig. 48 is a schematic of a vacuum system used in the specimen acquisition station;

Fig. 49 is an operation chart for the vacuum system of Fig. 48;

Fig. 50 is a front perspective view of the re-capping station of the LBP device;

Fig. 51 is a side elevational view of the re-capping station;

Fig. 52 is a front perspective view of a slide cassette used in the LBP device;

Fig. 53 is a detail perspective view of the slide cassette taken from Fig. 52;

Fig. 54 is a rear perspective view of the slide cassette;

Fig. 55 is a side elevational view of the slide cassette;

Fig. 56 is a top plan view of the slide presentation system of the LBP device; and

Fig. 57 is a side elevational view of the slide presentation system.

DETAILED DESCRIPTION OF BEST MODE

A full description of this vial-based specimen handling and processing system must begin with the vial itself, which consists of a container, a cover and a processing assembly (stirrer) in the vial.

SPECIMEN VIAL

Referring to Figs. 1, 2a and 2b, the vial 10 comprises a container 20, a cover 30 and a processing assembly 40. Processing assembly 40 is designed to carry out several functions, among them mixing, and for this preferred rotary embodiment will be referred to as a stirrer for the sake of convenience. Container 20 preferably is molded of a translucent plastic, preferably polypropylene, and has a substantially cylindrical wall 21, surrounding its longitudinal axis, joined to a conical bottom wall 22. Possible alternative plastics include ABS and polycyclohexylenedimethylene terephthalate, glycol (commercially available from Eastman Kodak Co. under the name EASTAR® DN004). A small portion 24 of wall 21 preferably is flat, the outer surface of the flat portion adapted to receive indicia, e.g., a bar code label, containing information concerning the specimen placed in the vial. Although only one flat portion is shown, the container could be

configured without a flat portion, or with two or more flat portions, each adapted to receive indicia. Alternatively, the indicia could be located on a curved portion of wall 21. The bottom end of flat portion 24 has an arcuate notch 25 which acts to keep the container in a proper orientation when handled by the LBP device, which as noted is designed to cradle the container and move it through various processing stations. A differently shaped notch (e.g., V-shaped) can be used as long as the notch properly mates with the LBP device. Other suitable mating structures can be used instead.

Four longitudinal ribs 26 project inwardly from wall 21. The upper ends 27 of ribs 26 form rests for the stirrer 40 when it is detached from cover 30 (see Fig. 10). The top of container 20 has an opening 28 and a standard right-hand helical thread 29 that preferably extends for one and one half turns and mates with a similar thread on cover 30. Other types of cover-to-container coupling may be used, such as a bayonet coupling, snap-fit arrangement, etc.

Cover 30 comprises a commercially available simple molded plastic threaded cap 31, and a novel liner 32 retained in the cap. Cap 30 preferably is molded of polypropylene, but ABS and EASTAR® DN004, among others, are alternative plastic material choices. Cap 31 has a flat solid top, and an externally knurled depending flange with an internal helical thread 33 that mates with thread 29 on container 20. Referring to Fig. 4, liner 32 is molded of plastic material, preferably polyethylene, and has a substantially flat base 34 sized to fit snugly within cap 31, behind thread 33, so that the liner is not readily separated from the cap. As seen in Fig. 1, liner base 34 serves as a gasket-type seal between the cap 31 and the rim of the container wall 21.

Liner base 34 has a coupler in the form of an annular projection 35 that preferably is slightly conical in shape, preferably forming an angle of about 5° to its central axis. In other words, the inner diameter of annular coupler 35 is greater at its proximal end, where it joins liner base 34, than at its distal end. Liner base 34 also has a central annular boss 36 that projects further from base 34 than annular coupler 35 so as to interact with stirrer 40, as described below. While the use of a separate liner mated to a standard cap is preferred, the cover could be integrally molded in one piece to include the annular coupler 35 and the central annular boss 36. Such a one-piece cover (or even the two-piece cover described above) could instead be configured to act as a plug-type seal by projecting into and sealing against the inside of the rim of container wall 21.

Referring to Figs. 1, 3 and 5, stirrer 40 is molded of plastic, preferably polypropylene, and has a circular base or bottom wall 41, sloped at its center, with a central inlet port 42; a central depending suction tube 43 with two diametrically opposed suction ports 44 near the bottom of the tube; and a dispersing (mixing) element in the form of laterally extending vanes 45. The upper portion of the stirrer 40 has a cup-shaped particulate matter separation chamber or manifold 46 defined by base 41 and an upstanding annular wall 47. The upper edges of wall 47 are beveled, the inner edge 48 preferably being beveled to a greater degree to facilitate placement of a filter assembly F in manifold 46, as described below. Possible alternative plastic material for the stirrer include ABS and EASTAR® DN004.

Annular wall 47 serves as a coupler for releasably coupling the stirrer 40 to cap liner 32, and is therefore dimensioned to fit snugly within annular coupler 35 (see Fig. 1). Specifically, there is a friction or press fit between couplers 35 and 47 such that normal handling of the closed vial, and normal handling of cover 30 when removed from container 20 (e.g., to place a biological specimen in the container) will not cause separation of the stirrer from the cover. Coupler 47 is dimensioned relative to coupler 35 so that there is a very slight initial diametrical interference, preferably about 0.31 mm. Coupler 47 is stiffer than coupler 35, so assembly of the stirrer to the cover involves slight deformation principally of coupler 35, resulting in a frictional force that keeps the stirrer and the cover engaged. Application of an external force to the vial that overcomes this frictional retention force will cause stirrer 40 to detach from cover 30 and drop by gravity further into container 20 (see Fig. 10).

The external separation force preferably is applied to the central portion of cover 30 (see the arrow in Fig. 10), which deflects cap 31 and liner 32 inwardly. As illustrated in Fig. 1, central boss 36 on liner 32 is dimensioned such that its distal end just contacts or lies very close to base 41 of the stirrer. Thus, when the central portion of the cover is depressed, central boss 36 will deflect further than annular coupler 35 on liner 32 and push stirrer 40 out of engagement with coupler 35. Inward deflection of liner 32 also causes coupler 35 to spread outwardly, thereby lessening the retention force and facilitating detachment of the stirrer. The separation force applied to cover 30 and required to detach the stirrer should be in the range of 5 to 30 lbs., preferably about 12 lbs.

Once detached from the cover 30, stirrer 40 comes to rest on the upper ends 27 of ribs 26. See Fig. 10. The particulate matter separation chamber (manifold) 46 thus is stably supported near the container opening and easily accessed by the LBP processing

heads, which will manipulate the stirrer so as to process the specimen directly in the container. At least three ribs 26 are required to form a stable support for the stirrer, but four are preferred because that number seems to promote more thorough dispersion of the particulate matter in the liquid during stirring. Should the stirrer inadvertently become detached from the cover at the point-of-care site, the physician or an assistant simply places the stirrer loosely in the vial so that it descends into the specimen and then screws the cover on as usual. This is not difficult because the ribs in the vial allow insertion of the stirrer in only one direction. Once the vial is closed with the specimen inside, the stirrer remains in the vial throughout processing and is sealed therein when the vial is re-capped.

A small percentage of patient specimens, as may be found in gynecological Pap test and other specimen types, contain large clusters of cells, artifacts, and /or cellular or noncellular debris. Some of these large objects, if collected and deposited on a slide, can obscure the visualization of diagnostic cells and, consequently, result in a less accurate interpretation or diagnosis of the slide sample. Since most of these features are not of diagnostic relevance, their elimination from the sample is, in general, desirable. To achieve this result, the side suction ports 44 in the stirrer suction tube 43 preferably are eliminated (see Fig. 10a) in favor of close control of the interface between the bottom of the suction tube 43 and the small projection 23 at the center of bottom wall 22 of the container 20. This interface effectively forms a metering valve whose geometry (orifice) 23a is created when the stirrer 40 rests on the ribs 26 of the container 20 (see Fig. 10). Proper sizing of the annular flow orifice 23a prevents large objects from entering the suction tube 43, while allowing the passage of smaller objects that may be diagnostically useful. While the orifice 23a has a thin passage section and a small metering area, clogging is not an issue due to its large diameter. The annular orifice 23a preferably has an outside diameter on the order of 0.105 in. and an inside diameter on the order of 0.071 in., yielding a passage width on the order of 0.017 in. This orifice size is optimized for gynecological specimens.

FILTER SYSTEM

Figs. 6 and 8 illustrate one embodiment of a filter assembly F according to the present invention. Figs. 3 and 6 illustrate one embodiment of a manifold 46 (in stirrer 40) according to the present invention. The filter system includes the filter assembly F and the manifold 46.

Referring to Figs. 6 and 8, the filter assembly F comprises a filter housing or holder 200, a porous frit 202, and a porous membrane filter 205. Fig. 8 shows these components more clearly in an exploded view. The holder 200 can be cup- or container-shaped, having a recess or cavity 206 for seating the frit 202 and a chamber 207 between the frit 202 and the holder 200. The frit 202 and the membrane filter 205 can be made of the materials disclosed in the Guirguis patents identified above, namely U.S. Patent Nos. 5,301,685 and 5,471,994, the disclosures of which are incorporated herein by reference.

In the present filter assembly F the membrane filter 205, the frit 202, and the holder 200 are assembled together as a unit. The frit 202, which has a cylindrical shape, is first seated in the holder 200. Then the membrane filter 205 is permanently affixed, adhered, joined, or fused to the holder 200. In the illustrated embodiment, the outer perimeter or edge of the membrane filter 205 is fused to the holder 200. In this regard, the holder 200 has a bevel or chamfer 208 formed around an outer circumferential corner 209. The chamfer 208 provides an angled surface to which the membrane filter 205 can be attached using a conventional bonding technique, such as ultrasonic welding. The holder 200 and the membrane filter 205 should be made of materials that will fuse together. Preferably both are made of polycarbonate, although an ABS holder will work with a polycarbonate membrane filter. Thermoplastic polyester could be used for the holder if the membrane filter is made of the same material. The frit 202 preferably is made of polyethylene.

Referring to Fig. 8, the holder 200 preferably is cylindrical and comprises a substantially cup-shaped body having a bottom wall or base 210 and a substantially upright cylindrical sidewall 211 extending therefrom and terminating in a rim 211a. The sidewall 211 has an annular shoulder 212 extending radially inwardly, toward the center. The shoulder 212 acts as a seat that accurately positions the frit 202. Frit 202 preferably is dimensioned so that the frit's outer or front face 213 is proud of (extends beyond) the rim 211a when the peripheral portion of the frit's rear face abuts the shoulder 212.

The inner diameter of the sidewall 211 can be dimensioned to frictionally engage and hold the frit 202 in place. In this respect, the frit's outer diameter can substantially correspond to the inner diameter of the sidewall 211 to mechanically, i.e., frictionally, hold the frit 202 in place. However, since the membrane filter 205 covers the frit 202, the frit need not be frictionally held to the holder. That is, the frit 202 can be loosely seated in the holder. Frictionally seating the frit 202 in the holder 200, however, maintains the frit 202 in place so that attachment of the member filter 205 can be done at a remote site. It

also simplifies and reduces the cost of mass production of filter assemblies because the holder 200 and the frit 202 can be joined to make a secure subassembly and stored for later attachment of the membrane filter 205.

After the frit 202 is seated in the holder 200, the membrane filter 205 is draped over the frit's outer face 213 and the exposed portion 214 of the frit's side wall 215 that extends beyond the holder 200, and is attached to the chamfer 208, as is better seen in Fig. 6. The frit's exposed outer sidewall portion 214 provides an annular surface area through which the specimen liquid can flow to provide a dual flow path, as schematically illustrated in Fig. 7a.

The filter assemblies F can be coded to denote different pore size and pore density (number of pores per unit cross-sectional area) as may be required for specific processing protocols. Color coding of filter assemblies is preferred, although any form of machine-detectable coding can be used, including distinguishing projections, such as small nipples, for tactile-based sensor recognition. The LBP device is provided with a sensor that can discriminate between these colors or other codes to ensure proper filter selection. The filter assemblies also can be provided in paper carriers for easy insertion into the LBP device.

Referring back to Fig. 8, the holder's bottom wall 210 has a central opening 204 through which vacuum can be applied to draw specimen liquid therethrough. The holder 200 further includes a central projection or protrusion 216 extending into the holder from the bottom wall 210. The central protrusion 216 is aligned with the opening 204 and positioned in the chamber 207, which is defined by the frit's inner face 218, the inner face 219 of the bottom wall 210 and the inner side 220 of the sidewall 211. The protrusion 216 is substantially hollow and has a plurality of side openings 221 that distribute vacuum to the chamber 207 and provide a substantially symmetrical flow through the chamber. The specimen liquid drawn through the membrane filter 205 and the frit 202 fills the chamber 207 and exits the chamber 207 through the side openings 221 and the central opening 204.

The protrusion 216 has an abutting surface 217 that faces and extends toward the holder's open face. The abutting surface 217 is configured to abut against the frit's rear face 218. In particular, the abutting surface 217 is slightly proud of the annular shoulder 212. That is, the abutting surface 217 lies slightly above or beyond the level of the annular shoulder 212 so that the frit's outer face 213 bows slightly outwardly when the frit is installed in the holder. For example, the abutting surface 217 can extend beyond the height of the annular shoulder 212 by about 0.002 inch. The resulting slight bow created

by the protrusion pushing out the central portion of the frit 202 ensures that the central part of the membrane filter 205 contacts the slide. The pressure applied to the slide during imprinting flattens the frit's front surface 213, ensuring full contact of the membrane filter 205 with the slide to more effectively transfer the collected particulates to the slide and minimizing any deposition artifacts. If this slightly bowed configuration is desired, the frit 202 preferably is securely seated in the holder 200, such as by friction as previously explained.

Due to the bowed frit configuration, the membrane filter 205 need not be taut. This simplifies the manufacturing process, reduces cost, and reduces the rejected part rate. Anything short of a major wrinkle can work effectively. As noted, the frit 202 preferably is slightly deformable, its compliance allowing it to flex and flatten against a glass slide post aspiration to transfer cells and other objects of interest from the filter to the slide. To accomplish this the frit should have an elasticity that allows it to be crushed flat by application of a force of 8 lbs. through a displacement of 0.0016 in. Good frit materials include sintered polyethylene and sintered polyester. The frit 202 may be a porous material, with spatially random pores, typically with pore sizes in the range of about 50-micrometer to 70-micrometer. A significant attribute of this material is that it is of low fluidic impedance relative to the material of the thin membrane filter 205 (which typically has pore sizes of about 5-micrometer to 8-micrometer). In other words, the pressure drop across the frit 202 is much less than the pressure drop across the membrane filter 205. Thus, fluid that passes through the filter flows freely through the frit. Alternatively, instead of having randomly positioned pores, the frit 202 may be made of a material or structure that has many parallel channels of small (e.g., 50-micrometer to 70-micrometer) inner diameters through which aspirated fluid and particulates may flow. Such a parallel-channel arrangement would behave as an inner fluid-pervious medium with an apparent low fluidic impedance. In fact, any material or device with the proper low fluidic impedance and deformability/resilience characteristics may be used in the specimen acquisition station, whether it has pores or not.

It has been found that flowing the specimen liquid substantially or mostly in an axial direction, i.e., perpendicular to the membrane filter, can accumulate layers or clusters of particulates, as schematically illustrated in Fig. 7b, particularly if the vacuum is applied through the membrane filter for a longer period than necessary. This can happen even with the Guirguis dual flow design, which provides some secondary flow components that are radially directed. See, for example, Figs. 4 and 12 of Guirguis' U.S. Patent Nos.

5,471,994 and 5,301,685. It seems that the secondary flow generated by that configuration is insufficient to create an effective flushing, or shearing action across the membrane filter. An earlier Guirguis patent, namely U.S. Patent No. 5,137,031, discloses a funnel- or cone-shaped manifold. In that arrangement, however, there is no secondary radial outflow at its periphery. As there is no flow other than directly through the filter itself, there is no substantial radial flow component. Accordingly, the specimen liquid only flows substantially perpendicularly to the membrane filter.

Referring to Fig. 6, the inner diameter of the upright wall 47 of the manifold 46 at the top of stirrer 40 is dimensioned to be slightly larger than the outer diameter of the filter assembly F, namely the holder's sidewall 211, so that the manifold 46 can receive and seat the filter assembly F, with the membrane filter 205 facing down, as illustrated. The filter assembly F can be loosely seated in the manifold 46. When the filter assembly F is seated in the manifold 46, the outer peripheral edge of the membrane filter 205 rests on the bottom wall 41. The bottom wall 41 is configured to have a well or recess that forms a manifold chamber M when the filter assembly F is seated in the manifold 46. The chamber M is thus bounded by the outer surface of the membrane filter 205 and the upper surface 41S of the bottom wall 41.

The present dual flow arrangement solves the problem of particulate build-up or accumulation on the face of the membrane filter. This arrangement causes a shearing force or action across the front face of the membrane filter that is sufficient to flush the particulates aside and keep them from building up or layering. Built-up or layered particulates have a weaker bond to the layer underneath them as they build up, because the suction power decreases as the pores of the membrane filter 205 become covered with particulates. A shearing force is created by imparting a tangential or substantially radial flow component to the specimen liquid across the front face of the membrane filter 205. This flow component is substantially parallel to the front face of the membrane filter, i.e., it is perpendicular to the built-up direction of the layers, and flushes the particulates radially outwardly, away from the front face of the membrane filter.

To provide a secondary or radial flow path, the manifold 46 is configured to provide a small spacing or gap G (see Fig. 6) at the periphery of the manifold chamber M, between the front face of the membrane filter 205 and the upper surface 41S of the bottom wall 41, to allow flushed particulates to exit the manifold chamber M, away from the front face of the membrane filter. The gap G must be large enough to prevent the particulates from clogging it. That is, if the gap G is made too small for the particulates being filtered,

the gap G can get clogged, cutting off the secondary flow. The minimum size of the gap ultimately depends on the particulate size, the viscosity of the specimen liquid, and the temperature of the specimen liquid. It has been determined that the gap G should be at least 0.004 in. to prevent clogging by cellular particulates.

Referring to Figs. 3 and 6, to create the gap G, which forms an outflow nozzle, the bottom wall 41 of manifold 46 includes a plurality of spaced standoffs or raised ribs 48a around the periphery of the manifold 46. The spaces 49 between the ribs 48a provide a passage for specimen liquid to exit the chamber M. In the illustrated preferred embodiment, the manifold 46 has an inner diameter of 23.4 mm, and has thirty-six ribs 48a, evenly spaced at 10°. The ribs are 0.150 mm high and arcuately blend into the surrounding shoulder with a radius R of 0.63 mm, as illustrated. Of course, the present invention contemplates other configurations of spaced ribs or standoffs, which are intended to precisely space the filter assembly from the bottom wall 41 so that a precise outflow area is created. Depending on the number and thickness of ribs or standoffs, the total outflow area can be reduced as much as 50% as compared to the inlet area.

It has been observed in the Guirguis type filter arrangement referred to above that specimen liquid traveling radially outwardly loses velocity. The present dual flow filter system compensates for the velocity slowdown by providing a shallow, substantially conical surface across which the specimen liquid flows. This surface forms a substantially conical distribution manifold chamber M confronting the membrane filter 205. The chamber M according to the present invention has an annular radial outlet O, through spaces 49, having an area that is about equal to or smaller than the maximum area of the central inlet I. Referring to Fig. 9, the "face" area of the radially directed annular flow passage is cylindrical and is defined (bounded) at any given radius R_1, R_x, R_y, ..., R_2 by the front surface of the membrane filter 205 and the conical surface 41S of the manifold. As the specimen liquid travels outwardly, the radius increases while the manifold height decreases. The manifold chamber M can be configured so that the height H_1, H_x, H_y, ..., H_2 decreases at a rate which maintains the face area of the annular passage substantially uniform from the inlet I to the outer perimeter outlet O of the manifold, yielding a substantially linear radial flow velocity across the face of the membrane filter 205.

In this regard, still referring to Fig. 9, the maximum theoretical radial flow area of a round manifold inlet I can be defined as the circumference ($2\pi R_1$) multiplied by the height of the manifold chamber H_1. In this instance, $2\pi R_1 H_1$ defines the total

circumferential area of the manifold inlet I. The maximum circumferential flow area of a round manifold outlet O can be defined as $2\pi R_2H_2$. If the outlet flow area is to equal the inlet flow area, then the inlet and outlet areas can be expressed as:

$$2\pi R_1H_1 = 2\pi R_2H_2$$

$$R_1H_1=R_2H_2$$

Using this expression, the heights, e.g., H_x, H_y, can be defined at their given radii, e.g., R_x, R_y from the inlet I to the outlet O. If the heights H_1, ..., H_x, ..., H_y, ...H_2 from the inlet to the outlet are plotted, the resulting surface 41S would be curved, not linear. However, it has been observed that a significantly curved lower manifold surface does not work as effectively as a linear surface 41S. Accordingly, the present preferred embodiment contemplates a linear or substantially or nearly linear surface 41S (which can be slightly curved) extending from the inlet to the outlet. Also, there is a minimum height H_2 of about 0.006 inch clearance for the specimen liquid to effectively flow. Based on this requirement, the minimum R_1 can be defined as $0.006R_2/H_1$ inches. With this configuration, as the specimen liquid is drawn through the filter, the specimen liquid traverses the front face of the membrane filter 205 in a direction that is substantially parallel to or approaching nearly parallel to the front face of the membrane filter, creating the desired shearing action.

Empirical study has revealed that for a linear conical surface 41S, the area of the outlet O preferably should be less than or equal to the maximum area of the inlet I. That is, R_1H_1 R_2H_2. For example, the exemplary manifold can have the following dimensions (all units here in mm): $R_1 = 1.24$, $H_1 = 1.32$, $R_2 = 10.00$, $H_2 = G = 0.15$. The maximum inlet area would thus be 3.27π mm^2 and the outlet area 3.00π mm^2, which is slightly less than the maximum inlet area, but greater than the average inlet area, which can be defined as 50% of the maximum inlet area (1.64π mm^2). Thus, the outlet area can fall between the maximum inlet area and the average inlet area. Another example can have the following dimensions (all units here in inches): $R_1 = 0.040$, $H_1 = 0.060$, $R_2 = 0.400$, $H_2 = 0.006$. The maximum inlet area would thus be 0.0048π in^2, which is equal to the outlet area.

In summary, the manifold chamber M that confronts the substantially flat membrane filter should have a shallow, funnel-shaped configuration and a peripheral outlet so as to create a substantial radial flow across the outer surface of the membrane filter. The radial flow creates a shearing action that washes or flushes away any

particulates that are relatively weakly attached so as to leave a very thin layer of particulates – a monolayer – on the surface of the membrane filter.

LBP DEVICE AND METHOD

Figs. 11-57 illustrate a preferred embodiment of an LBP device according to the present invention. The LBP device is an automated machine for preparing slides for viewing, imaging or optical analysis. The LBP device can use the above-described dual flow filtering system (Figs. 6, 7a, 9) to collect monolayers or thin layers of cells and transfer them onto slides.

Referring to Fig. 11, the illustrated embodiment of the LBP device can be compartmentalized into at least six discrete processing stations: data acquisition station (bar code reader) 230; uncapping station 400; primary stirring station 500; filter placement station 600; specimen acquisition station 700; and re-capping station 800. These six stations are structured for parallel processing, meaning that all these stations can operate simultaneously and independently of the other. The LBP device also includes a separate data reading station, a slide presentation station, a slide handling station, and a cassette handling station, all of which can be incorporated as an integrated system 900. The LBP device further includes a transport mechanism 240 for moving the specimen containers to the various operating stations. It can further incorporate an auto loading mechanism 300 that automatically loads and unloads specimen vials onto and from the transport mechanism. All stations are computer-controlled. Fig. 11a shows the operating sequence of the LBP device. This is the top-level table from which the operating software is structured.

Fig. 12 shows the basic structural elements of the LBP device, namely a frame 260 preferably made of extruded aluminum, preferably on casters (not shown) for mobility, and a machined aluminum base plate 262 supported by the frame and on which the main operating mechanisms are mounted. Beneath the base plate is a compressor 264 for supplying compressed air for powering some of the components; a vacuum pump (not shown) which provides a vacuum source for various components; stainless steel shelves for holding the vial trays used in the auto loading mechanism 300; and electrical components, including power supplies and controllers, and miscellaneous equipment. A compressor would not be required if electrically-powered actuators were used instead of air-powered actuators. A user interface, e.g. a touch-sensitive LCD display (not shown), is mounted to the left of the transport mechanism 240 and gives the technician control over machine operation beyond the normal automated processing protocols. See Fig. 25, which

shows examples of a log-in screen (top) and a navigation screen (bottom) as they might appear on the user interface. Of course, other screens would be presented to the user as he/she interacts with the user interface.

An "economy" version of the LBP device can take the form of a counter-top model for processing a more limited number of specimens at a time. In such a model certain components can be eliminated, such as frame 260 and auto loading mechanism 300, while other components can be scaled back, such as the capacity of filter placement station 600. External sources of vacuum and compressed air could be used to power such a device, while other components (power supplies, controllers, etc.) could be repositioned to one or more modules adjacent to or on a modified machine base plate. Various ways of implementing these modifications will be readily apparent to those skilled in the art.

TRANSPORT MECHANISM

Referring to Fig. 11, the transport mechanism 240 comprises an endless link-belt conveyor 242 driven by a stepper motor (not shown) around precision sprockets 242, 244. The conveyor has a plurality of receptacles or carriers 246, linked by pins 248, for receiving a corresponding number of specimen vials. The illustrated embodiment in Fig. 11 has 30 receptacles, numbered 1 through 30. Depending on the sample vial size and the length of the conveyor, the LBP device can use fewer than or greater than 30 receptacles, as desired or feasible, sufficiently long to permit all processing to be completed in a single line.

The receptacles 246 of the link-belt conveyor are guided between the sprockets by pairs of guide rails 250 forming tracks, and has a conventional position correction system (not shown) to accurately position the receptacles. The LBP device can track the position of each receptacle and step-drive or index them in a conventional manner. For instance, the LBP device can include linear position sensors, such as optical sensors or a photo-interrupter on each link, that can feed the position to a controller for registering carrier position and precisely indexing each carrier at each of the processing stations along the processing path. The manner of driving the conveyor for precise alignment and positioning is conventional and thus will not be described further.

The guide rails 250 that form tracks in Z and Y axes engage slots machined in the sides of the receptacles. See, for example, Figs. 29, 33, 37 and 43. The mechanical tracks and drive sprockets can be constructed of a self-lubricating plastic for operation without the need to add an external lubricant. The receptacles 246 each can have a window 247 (see Fig. 12) for allowing access to laser or optical scanning of the bar code on the

specimen containers. The conveyor can be hard-coated aluminum, ®-impregnated with PTFE7 for easy cleaning. The link pins 248 can be precision ground and hardened. The link pins can be axially fixed in location in the non-rotating link bore. Rotating link bores can be fitted with a suitable bearing material capable of operation without additional lubricant. For operator safety, the conveyor operation can be interlocked with the cover of the machine (not shown).

The receptacles 246 are also configured so that they receive or seat the specimen vials in a particular orientation. That is, the specimen vials and the receptacles are complementarily configured or keyed so that the vials can only be seated in the receptacles in a particular orientation. For example, the vials can be "D" shaped, namely having a flat side (see Figs. 2a, 2b), and the receptacles can be "D" shaped so that the flat sides align with each other. In this way the vials do not rotate relative to the receptacles, while allowing unrestricted vertical movement relative to the receptacles. In addition to the D shape, each vial can have a bottom notch 25 (see Fig. 2a), and the receptacles can have a mating peg or stud (not shown) that keys into the notch 25. While the illustrated notch and peg are arcuate, they can take on other mating shapes (e.g., V-shaped).

VIAL LOADING/UNLOADING MECHANISM

Figs. 12, 13 and 14 show the automated vial loading and unloading mechanism 300. A pivoted pick-and-place arm 304 is mounted on an elevator carriage 306 driven by a vertical (Y-axis) lead screw motor 308 atop a vertical standard 310. Arm 304 has a conventional electrically- or pneumatically-operated jaw-type gripper 312 adapted to grasp and move specimen vials 10 in three degrees of freedom. Arm motion in horizontal planes is afforded by lateral lead screw motor 314, which is pivotally mounted in a clevis-type bracket 316 to elevator carriage 306. Instead of a jaw-type gripper as shown, the pick-and-place arm can be equipped with a conventional pneumatically operated suction-head type gripper as shown in Fig. 15. Such a gripper has a silicone rubber bellows 318 which seals against the cover 30 of a vial when placed against the cover and subject to suction through a suction line 320. Whether mechanical or pneumatic, actuation of the gripper is accomplished through the programmed operation of the machine as is understood by those skilled in the art.

Referring to Figs. 17-20, specimen vials 10 are stored in special injection molded plastic vial trays 330 that slide into the machine on shelves 320 (see Fig. 12). To avoid confusion, it should be pointed out that Figs. 13-15 show a different form of tray (made of stamped steel), but the operation of the mechanism that rotates the trays, regardless of

their construction, is the same. The plastic vial trays 330 are the preferred form, and are preferably made of polypropylene. The term "tray" as used herein is not limited to the embodiments shown, and should be construed to cover any type of carrier, rimmed or rimless, that can support and move a generally planar array of discrete articles generally in the manner described herein.

Each tray 330 has forty-one circular recesses 332 sized and configured to receive specimen vials 10 only in one orientation. The upper edge of each recess 332 preferably has a beveled edge 333, which facilitates smooth insertion of vials. The recesses are arranged in a close-pack array of four concentric rows, preferably as follows. The outermost row has sixteen recesses; the next row in has eight recesses; the third row in has nine recesses; and the innermost row has eight recesses. The receptacles of adjacent rows are offset for closer spacing. The receptacles of the second row are radially aligned with the receptacles of the fourth (innermost) row. The receptacles of the outermost row are spaced at 18° on center. The receptacles of each of the other rows are spaced at 36° on center. Of course, other receptacle arrays could be used as long as they permit access of all vials by the pick-and-place arm 304. Each receptacle has a unique and addressable location, so that any vial can be accessed at will and in any sequence.

As noted above, orientation of specimen vials during the processing is critical, so the proper orientation of the stored vials in these trays ensures that the pick-and-place arm 304 will properly position each vial in a conveyor receptacle 246. Accordingly, each recess 332 has at its bottom (see Fig. 19) a fixed indexing peg 334 that is sized to fit into notch 25 in the vial. The pegs 334 are installed, e.g., by adhesive, in grooves 335 that are molded into the tray adjacent the bottoms of the recesses 332. Some of the pegs have been omitted from Fig. 19 for illustrative purposes.

The pegs 334 are arranged at specific angles with respect to the median plane of the tray 330 such that each vial removed from the tray is delivered to a transport receptacle with its notch aligned with the mating peg in that receptacle, and vice versa. Each of these angles is dictated by the rotational position of the tray 330 when a vial in a specific recess 332 is to be accessed by the pick-and-place arm 304, and the angular rotation of the pick-and-place arm from the point of vial pick-up to the point of vial placement in the conveyor receptacle 246. The determination of these angles is considered to be within the abilities of one of ordinary skill in the art.

The tray 330 also has three upstanding guide posts 336, each with a spring-loaded ball 338 at its tip, which cooperate with guides (not shown) above each shelf 302 and serve to guide the tray into the machine as it is inserted and ensure its proper orientation. The guide posts 336 also serve as stacking posts when the trays are stacked for storage (see Fig. 20), the balls 338 engaging dimples 339 (see Fig. 19) in the bottom of the superior tray.

The tray 330 also has a large flared notch 340 which is oriented toward the machine when the tray is inserted on a shelf 302. The innermost portion of the notch 340 has opposed keyways 342 which are adapted for engagement by floating keys, as described below. The keyways preferably are formed in a milled brass hub insert 343 that is recessed flush with the top of the tray and secured thereto by screws.

Referring to Figs. 14, 15 and 15a, a rotary outer spindle 350 is journaled at its top and its bottom in bearings 352, 354, respectively. Outer spindle 350 engages and rotates only one tray at a time so that the pick-and-place arm 304 can access vials therefrom by moving downwardly through an opening 266 in base plate 262 and past any idle trays via their homed notches 340. Fig. 14 shows the home positions of the trays in dashed lines, with their notches 340 aligned and embracing outer spindle 350. Spindle 350 is rotated in a precision manner from the bottom by a computer-controlled rotation stepper motor 356 and a timing belt 358 engaging timing gears 360, 362. A downwardly facing optical rotary position sensor 363 located over the aligned tray notches detects when and how far a tray is rotated from its home position and provides control feedback for rotation of stepper motor 356.

Within outer spindle 350 is an inner spindle 364 carrying eight pairs of opposed keys 365, one pair for each tray. The keys 365 project from outer spindle 350 through opposed slots 366 in the outer spindle (see Fig. 15a, which is a sectional view through the spindles and the center portions of the bottom two trays). The inner spindle 364 is moved vertically within the outer spindle 350 by an internal lead screw 372. Lead screw 372 is rotated by lead screw stepper motor 374 through a timing belt 376 and timing gears 378, 380. A key "home" sensor 382 (see Fig. 15) is located at the top of inner spindle 364 to provide a reference point, i.e., when the machine is turned on, it will "home" the inner spindle to the key home sensor 382 and then reference its movements from there.

The even vertical spacing of the pairs of keys can be seen in Fig. 15. This spacing, or pitch, differs from the pitch of the keyways 342 in a full complement of installed trays 330. Accordingly, which keyways are engaged by the keys depends on the vertical

position of inner spindle, and only one pair of keyways (tray) can be engaged at any time. The enlarged view of Fig. 15a shows that the keyways 342 of bottom tray 330-1 are engaged by keys 365, while the keyways of the tray above it, 330-2, are not engaged by any keys. Movement of inner spindle 364 by one-eighth the pitch difference disengages one tray and engages the immediately adjacent tray. The operation of the loading and unloading mechanism is unaffected by the absence of one or more trays from the tray slots, which are defined by shelves 302.

When a selected tray is to be accessed by the pick-and-place arm 304 (as determined by the computer controller), the lead screw motor 374 moves the inner spindle the appropriate distance so that the appropriate keys engage the keyways of the selected tray. The rotation motor 356 then rotates the keyed tray to the proper angular position so the arm 304 can access a particular recess 332. The superposed arrangement of the trays, the way in which a selected tray is accessed by the gripper 312 through the flared notches 340 of superior trays, and the close-pack spacing of the recesses 332 in each tray make for an extremely compact, high capacity and efficient vial handling system that is readily incorporated into the compact base of the LBP device.

In the embodiment shown, the LBP device can accommodate up to eight trays holding forty-one specimen vials each. One of the forty-one recesses can be reserved for a cleaning vial, which would contain a cleaning solution and be run through the LBP device to clean the various parts of the device that normally come into contact with specimen fluid. Alternatively, the forty-first vial could contain a typical control specimen for calibration purposes. Thus the LBP device can accommodate up to at least 320 vials containing specimens to be processed. The device is therefore capable of operating continuously unattended for a long duration – at least eight hours – so that specimen processing can be carried out even when laboratory personnel are not normally present, such as at night.

When the trays 330 are bar-coded or otherwise labeled with machine-readable identifying data, they can be used in an automated storage device that can access a particular tray on command. The tray-identifying data can be input into the integrated data management system so that the location of any specimen vial in tray storage can be readily ascertained.

A cost reduction in tray-based storage of specimen vials can be achieved by using a liner-type system in conjunction with trays 330. For example, vials can be supported and stored in thin sheet-like liners (not shown) that conform to trays 330 and slip readily

into recesses 332. The liners are stiff enough to be self-supporting when fully loaded, can be stacked, and can be housed in wheeled carts for ease of mobility.

DATA ACCESSIONING AND SPECIMEN MANAGEMENT

It is, of course, important to keep track of each specimen vial and the specimen slides produced from each vial. Accordingly, the LBP device typically communicates with the integrated data management system (DMS) 104 through an accessioning station 102 or other computer. Fig. 21 schematically illustrates specimen vial handling and the flow of data that is integrated into to operation of the LBP device. The communication link between the LBP device and the DMS can be made via ethernet or other protocol using a direct peer-to-peer connection, or through a server-based network.

The specimen processing operation begins with collecting or transferring data from the labeled specimen vial, e.g. via a bar code reader on a data entry terminal or accessioning station, to the DMS via either a direct connection or over a network. Specimen tracking data can include, for example, the patient's name, test identification (ID) number, patient data, and any special processing instructions. For example, the bar-coded specimen vial can be linked to the patient information initially by a paper requisition form and subsequently by an assigned, unique numerical ID in the database. In a preferred embodiment, the patient and test information including the vial bar code can be entered into the networked DMS database at the point-of-care site (e.g., physician's office), thereby eliminating entirely the need for a paper requisition form. U.S. patent No. 5,963,368 (incorporated herein by reference), which is assigned to AccuMed International, Inc. (now Molecular Diagnostics, Inc., or MDI) discloses a similar concept as applied to a computer-controlled instrument for analyzing biological specimens (a microscope) and storing data from each analysis. The '368 patent is exclusively licensed to MonoGen, Inc. (the owner of this application) in the field of liquid-based cytology in combination with or for use with non-fluorescence based image analysis devices, processes, systems and/or instruments. MonoGen's commercially available pathology work station and data management system implement the concept disclosed in the '368 patent.

Each specimen vial includes an identification (ID) symbol or label (e.g., bar code) and/or a stored information label or symbol such as a hologram or a memory chip or device. The present embodiment contemplates reading an ID label using an optical reader, such as a bar code reader, which provides the information to a DMS for sharing information between different work stations or instruments at the same or different locations, such as laboratories, doctors' offices, hospitals, or other patient care providers.

Fig. 21a depicts an overall laboratory system wherein the DMS is expanded to link specimen/patient data through a server to a variety of specimen processing devices and/or computerized work stations for fully integrated specimen management.

A separate bar code reader 230 (see Fig. 11) is mounted on the LBP machine itself, and scans all specimen vials prior to processing through a slit in each transport receptacle 246. Each of the transport receptacles 246 is tracked using this symbol or code, such as a bar code that can be read with a conventional optical reading device. The bar code readers used in the LBP device can be any commercially available type, such as Keyence BL-600, with a minimum BCR target code capability of Interleaved 2 of 5, Code 128c, or EAN-128. The bar code readers preferably are sealed in liquid-tight enclosures for operator protection. After reading, specimen vial/transport receptacle ID data are transmitted to the DMS of the host database or work station. The host database or local work station can then transmit back to the LBP device the specific processing protocol to be performed on that individual specimen.

Some of the most important functions of the data management system (DMS) include:

Obtaining data on the patient and the specimen during accessioning, and making this available to each instrument as required to set processing parameters and to provide medical data to the slide reviewer;

Maintaining chain of custody of specimens and slides to ensure data integrity;

Compiling data and printing required forms for regulatory, compliance, and laboratory management reports;

Generating medical reports and ensuring integrity using safeguarded digital electronic signatures;

Managing billing for instruments on "per use" charges;

Storing optimal processing protocols for each process and supplying to the instrument in accordance with the specimen type and/or user requirements; and

Facilitating remote diagnostics and repair, and providing user manuals and troubleshooting guides.

Fig. 21b shows an example of a relational database table that can be used to accomplish these tasks.

The DMS can provide paper-free data flow among the different stages of the cytology process, saving a significant amount of personnel time and cost, reducing transcription errors, improving accuracy, and eliminating the space required to store paper

records. By automating and managing data acquisition, storage and retrieval, each operation becomes more efficient, significantly reducing the turn-around time for specimens. Specimen quality is enhanced by automated calibration and cross-checking routines that identify potential problems early. Flexible foreign language support for worldwide sales assists laboratories in multicultural environments.

The DMS provides a common user interface that provides detailed information on the operation of each connected laboratory device and work station, and together with online user manuals and training aids eases use and minimizes training. The DMS handles the exchange of all relevant patient and specimen data with the users' own LIS (or other data management systems) through a provided software interface. Moreover, remote instrument diagnostic capabilities ensure maximum interruption-free operation. The reduction in paperwork, ready cross-compatibility with other instruments and existing computer networks, and integration with the central hospital or laboratory information system provides significant user benefits.

In typical operation, the laboratory: (1) receives a requisition from the healthcare provider along with the pre-bar-coded specimen vial, (2) assigns a unique ID number (accession number) to the specimen, and (3) based on information on the requisition, enters a specific LBP test ID to specify the process to be used. Fig. 23 shows an example of the accessioning (data entry) screen that is presented to the technician, into which the vial bar code, accession number and LBP process code are entered. When the specimen vial is loaded into the LBP device for processing, the LBP device automatically reads the bar code on the specimen vial and transmits the bar code number (106) to the DMS, which sends back the processing parameters for the selected test, and the number of slides to be produced. The LBP device returns an acknowledgment (108) and processes the specimen, making one or more slides as instructed via the DMS. Immediately before the LBP device imprints a specimen slide with material filtered from a specimen vial, the LBP device reads the bar code from the pre-bar-coded slide that is to receive the specimen sample. The LBP device sends each slide bar code (110) and its associated vial bar code to the DMS which updates the patient database with the slide bar code number, cross-references it to the correct vial number, and signals (112) the LBP device to proceed. The LBP device then imprints a cytological sample from the specimen onto one or more slides and readies the onboard data log for the next specimen to be processed. Fig. 24 shows an example of a DMS menu screen showing data items that are now linked in the DMS database, including the vial number, slide number(s) and patient data. The DMS can

produce a printable report listing slide ID numbers and associated vial ID numbers, patient data and processing protocols.

At a minimum the protocol variables include specimen mixing parameters (stirring speed and time) and filter selection. Typically, primary stirring speed can be varied from 500 rpm to 3,000 rpm selectable in 50 rpm steps. The stirring interval can be varied from 5 to 120 seconds, selectable in 5 second increments. Choice of filter type is based on average pore size diameter: either 5 micron (red housing), e.g. for non-gynecological specimens, such as sputum specimens, or 8 micron (white housing), e.g. for gynecological specimens, depending on the test protocol selected.

The LBP device is capable of processing mixed sample-runs (i.e., runs that may include vials containing various types of specimens) interchangeably and without the need for batch processing of same-type specimens. Specimen processing can include at least 100 different processing protocols resident within the DMS and accessible to users. Predefined procedure codes (test ID's) such as the following can be used to simplify operator input and specify which processing protocol is used:

1	breast cyst, L
2	breast cyst, R
3	bronchial brushing
4	bronchial washing
5	bronchoalveolar lavage
6	cerebrospinal fluid
7	colonic brushing/wash
8	esophageal brushing/wash
9	gastric brushing/wash
10	gingival (buccal) scrape
11	gyn PAP test
12	intestinal brushing/wash
13	nipple discharge, L
14	nipple discharge, R
15	ovarian cyst, L
16	ovarian cyst, R
17	pericardial effusion
18	peritoneal effusion
19	pleural effusion

20 rectal brushing/wash
21 sputum, induced
22 sputum, spontaneous
23 urine, catheterized
24 urine, voided

Each specimen is processed with a new filter to prevent the possibility of cross contamination. In the present embodiment, either of two or more different filter types can be specified for versatility in test selection (the device's eight filter tubes allow for up to eight different filter types). Processing parameters for each type of specimen preparation can be determined remotely and in advance, and communicated to the processing device using a bi-directional communication link utilizing the specimen vial bar code as the key identifier. The LBP device can utilize default (pre-loaded into the DMS) process protocols as well as laboratory-generated process protocols that users can add to the DMS.

An overfilled-vial sensor (not shown) can be positioned at or just downstream of the bar code reader 230 to detect whether an excessive amount of fluid is present in each translucent vial. Opening and processing an overfilled vial can result in hazardous spillage or ejection of biological fluid. Accordingly, if an overfilled vial is detected, the DMS will be so notified and the complete LBP processing protocol for that vial will be canceled, allowing the overfilled vial to proceed through the processing path unopened. Alternatively, an overfilled condition can be sensed at the conveyor holder 246 into which vials are loaded by the vial loading mechanism 300. If an overfilled vial is detected there, the DMS will be so notified and the loading mechanism will be instructed immediately to return the overfilled vial to its tray 330.

A similar approach can be used to deal with other anomalies detected as each vial is loaded into the conveyor. For example, a sensor (not shown) can be used to detect an unreadable bar code on the vial, or detect when a vial is improperly position in the holder 246. When any such condition is detected, the DMS will be so notified and the loading mechanism will be instructed immediately to return the overfilled vial to its tray 330.

Fig. 22 is a block diagram showing the components of a general purpose computer system or work station 270, which can be used to run the DMS. The computer system 270 typically includes a central processing unit (CPU) 272 and a system memory 274. The system memory 274 typically contains an operating system 276, a BIOS driver 278, and application programs 271, such as a DMS. In addition, the computer system 270 can

include input devices 273, such as mouse, keyboard, microphone, joystick, optical or bar code reader, etc., and output devices, such as a printer 275P, and a display monitor 275M.

The computer system or work station can be connected to an electronic network 280, such as a computer network. The computer network 280 can be a public network, such as the Internet or Metropolitan Area Network (MAN), or other private network, such as a corporate Local Area Network (LAN) or Wide Area Network (WAN), or a virtual private network. In this respect, the computer system 270 can include a communications interface 277, such as ethernet, USB, or Firewire, which can be used to communicate with the electronic network 280. Other computer systems 279, such as a remote host database, other types of work stations including automated analyzers, and computers or databases (e.g., LIS) of a hospital, laboratory, or other medical establishment, can also be linked to the electronic network 280. Other LBP devices, as well as other types of specimen processing instruments (e.g., automated slide stainers and coverslippers) 279a can also be connected to each other and the DMS via the network.

One skilled in the art would recognize that the above-described system includes typical components of a general purpose computer system connected to an electronic network. Many other similar configurations can be used to control the LBP device and its processes. Further, it should be recognized that the computer system and network disclosed herein can be programmed and configured by one skilled in the art to implement the methods, system, and software discussed herein, as well as provide requisite computer data and electronic signals to implement the present invention.

In addition, one skilled in the art would recognize that the "computer" implemented invention described further herein may include components that are not computers per se, but include devices such as Internet appliances and Programmable Logic Controllers (PLCs) that may be used to provide one or more of the functionalities discussed herein. Furthermore, while "electronic" networks are generically used to refer to the communications network connecting the processing sites of the present invention, one skilled in the art would recognize that such networks could be implemented using optical or other equivalent technologies. One skilled in the art would recognize that other system configurations and data structures can be provided to implement the functionality of the present invention. All such configurations and data structures are considered to be within the scope of the present invention. In this context, it is also to be understood that the present invention may utilize known security and information processing measures for transmission of electronic data across networks. Therefore, encryption, authentication,

verification, compression and other security and information processing measures for transmission of electronic data across both public and private networks are provided, where necessary, using techniques that are well known to those skilled in the art.

UNCAPPING STATION

One of the advantages of the present vial-based LBP device and system is that it minimizes operator exposure to the specimens, which can contain potential biohazards. Referring to Figs. 26-31, the LBP device has an uncapping mechanism 400 that first automatically separates the stirrer 40 in the vial from cover 30, and then removes and discards the cover – all without intervention by an operator. See Fig. 26, which shows the stirrer resting on vial ribs 26 after the cover 30 is removed.

A closed specimen vial 10 which has arrived at the uncapping station in its transport receptacle 246 is met by an uncapping head 402 which is lowered onto the cover 30 of the specimen vial. See Figs. 27 and 28. Uncapping head 402 has four tapered legs 404 that form a tapered gripping cavity having chisel-like inner edges 406 spaced and sized to progressively tighten onto cover 30 as head 402 is lowered. Once the cover is tightly engaged by the legs, a central spindle or plunger 408 is lowered into contact with the center of cover 30 and applies a downward force to the cover to cause the stirrer 40 to detach from the cover 30, as described above, and drop down in the vial onto ribs 26. Then the plunger is retracted and the uncapping head 402 is rotated counterclockwise (Fig. 28) to unscrew cover 30 and remove it from container 20. Thereafter the uncapping head with the removed cover in its grip moves laterally to the position shown in dashed lines 410 in Figs. 29 and 11, and plunger 408 is again lowered, this time to eject cover 30, which falls into a waste chute or bin (not shown) beneath the uncapping head. Alternatively, a movable waste chute can be brought beneath the uncapping head to catch the ejected cover, so that lateral movement of the uncapping head is not required. Covers are not reused to eliminate the possibility of cross-contamination.

The plunger 408 is driven by a pneumatic cylinder 412, mounted on an L-bracket 415 at the top of the uncapping head, that can apply a force on the cover of up to about 30 lbs. A coil spring 413 returns the plunger to its retracted position when cylinder 412 is deactivated. The head 402 is capable of applying an uncapping torque through the gripping legs of up to about 10 lb-ft, which is sufficient to loosen the cover. The gripping legs can be of the self-energizing type so that precise alignment with the cover or small variations in cover geometry do not frustrate their grip.

The uncapping mechanism has a mounting frame 414 supported on blocks 416 that slide laterally of the processing path on rails 418. A Y-axis stepper motor 420 and lead screw 422 effect lateral motion. The uncapping head 402 is rotatably mounted in a bearing block 424. Bearing block 424 is secured to a C-frame 426 that is vertically slidable on mounting frame 414. Vertical movement of C-frame 426 and, hence, uncapping head 402 is effected by Z-axis stepper motor 428 and lead screw 430. Lead screw 430 can be vertically compliant to accommodate upward movement of the cover 30 as it is unscrewed. However, it is preferred that stepper motor 428 be actuated during the uncapping sequence so that head 402 rises at about the same rate as, but no faster than, the unthreading cover. Uncapping head 402 is rotatably driven by uncapper motor 432 through a gear reduction unit 433, a timing belt 434 and timing pulleys 436, 438.

The uncapping head described above would also work with vials having a conventional "press and turn" bayonet-type coupling between the container and the cover. The downward force of the plunger 408 would be sufficient to release the internal anti-turn lock of the coupling, allowing the gripper to rotate and remove the cover. Vials having covers that do not require rotation for removal, e.g., a snap-on cover, would require a differently designed uncapping head, tailored to the type of cover connection involved.

Alternatives to the above-described plunger 408 can be employed at or upstream of the uncapping station for applying the required external force to the covered vial to effect separation of the stirrer from the cover. For example, a cam, lever arm or other movable mechanical element can contact and press down on the cover. Alternatively, an abrupt upward external force can be applied to the vial to yield an acceleration force that overcomes the frictional retention force between couplers 35 and 47, effectively pulling the stirrer out of engagement with the cover. This can be done by, e.g., moving the closed vial rapidly downwardly to rap the bottom of the container 20 against a rather hard surface, e.g., by mechanically and/or pneumatically thrusting the closed vial into the transport carrier 246 that will hold the vial during the subsequent processing steps, or by dropping the vial down a chute into the carrier a sufficient distance to dislodge the stirrer. Another way to exert an abrupt upward external force on the vial is to strike the bottom of the container 20 with a striking member. This can be accomplished by, e.g., cradling the container 20 and momentarily thrusting a striker against the bottom of the container, e.g. through a bottom opening in the vial carrier 246, by pneumatic and/or mechanical means. The design of these and other variants of suitable automated mechanisms for accomplishing these tasks is within the grasp of those skilled in the mechanical arts.

PREPROCESSING (PRIMARY STIRRING) STATION

After uncapping is completed, the transport mechanism indexes the specimen container to a station where preprocessing occurs. The preprocessing station is the location at which preprocessing operations, such as specimen dispersal within its container, are performed prior to the container and its specimen moving to the specimen acquisition station. The preprocessing station typically performs a dispersal operation. In the preferred embodiment, the dispersal operation is performed by a mechanical mixer, which rotates at a fixed speed and for a fixed duration within the specimen container. In this example, the mixer serves to disperse large particulates and microscopic particulates, such as human cells, within the liquid-based specimen by homogenizing the specimen. Alternatively, the specimen may contain subcellular sized objects such as molecules in crystalline or other conformational forms. In that case, a chemical agent may be introduced to the specimen at the preprocessing station to, for example, dissolve certain crystalline structures and allow the molecules to be dispersed throughout the liquid-based specimen through chemical diffusion processes without the need for mechanical agitation. In this example, the chemical preprocessing station introduces its dispersing agent through the preprocessing head.

In the illustrated preferred embodiment preprocessing occurs at the primary stirring station 500, which uses a specified or instructed stirring protocol to stir the specimen, if needed, using the stirrer 40 in the container, at a specified speed (rpm) for a specified duration. The stirring protocol chiefly depends on the specimen, as described above, and is normally intended to disaggregate any mucous material and disperse it and/or other particulate material in the specimen liquid.

Referring to Figs. 32-35, the primary stirring station 500 has a stirring head 502 in the form of an expanding steel collet. The collet is formed at the lower end of a shaft 503 which splits into six flexible fingers 504 defined by six equally spaced slits 506. Shaft 503 is rotatable in a bearing block 508 secured to a C-frame 510 that is vertically slidable on a mounting frame 512. Vertical movement of C-frame 510 and, hence, stirring head 502 is effected by a Z-axis stepper motor 514 and a lead screw 516. Stirring head 502 is rotatably driven by a stirring motor 518 through a timing belt 520 and timing pulleys 522, 524.

The inner surfaces of the collet fingers 504 taper uniformly inwardly toward the lower end of the collet. A central plunger 526, movable vertically by a pneumatic cylinder 528 atop a bracket 530, expands the fingers 504 outwardly when it descends and

encounters the narrowing passage defined by the tapering fingers. Thus the diameter of the lower end of the stirring head (collet) 502 increases when the plunger descends. This end is sized to fit loosely but closely within the annular wall 47 at the top of stirrer 40 when the collet is not expanded. When plunger 526 descends, the fingers 504 expand outwardly to wedge against the inside of wall 47, in manifold M, securely engaging the stirrer.

In operation, the stirring head 502 is first lowered so that the collet enters the manifold M. The dashed motor and bracket lines in Figs. 33 and 34 indicate this lowered position. Then plunger 526 descends to lock the stirring head to the stirrer. Then the stepper motor 514 is operated to slightly raise the stirring head and the attached stirrer 40. This vertical movement need only be very small, such as 0.050 in., just to free the stirrer from the ribs 26 and prevent interference with the container during stirring. Then DC stirring motor 518 is operated in accordance with the specimen-specific stirring protocol. Stirring speed can vary, and is usually in the range of about 500 rpm to about 3,000 rpm. The stirring time can vary from about 5 seconds to about 90 seconds. The base or bottom wall 41 of the stirrer acts as a slinger to thrust any liquid that may rise along the stirrer against the container wall, and prevents the escape of liquid from the container. Withdrawing the plunger 526 from the collet releases the stirrer 40 from the collet 502 so the specimen container can move on to the next station.

A contracting collet could be used instead of expanding collet 502. In that case, the collet fingers would fit around the outside of annular wall 47, and would be squeezed together to clamp around the wall by a descending sleeve that surrounds the fingers.

FILTER PLACEMENT STATION

At the filter placement station 600 an appropriate filter assembly F (see Fig. 5) is loaded into the open manifold M at the top of the stirrer 40. Filter assemblies can come in different filter configurations for automated machine recognition. For example, one set of filter assemblies can be colored red (5 micrometers), another set white (8 micrometers), each having different filtering properties, and a color sensor can detect which type of filter is before it and cause the proper filter to be loaded. The filter assemblies are dispensed by a pusher from a magazine having multiple filter tubes.

Figs. 36-40 show the structure and operation of the filter placement station. Referring to Figs. 37 and 40, a filter dispensing head 610 comprises a filter magazine in the form of a turret 612 rotatable on a spindle 614 by a stepper motor 616. Vertical post 611 provides the main support for the turret. Turret 612 has a top support plate 618 with

eight equally spaced holes 620 near its periphery, each hole opening through the edge of the plate 618 with a slot 622. A bottom guide plate 624 on spindle 614 has a similar arrangement of holes that are aligned with the holes and slots in the top support plate.

Eight steel filter tubes 626, each having an upper support shoulder 628, are supported vertically in holes 620 and the aligned holes beneath them, with shoulders 628 resting on the top of top plate 618. Each filter tube 626 has a full-length slot 630, and its bottom portion is split into four springy fingers 632 by slots 634. Just above the bottom end the fingers 632 curve inwardly, forming rounded inner shoulders 636 against which a filter assembly F rests. The filter tube is dimensioned such that the shoulders 636 keep up to a full stack of filter assemblies F from falling out of the tube, but deflect to allow a filter assembly to pass when the stack is pushed downwardly without damage to the filter assembly. Fingers 632 thus form a springy choke.

Fig. 39 shows the position of the filter magazine 612 in relation to the processing path and the adjacent processing stations, namely the primary stirring station 500 to the left, and the specimen acquisition station 700 to the right, all located on one side of the processing path as defined by guide rails 250. On the other side of the processing path opposite the filter magazine 612 is the assembly that supports and drives a pusher arm 640. This assembly comprises a support post 642 supporting a Z-axis lead screw 644 driven by a stepper motor (not shown) which moves a shuttle 646 that carries pusher arm 640. A filter sensor 650 positioned opposite bottom guide plate 624 monitors the passage (drop) of the lowest filter assembly F in the filter tube presented to (i.e., directly above) the specimen container. Sensor 650 also detects when the filter tube is empty. A second sensor 651 monitors filter type.

Filter assemblies of the same type are stacked in the proper orientation, with the membrane filter side (beveled edge) facing down, in each tube. For example, 54 filter assemblies can be housed in each tube; thus a total of 432 filter assemblies can be loaded into the magazine. Fifty-four filter assemblies can be prepackaged in a stack that is inserted into a filter tube with a wrapper tab projecting from slot 630, and unwrapped by pulling the tab outwardly. Alternatively, filter assemblies of the same type can be dumped onto a vibratory feeder, which can recognize their orientation by geometric configuration, and properly orient and feed the filter assemblies onto the tubes. Several of these feeders can be used, one for each type of filter assembly.

In operation, with the pusher arm 640 in its home (top) position, indicated by the dashed shuttle outline in Fig. 38, the filter magazine 612 is rotated by stepper motor 616

until sensor 650 detects the presence of the specified type of filter assembly in the filter tube before it. Shuttle 646 then moves downwardly with pusher arm 640 moving through slot 630 to press the stack of filter assemblies in that tube downwardly, until the lowest filter assembly drops from the tube into the manifold M in stirrer 40. When filter drop is sensed, the shuttle 646 with its pusher arm 640 stops its advance. In an alternative arrangement, a weight sensor can be used to monitor the weight of the filter stack, and detect by weight change when a filter assembly has dropped from the stack and when the filter tube is empty.

The use of eight filter tubes 626 in magazine 612 enables unattended processing of all of the specimens housed in the trays of the vial autoloader 300. For a counter-top model of the type described above, however, a single filter tube supported in a fixed position above the processing path would suffice for processing specimens that require the same type of filter.

SPECIMEN ACQUISITION AND CELL DEPOSITION STATION

Referring to Fig. 41, specimen acquisition station 700 has a suction head 702 that descends to engage the upper portion of the stirrer 40. Before drawing a vacuum on the specimen through the filter assembly F, the suction head grips, slightly lifts and rotates the stirrer 40, this time more slowly than at the primary stirring station (typically no more than 500 rpm for a 5 second interval), to re-suspend the particulate matter in the specimen liquid. The re-stir motor can be a Maxon 24 volt DC planetary gear-reduced type. Then suction is applied through suction line 750 to aspirate specimen liquid from the container 20 through suction tube 43, into the particulate matter separation chamber (manifold) 46 and through the filter assembly F, leaving a monolayer or thin layer of uniformly deposited cells on the bottom surface of the filter as described above. It may also be possible to rotate the stirrer slowly while the specimen liquid is being aspirated.

Fig. 6 shows how the suction head cooperates with the annular wall 47 of the stirrer manifold and the filter assembly F therein. The outer portion 704 of the suction head envelops the wall 47 and has an O-ring 760 that seals against the outside of wall 47. The inner portion 706 of the suction head has two concentric O-rings 762, 764 that seal against the top of filter holder 200. Suction applied through port 750 creates a vacuum around central opening 204 and within filter holder 200, which draws liquid into the manifold 46 and through the filter 202. An O-ring 766 is interposed between the inner and outer portions of the suction head.

Referring to Fig. 42, when aspiration of the specimen is complete, the suction head 702 is raised. The inner portion 706 of the suction head is extended at the same time by action of a pneumatic cylinder (not shown) mounted above the suction head. As the suction head 702 is raised, the outer portion 704 disengages from the stirrer 40, but the filter assembly F is retained on the inner portion 706 by application of a vacuum through suction line 752 to the annular space between O-rings 762 and 764. Thus the suction head 702 removes filter assembly F from the stirrer, and can continue to apply light suction via suction line 750 through the filter to effect a desired degree of moisture control of the cellular material on the filter.

The suction head 702 then moves laterally away from the transport conveyor by pivoting 90° about a vertical axis to the cell transfer position "P" shown in Fig. 46, to position the filter assembly F over a microscope slide S delivered from a slide cassette at slide presentation station 900. This pivoting movement of suction head 702 can also be seen in Figs. 11 and 39. The inner portion 706 of the suction head 702 then moves downwardly to press the filter against the slide S with a tamping force in the range of 4 to 8 lbs. and transfer the monolayer of cells thereto. The phantom lines in Fig. 42 show this change in position of suction head 702 and contact of the filter with slide S. Instead of being pivotally mounted, the suction head 702 could be mounted for rectilinear movement to and from a different deposition site where slides are presented, e.g., above the processing path.

Referring to Figs. 43-46, suction head 702 is rotatably mounted on a boom 716 that also carries the re-stirring motor 718, which rotates suction head 702 through a timing belt 720. Boom 716 is pivotally supported about a vertical axis 721 on a slide 722, which is vertically movable along frame support 724 by means of a Z-axis stepper motor 726 and a lead screw 728. Motor 726 thus moves the entire suction head vertically. Pivoting motion of boom 716 is effected by stepper a motor 717 operating through a gear train (not shown). Vertical motion of the inner portion 706 of the suction head is effected by a pneumatic cylinder and return spring (not shown) mounted above the suction head to an L-bracket 719, substantially identical to the arrangement 412, 413, 415 (see Fig. 29) used to move the plunger 408 of the uncapping head 402.

The frame support 724 is mounted on a slide 730 so as to be movable laterally of the transport path. A Y-axis stepper motor 732 and a lead screw 734 effect this movement. After the slide is printed the suction head is raised by the Z-axis motor, and

the Y-axis stepper motor 732 advances the entire assembly to the dashed line position "X" shown in Fig. 43. Then the suction head pivots back to its original orientation, transverse to the transport path (position "S" in Fig. 46). The Y-axis stepper motor 732 then pulls the entire assembly back toward its original position (solid lines in Fig. 43). As the suction head 702 moves (to the right as seen in Fig. 43), the still-retained filter assembly F is "scraped" off the suction head by the edge 736 of an open-top used filter (waste) tube 738 (see also Figs. 11 and 39). This leaves suction head 702 free to engage a fresh filter assembly.

The vacuum source that communicates with the suction head 702 pulls a slight vacuum, e.g., in the range of 3 in. to 10 in. Hg (adjustable by a regulator), through suction line 750 to aspirate specimen liquid and draw it through the filter assembly F. The separately regulated vacuum applied through suction line 752 for holding the filter assembly to the suction head 702 is higher, on the order of 20 in. Hg.

Formation of high-quality specimens on microscope slides depends critically on the deposition of a monolayer of cells of specified concentration (i.e., number of cells per unit area) on the surface of the filter that will contact the slide. That, in turn, depends critically on the aspiration rate and/or the aspirated flow volume. Since cell concentration on the filter surface is a function of the number of filter pores blocked by the solids suspended in the specimen liquid, the percent of flow reduction from the maximum open filter condition correlates to the blockage or amount of accumulation on the filter. Because of the nature of biological specimens, solid particle concentration is a significant variable in the process and must be taken into consideration. Also, it is important to identify the total volume of material filtered on a real time basis for other processing operations.

The specimen acquisition station thus further includes a deposition control system for controlling the liquid draw vacuum duration by monitoring the flow rate and/or aspirated volume. The monitored flow rate or aspirated volume can be used to signal vacuum cut-off and/or suction head retraction, which correlates to the specified concentration of cells collected on the membrane filter surface. If a specified concentration factor is not achieved before a specified volume of fluid is aspirated, the system can also issue a retract signal.

Different types of deposition control systems or modules can be used for these purposes. Fig. 47 schematically shows one such system, which has a meter in the form of a digital level detector positioned along a fluid column. This "bubble flow" system can

use sensors in the form of a plurality of LED emitters and corresponding number of photosensors, such as Omron sensor, EE-SPX613 GaAs infrared LED, placed along the length of the column. Any other type of sensors may be used. Alternatively, LED sensors such as the Omron sensors mentioned above can be used without corresponding emitters when they are positioned just at the edge of a glass tube. The meniscus edge of the liquid in the tube diffracts the light passing through the tube, and the sensor will detect the shifted light pattern when the rising meniscus edge reaches the sensor.

The fluid column is formed in a vertically extending transparent tube or cylinder 770, e.g., one made of Pyrex glass 9 mm in diameter by 1 mm thick. The aspirated specimen fluid is drawn from the specimen container through the membrane filter, and pulled into the glass cylinder 770 via suction line 750 and a 3-way valve 778, by means of a vacuum source 772 connected to the top of the cylinder. The sensors 774 are positioned evenly along the length of the cylinder 770, preferably at 1.5 ml capacity intervals, and are interfaced with a controller or microprocessor 776.

In operation, in the normal state, with no fluid in the tube 770, the sensor relay line is "low." Vacuum begins to draw fluid into the tube through the filter, and the controller marks the beginning of the draw sequence. When the fluid reaches the first sensor, the first sensor relay line goes "high." The controller marks the time it took for the fluid to reach the first sensor, indicating the nearly free-flow condition of the filter, and the relative viscosity of the fluid in the test. When an additional 1.5 ml of fluid is drawn into the tube, the second sensor relay line goes "high." The time interval for the first 1.5 ml of fluid (between the first and second sensors) is noted by the controller, and this becomes the reference time base. As each additional 1.5 ml of fluid is drawn into the system (and is detected by succeeding sensors), the time base for that increment is computed. When the incremental time base reaches an empirically derived percentage (e.g., 120%) of the original (reference) time base, the controller indicates that cell collection is completed, and a stop signal is transmitted, preferably to retract the suction head 702 from the manifold in the specimen container. The empirically derived figure mentioned above is variable with the protocol and directly controls the cellularity of the specimen sample.

The best approximation of the free-flow condition of the filter is obtained if the time it takes for the fluid to reach the first sensor 774 is kept to a practical minimum. This can be accomplished by incorporating the first sensor into the suction head itself, as schematically illustrated in Fig. 47a. In this embodiment, inner portion 706 of the suction head carries an emitter 774a and an opposed sensor 774b, which detects the leading edge

of the fluid column very close to the filter assembly F. The outer portion 704, which has teeth 775 engaged by timing belt 720 (not shown), is rotatable about the inner portion 706 (note interposed bearing 773) to rotate the stirrer (not shown) and stir the specimen prior to aspiration.

During the specimen drawing operation, the controller records the cumulative or total aspirated volume. If the cumulative volume reaches a predetermined level before reaching the predetermined flow rate reduction from the reference flow, the controller will also issue a stop signal and a flag indicating that the stop signal issued not as a result of desired reduced flow, but by reaching the maximum liquid draw limit. A slide formed under the flagged condition will likely form a hypo-cellular condition. The controller can imprint the slide and indicate to the DMS that a hypo-cellular condition likely exists. Accordingly, if the flagged condition exists, the controller issues a signal to purge the liquid in the cylinder 770 and initiate a second draw. The cylinder is purged of all liquid after each sample is taken.

Referring to Fig. 48, the deposition control system can have a purge value so that when the draw cycle is completed, the stop signal generated by the controller 776 will open the purge valve to vent the vacuum supply line to the atmosphere and divert the liquid remaining in the cylinder 770 into a waste container. The cylinder 770 can be maintained under a negative pressure. The system is then ready for the next cycle. Specifically, the system can have a 2-way solenoid valve V-3 in the suction line with one port 780 open to the atmosphere. The bottom of the cylinder 770 is connected to a valve manifold 782 with two solenoid valves V-2, V-4. The solenoid valves can be Lee LF series designed for use in vacuum systems, 2-way valve LFVA 2450110H, viton seal, 24 volt and 3-way valve, LFRX 0500300B, viton seal, 24 volt. The 2-way valve V-4 can port the specimen liquid to the bubble flow cylinder 770, or to vacuum by-pass 784. The 2-way valve V-2 can control the filter dehydration vacuum source. Fig. 49 illustrates the valve logic.

The deposition control system can use an analog level indicator instead of the digital sensors 774. The analog level indicator senses capacitance of the aspirated liquid. The difference is only in the method of sensing the volume and fill rate of the liquid in the cylinder 770. Here two spaced electrodes are used, one around the outside of the cylinder 770 and the other positioned down the center of the cylinder the cylinder, separated from the aspirated liquid by a dielectric. A high frequency, such as 10 kHz, low voltage current is applied across the electrodes. Capacitance in this system is measured by a bridge

circuit, which provides an analog indication of capacitance in the circuit. As fluid fills the column, capacitance in the circuit increases. A 10X differential in direct capacitance is easily obtained with this system. Capacitance is indicated on a real time basis and can be sampled frequently enough to provide control of the sampling system. This arrangement, like the first two, uses a computer or microprocessor and a bubble flow technology to measure the flow rate and the total fluid volume in real time. The predetermined volume increment for these arrangements can be in the range of about 0.1 ml to 5.0 ml, and preferably is in the range of about 1.0 to 2.0 ml.

A different system can use an ultrasonic indicator for measuring fluid movement through a tube. The ultrasonic system uses ultrasonic wave propagation through a moving liquid. In this regard, the third system employs an ultrasonic emitter and detector clamped across the liquid draw tube (suction line 750) operating on the distal end of the filter assembly F. This system provides a digital indication of fluid flow in the tube, the total volume aspirated through the tube being calculated by a flow interval calculation. It measures phase shift from the ultrasonic wave generator source to a detector for measuring flow speed.

Another way to measure aspirated fluid volume and control the duration of the specimen draw is to detect the change in the weight of the specimen vial. This can be accomplished by using a sensor that makes a high-precision measurement of the weight or mass of the vial containing the specimen that is being aspirated. Vial weight or mass is repeatedly measured at a high frequency such that the rate of change of the weight or mass of the vial is accurately determined. Specimen aspiration is completed when the rate of change in weight or mass has diminished by a predetermined amount or percentage from the initial rate. The weight sensor can be, e.g., a load cell in each conveyor receptacle 246, or a single load cell beneath the conveyor at the specimen acquisition head that rises to engage the container above it. In either case, the specimen acquisition head can be raised slightly during aspiration to unload the container so that the load cell can measure only the combined weight of the container and the remaining specimen.

Although specimen acquisition preferably is accomplished through aspiration (using a vacuum), it can also be accomplished by pressurizing the container 20 through an appropriate head that seals against the top of the container and forces specimen liquid up through tube 43 and through the filter assembly by means of positive pneumatic pressure. The fluid volume control schemes and mechanisms described above would also work in conjunction with such a pressurized specimen acquisition system.

The cell concentration can be selected from low to high by defining flow control cut-off. For a typical low cellularity result, the cut-off can be 80% of the 120% reference discussed above, and for high cellularity the cut-off can be set at 60% of the reference, selectable in 5% increments. The number of slides per specimen can range from one to three. Some of the typical default protocols are as follows:

GYN: 1,000 RPM stir, 30 second interval, 8-micrometer filter, 60% - high cellularity, one slide.

Urine: 1,000 RPM stir, 20 second interval, 5-micrometer filter, 70% - medium cellularity, one slide.

Lung sputum: 3,000 RPM stir, 120 second interval, 5-micrometer filter, 80% - high cellularity, two slides.

RE-CAPPING STATION

After completing the specimen processing cycle, the specimen container is resealed with the stirrer still inside the container. It is preferred to use a thin, polypropylene-coated aluminum foil to form the new cap, which is available in roll form. The foil is drawn across the open end of the specimen container, thermally bonded to the container at a seal temperature of about 365° F applied for about 3 seconds with a seal force of 3 pounds, and cut from the roll. Of course, any other type of re-capping material can be used as long as it is compatible with the vial material and creates a safe and reliable seal. For example, a foil backed with a thermosetting resin adhesive could be used; a sticky-backed foil could be used that does not require heat to effect a seal; or a plastic seal material can be bonded to the container ultrasonically. To enhance unattended operation, an automatic threader could be included for threading a new roll of sealing material into the re-capping mechanism. Cutting caps from a roll can be eliminated if roll-mounted pre-die-cut closures having peel-off tabs are fed to the re-capping mechanism.

Referring to Figs. 50 and 52, the re-capping mechanism 800 has a side support plate 802 secured to the machine base plate. The side support plate carries a main frame 810 having a top plate 812 with slots 814, 816, and two side plates 818, 820. A driver capstan 822 is journaled in side plates 818, 820. A foil advance motor 824, mounted on a bracket 826, drives the capstan. A pressure roller 828 is pivotally mounted to the main frame 810 and resiliently engages the capstan under the influence of a spring 830. Capstan 822 and pressure roller 828 define between them a throat through which the foil runs, and have resilient surfaces which grip the foil for positive feed. A handle 832 allows

the throat to be opened manually to allow the end of the foil to be fed into the throat after first passing through slot 814. A spindle 804, carried side support plate 802, supports a replaceable roll of foil.

Fig. 51 shows the foil path 834 through the throat. An L-shaped cutter 836 is pivoted at its elbow to the rear of main frame 810. One end of a single-acting pneumatic cutter actuator cylinder 838 is mounted on a bracket 840, and the other end of the cylinder is linked to the upper leg 842 of cutter 836. The lower leg of the cutter has a blade 844 that normally rests above the foil path downstream of the throat, held in that position by a spring 845 linked between the upper leg 842 and the support plate 802.

A rear post 850 pivotally supports an arm 852 that extends forwardly toward main frame 810. Arm 852 carries a heated platen 854 and a foil guide fork 856 having two tines that extend toward the throat and are spaced apart so as to allow the platen 854 to pass between them. Arm 852 is kept elevated, in the rest position shown in Fig. 51, by a spring 858. During the re-capping operation a single-acting pneumatic cylinder 860 pulls down on the arm 852 to lower the platen 854 and the guide fork 856. Note the position of a container 20 in a transport receptacle (not shown) beneath the platen 854.

In operation, the foil advance motor turns the capstan 822 to feed a measured length of foil past the cutter blade 844, into the fork 856, and to the position shown by the dashed line in Fig. 51. A photocell 862 detects the leading edge of the foil and signals the motor to stop. Then cylinder 838 is actuated to cut the foil, and cylinder 860 is actuated to pull arm 852 down to the seal position. The cut length of foil is sandwiched between the platen 854 and the container 20, and the container is sealed. After about three seconds cylinder 860 is deactivated and the arm 852 rises, returning to its rest position. A vacuum assist (not shown) optionally may be used to help hold the cut length of foil in position on the platen prior to sealing.

The foil caps applied by the re-capping mechanism are approximately square in shape. The corners of the foil caps can protrude from the vials and interfere with other re-capped vials that are returned to the trays 330. Accordingly, a foil folding ring 870 (seen in phantom lines in Fig. 51) preferably is provided which acts to fold the edges and corners of each foil cap down along the side of the container. The foil folding ring 870 preferably is mounted to act on the vial in the transport position immediately downstream of the re-capping mechanism, i.e., position "FF" in Fig. 51, and may be mounted on the re-capping mechanism itself, e.g., to main frame 810, so that actuation of cylinder 860 serves simultaneously to apply a foil cap to one container and fold the edges and corners of the

foil cap of the preceding (downstream) container. Alternatively, the foil folding ring or an equivalent foil folding mechanism can be mounted further downstream of the re-capping mechanism so as to act independently thereof.

Foil folding ring 870 is a metal ring having an inner diameter that is slightly larger than the outside diameter of the threaded portion of the container 20. The ring 870 is mounted on an arm (not shown) that moves downwardly when actuated to lower the ring 870 over the upper end of the container. As the ring encircles the container, it folds the overhanging portions 872 of the foil cap against the side of the container. When the ring rises after folding the foil, the container is held in position in its transport receptacle by a pin (not shown) that is mounted on a leaf spring (not shown) and is situated in the center of the ring 870. The leaf spring is carried by the arm that holds the ring, so the pin resiliently presses down against the center of the foil cap until the arm and the ring retract fully.

The foil seals applied to the processed containers are easily punctured by a syringe or a pipette to obtain further liquid specimen samples. The seals are very durable, however, withstanding rough handling and preventing leakage in low ambient pressure conditions, e.g., in aircraft flying as high as 40,000 ft. Further, the appearance of the foil seal makes it readily distinguishable from the cover of an unprocessed vial, making handling by low-skilled operators virtually foolproof. To avoid the potential of puncturing the foil seal inadvertently, the re-sealed container can be capped with an unused screw-on cover of a distinct color.

SLIDE HANDLING AND PRESENTATION

The LBP device can use 30 and 40 slide plastic magazines (cassettes), which can accept standard 25 mm x 75 mm x 1 mm and 1 x 3 x 0.040 in. slides. Metric and inch based slides can be used interchangeably. Figs. 52-55 show a 40-slide cassette C suitable for use in the LBP device. The slide cassette is in some respects similar to that disclosed in U.S. patent No. 5,690,892 (incorporated herein by reference), but is specially adapted for use in other devices as well, such as an automated stainer, an automated image analyzer, and a pathology work station, so that the slides do not have to be unloaded and reloaded into different magazines for use in those devices. Machine-readable indicia on the cassette, such as a bar code or an embedded microchip, provides cassette information that can be linked by the DMS to the bar codes on the slides in the cassette so that the location and status of any cassette and any slide in that cassette can be tracked in a laboratory system. The cassettes are stackable for compact storage and easy retrieval.

Specifically, the slide cassette is molded of plastic and has a generally rectangular shape with an open front 902, a rear wall 904, a top wall 906, a bottom wall 908 and side walls 910. The top wall 906 bears bar-coded information 909. A guide flange 912 extends laterally outwardly from each side wall. Rear wall 904 has a rectangular central opening 914 through which a slide shuttle can pass (see below) to extract and return one slide at a time. An inwardly projecting ridge 916 around the central opening acts as a stop against which the slides abut when they are inserted into the cassette. The preferred material for the cassette is ABS plastic; alternative choices include polyurethane, thermoplastic polyester, and polypropylene. The open front face is sized to accommodate the rear of another like cassette so as to be stackable.

The slides are supported on shelves 918 at each side of the cassette. In the illustrated embodiment there are 41 pairs of left and right shelves, and each pair (except for the top pair) supports one slide that spans the space between the shelves. Referring to the detailed view in Fig. 53, each shelf (except for the top and bottom shelves) has a raised top ledge 920 on which the slide rests and an underside beam spring 922 for applying a force to pinch and thereby frictionally restrain the slide against the top ledge directly beneath it. This arrangement keeps the slides from falling out of the cassette, even when the cassette is held face down, yet enables each slide to be moved out of and back into the cassette by the slide presentation apparatus, described below, without blocking, scratching or interfering with the slide-mounted specimens. Each shelf 918 also has a lead-in ramp 924 which guides the slide during insertion into the cassette. Each shelf 918 (including spring 922) preferably is integrally molded into the cassette and is attached to both the rear wall 904 and a side wall 910. However, separately fabricated springs, plastic or metal, may be inserted between the shelves instead.

Each side wall is provided with multiple drainage ports 926 which allow fluid to drain from the cassette after removal from a staining bath. The last (top and bottom) drainage ports 923 on each side also cooperate with a hanger assembly of a stainer for moving the cassette from one staining bath to another. During the staining operation the cassette is oriented generally on its side, hung from the last two drainage ports on the upper side. An all-plastic construction makes the cassette compatible with acid baths and all types of staining bath compositions.

Referring to Fig. 54, rear wall 904 has two rows of apertures 927 that form two integrally molded gear racks 928, which are adapted to engage pinion gears 936 (see below) for moving the cassette longitudinally so that each slide can be accessed by the

slide shuttle. Two spaced parallel racks and two pinion gears enhance the smoothness and accurate positioning of the cassette, as compared to a single rack and single pinion. Also integral with the rear wall is a row of 40 cassette position sensing slots 929 extending through the rear wall and coincident with the positions of the slides to allow for optical sensing of each slide. Further, rear wall 904 has a row of 40 blind recesses 925 (these do not extend completely through the rear wall) that allow for accurate sensing of cassette position when it is driven via the gear racks 928.

The molded cassette preferably is supplied wrapped in sealed plastic for cleanliness, with slides installed. It is therefore well suited for shipping, relatively low in cost, disposable yet reusable. It has a high storage capacity and is stackable with others, thus providing high density storage for specimen samples.

Slide cassettes populated with slides are manually loaded into the LBP device in an elevated in-feed track 930 (see Fig. 11) located behind the filter loading station 600 and the specimen acquisition station 700. No latching is required to enter cassettes into the system. Up to ten unprocessed cassettes can be loaded in the LBP device at any one time, but only in a single orientation. The cassettes can be marked with a top indicator, and will not be accepted if they are installed backwards or upside down. The cassettes are loaded with their open fronts facing to the right as seen in Fig. 11, with the lead cassette between vertical rails 932.

The lead cassette moves down incrementally whenever a new slide is to be withdrawn from the cassette for specimen printing. This is accomplished by a stepper motor (not shown) driving pinion gears 936 that engages the racks 928 on the back of the cassette C (see Fig. 54). When all slides in the cassette have been processed, the cassette descends all the way to outfeed track 940, and a stepper motor/lead screw pusher 938 moves the cassette to the right into outfeed track 940, and then retracts. Then the next cassette in the infeed track 930 is advanced by a motor/lead screw pusher (not shown) to the front position between vertical rails 932, where it is engaged by the pinion gears 936 and moved downwardly until the first (lowest) slide comes into position for extraction. Each of the feed tracks can have a home sensor, which can be Omron self-contained shutter type, and a cassette full sensor, which can be Keyence fiber optic.

Figs. 11, 56 and 57 show the slide presentation system, which uses a slide shuttle feed system 960, e.g. AM Part No. 5000-1, for extracting one slide at a time from the cassette along the X-axis and placing it on a Y-axis handler, which moves the slide to the pressing (print) position. The aforementioned U.S. patent No. 5,690,892 discloses a

similar slide cassette and shuttle arrangement used in a pathology work station (microscope). The Y-axis handler 962 has a slide platen 964 secured to a follower 966, 967. The handler is driven by a stepper motor 970 and a lead screw 972, guided along a rail 968. A slide is held to the platen under a fixed shoulder 974 (against a spring 976) and a pivoted arm 978 which is spring-biased in the counterclockwise direction as seen in Fig. 56.

When the handler 962 moves to the left, arm 978 moves off an adjustable stop 980 and rotates over the slide. The full Y-axis slide travel (shown as "T" in Fig. 57) brings the center of the slide to the print position "P" (note the dashed line position of the slide and the handler in Fig. 56). On its way to the print position the bar code number on the slide is acquired by a bar code reader 982 and transmitted to the host data base. When the print position is reached the suction head 702, which has pivoted along arc "A" about axis 721, lowers the filter assembly F into contact with the slide, as described above, depositing (printing) the specimen on the slide. Vacuum on the filter is maintained throughout the printing cycle to prevent over–hydration of the sample and unintentional dripping.

After printing the slide moves back to the right, pausing under a fixative dispensing head 984. Here a solenoid-driven pump (not shown), such as Lee LPL X 050AA, 24V, 20 microliter per pulse, yielding 12 microliters per pulse (maximum of 2 pulse/second), applies fixative to the specimen. The total volume can be determined by the number of solenoid cycles. The total fixative volume dispensed is programmable in 20 microliter increments. It can have a flexible connection to a dispensing sapphire jet nozzle with a 0.030 in. orifice. The liquid can be gravity-fed from a reservoir to the pump. The reservoir can be a tank and can have a "fluid low" sensor connected to the operating system. More than one fixative dispenser can be employed to provide alternative fixatives as determined by processing protocols.

After the specimen is fixed, the completed slide moves all the way to the right, where it is transferred by the slide shuttle mechanism back to its original position in the cassette. When the cassette is fully processed, the entire cassette is ejected into the outfeed track 940, as described above.

A COMPLETE LABORATORY SYSTEM

The present LBP device does not require that specimens be pre-processed before loading, and can automate every step of the slide preparation process. Moreover, the device does not require the operator to open any of the specimen containers -- an important

operator safety feature. The LBP device can automatically prepare high quality cytology slides from all specimen types, including mucous-containing GYN and non-GYN specimens, using the integral high-speed, high-shear mixing station that facilitates mucous disaggregation. The incorporated dual-flow filter system allows production of slides with optimal cell separation, cell concentration, cell dispersion, and optimal preservation of antigens, DNA, and morphologic characteristics to enhance the performance of subsequent testing. The slide cassettes, containing up to 40 slides each, will be utilized in the follow-on laboratory processing devices to avoid the labor-intensive need to transfer slides to different racks before continuing with slide processing. Data on the patient, the specimen, the vial, the cassette and the slide can be transferred automatically to the LIS over the user's network, via a DMS software interface.

The present LBP device can provide eight hours of unattended operation. Thus, if the operator re-loads the device before leaving for the day, a single-shift laboratory can produce two shifts of output per day without added personnel or equipment costs. The total throughput can exceed 160,000 slides per year, at a per-test cost significantly below that of the current leading LBP system.

The LBP device also has the capability to process specimens for current and future molecular diagnostic tests including quantitative DNA analyses, and tests utilizing markers & probes. Features built into the device include the capacity to employ multiple fixative dispensers in order to provide non-routine fixatives that may be required for special molecular diagnostic tests.

The complete laboratory system, illustrated, e.g., in Fig. 21a, includes a pathology review station, a computer-aided microscopy work station used by pathologists to review specimen slides and sign out cytology cases. As with all components of the laboratory system, the pathology review stations are networked to the DMS and thereby to all other devices on the system, for rapid access to patient data and specimen processing information. The pathology review station accepts slide cassettes for automated loading and review of specimen slides. Computerized, fully automated image analyzers will perform quantitative analyses of DNA and molecular diagnostic tests, receiving their operating instructions and reporting their results via specimen bar codes using the integral DMS. See, for example, AccuMed/MDI U.S. patent Nos. 5,963,368; 6,091,842; and 6,148,096, which are incorporated herein by reference.

The laboratory system will also include, for example, slide autostainers and autocoverslippers (and/or combination automated stainer/coverslipper devices) controlled

via the DMS that utilize the same slide cassette as the present LBP device. Cassettes containing processed slides can be utilized directly in these additional devices without the need to unload slides and reload them into separate racks.

The inter-connectivity and high degree of automation of the processing and analytical devices making up the laboratory system will enable high-quality, high-throughput specimen processing and analysis at relatively low cost.

INDUSTRIAL APPLICABILITY

The above disclosure presents a safe, effective, accurate, precise, reproducible, inexpensive, efficient, fast and convenient vial-based system and method for collecting, handling and processing liquid-based cellular specimens, providing fully integrated specimen and information management in a complete diagnostic cytology laboratory system.

CLAIMS

1. An automated method for individually processing multiple specimens of particulate matter-containing liquid in respective containers, the method comprising:

transporting the containers seriatim along a processing path to present them to a mixing head and subsequently to a specimen acquisition head, the mixing head adapted to mix the specimen in any container presented to it, and the specimen acquisition head adapted to aspirate previously mixed particulate matter-containing liquid from any container presented to it and pass the aspirated liquid through a respective filter so as to collect a particulate matter sample on a surface of the filter;

actuating the mixing head in response to presentation of a container thereto so as to carry out the mixing operation independently; and

actuating the specimen acquisition head in response to presentation of a container thereto so as to carry out the aspirating operation independently.

2. An automated method according to claim 1, wherein operation of the mixing head is carried out in accordance with a protocol specific to the specimen presented thereto, and operation of the specimen acquisition head is carried out in accordance with a protocol specific to the specimen presented thereto.

3. An automated method according to claim 1 or claim 2, further comprising pressing seriatim each filter through which aspirated liquid has passed against a respective slide positioned in proximity to the processing path to transfer the particulate matter sample to the slide.

4. An automated method according to claim 1 or claim 2, wherein the specimen acquisition head is adapted to mix the specimen in each container presented to it, the method including actuating the specimen acquisition head to mix the specimen immediately prior to the aspirating operation.

5. An automated method according to claim 4, wherein the specimen acquisition head mixes the specimen more slowly than the mixing head.

6. An automated method according to claim 5, further comprising pressing seriatim each filter through which aspirated liquid has passed against a respective slide positioned in proximity to the processing path to transfer the particulate matter sample to the slide.

7. An automated method for individually processing multiple specimens of particulate matter-containing liquid in respective containers, each container having therein a mixer with an upper particulate matter separation chamber adapted to receive a filter and a depending aspiration tube communicating with the separation chamber, the method comprising:

transporting the containers seriatim along a processing path to a plurality of operating heads spaced so that the operating heads can operate simultaneously on different specimens, the plurality of operating heads comprising:

a mixing head adapted to engage and move the mixer in any container presented to the mixing head to mix the specimen therein,

a filter loading head downstream of the mixing head having a filter magazine and adapted to dispense a filter into any particulate matter separation chamber presented to the filter loading head, and

a specimen acquisition head downstream of the filter loading head adapted to seal against the particulate matter separation chamber presented and apply suction thereto to aspirate previously mixed particulate matter-containing liquid from the container and pass the aspirated liquid through the filter in the separation chamber so as to collect a particulate matter sample on a surface of the filter; and

actuating each of the operating heads in response to presentation of a container thereto so as to carry out the respective operation of each operating head independently.

8. An automated method according to claim 7, wherein operation of the mixing head is carried out in accordance with a protocol specific to the specimen presented thereto, and operation of the specimen acquisition head is carried out in accordance with a protocol specific to the specimen presented thereto.

9. An automated method according to claim 7 or claim 8, further comprising pressing seriatim each filter through which aspirated liquid has passed against a respective slide positioned in proximity to the processing path to transfer the particulate matter sample to the slide.

10. An automated method according to claim 7, wherein the filter magazine of the filter loading head is adapted to store at least two types of filters, and the filter type dispensed into the particulate matter separation chamber is governed by information specific to the specimen presented.

11. An automated method according to claim 7, claim 8 or claim 10, wherein the specimen acquisition head is adapted to mix the specimen in each container presented to it, the method including actuating the specimen acquisition head to mix the specimen immediately prior to the aspirating operation.

12. An automated method according to claim 11, wherein the specimen acquisition head mixes the specimen more slowly than the mixing head.

13. An automated method according to claim 12, further comprising pressing seriatim each filter through which aspirated liquid has passed against a respective slide positioned in proximity to the processing path to transfer the particulate matter sample to the slide.

14. An automated method according to claim 7, claim 8 or claim 10, wherein each container has a removable cover and is loaded into the processing path with the cover in place, and said plurality of operating heads further comprises an uncapping head along the processing path upstream of the mixing head and adapted to grip and remove the cover from a container presented thereto.

15. An automated method according to claim 14, wherein said plurality of operating heads further comprises a container recapping head along the processing path downstream of the specimen acquisition head and adapted to apply a sealing cap to an uncapped container presented thereto.

16. An automated method according to claim 15, further comprising unloading processed and recapped containers from the processing path, and loading unprocessed specimen containers into the processing path in positions vacated by processed and recapped containers.

17. An automated method according to claim 16, wherein container unloading and loading is carried out while movement of all containers along the processing path is arrested.

18. An automated apparatus for individually processing multiple specimens of particulate matter-containing liquid in respective containers, the apparatus comprising:

a conveyor having a plurality of spaced container supports for supporting and advancing containers seriatim along a processing path;

a mixing head along the processing path adapted to mix the specimen in any container presented thereto by the conveyor;

a specimen acquisition head along the processing path downstream of the mixing head adapted to aspirate previously mixed particulate matter-containing liquid from any container presented thereto by the conveyor and pass the liquid through a respective filter; and

a controller governing operation of the mixing head, operation of the specimen acquisition head and movement of the conveyor, the controller responding to presentation of a container to the mixing head to cause the mixing head independently to mix the specimen in the container presented thereto, and the controller responding to presentation of a container to the specimen acquisition head to cause the specimen acquisition head independently to aspirate previously mixed particulate matter-containing liquid from the container presented thereto.

19. An automated apparatus according to claim 18, wherein the controller causes the mixing head to operate in accordance with a mixing protocol specific to the specimen presented thereto, and causes the specimen acquisition head to operate in accordance with an aspiration protocol specific to the specimen presented thereto.

20. An automated apparatus according to claim 18 or claim 19, further comprising a slide presentation station in proximity to the specimen acquisition head, wherein the specimen acquisition head is movable relative to the processing path and is adapted to acquire and remove the filter from the separation chamber after aspiration of the liquid specimen and press the filter against a slide to transfer the particulate matter sample to the slide, and the controller allows the conveyor to advance after the filter is removed by the specimen acquisition head.

21. An automated apparatus according to claim 18 or claim 19, wherein the specimen acquisition head is adapted to mix the specimen in each container presented to it, the controller actuating the specimen acquisition head to mix the specimen immediately prior to the aspirating operation.

22. An automated apparatus according to claim 21, wherein the specimen acquisition head mixes the specimen more slowly than the mixing head.

23. An automated apparatus for individually processing multiple specimens of particulate matter-containing liquid in respective containers, each container having therein a stirrer with an upper particulate matter separation chamber adapted to receive a filter and a depending aspiration tube communicating with the separation chamber, the apparatus comprising:

a conveyor having a plurality of spaced container supports for supporting and advancing containers seriatim along a processing path;

a plurality of operating heads arranged serially along the processing path and spaced such that when one container support is positioned at one of the operating heads other container supports are positioned respectively at the other operating heads so that the operating heads can operate simultaneously on different specimens, the plurality of operating heads comprising:

a stirring head having a rotatable gripper adapted to engage and spin the stirrer in any container presented to the stirring head,

a filter loading head downstream of the stirring head having a filter magazine and adapted to dispense a filter into any particulate matter separation chamber presented to the filter loading head, and

a specimen acquisition head downstream of the filter loading head adapted to seal against the particulate matter separation chamber presented and apply suction thereto to aspirate previously stirred particulate matter-containing liquid from the container and pass the same through the filter in the separation chamber so as to collect a particulate matter sample on a surface of the filter; and

a controller governing operation of the operating heads and movement of the conveyor, the controller responding to presentation of a container to each operating head to cause such operating head to operate independently on the specimen in the container presented thereto.

24. An automated apparatus according to claim 23, wherein the controller causes the stirring head to operate in accordance with a stirring protocol specific to the specimen presented thereto, and causes the specimen acquisition head to operate in accordance with an aspiration protocol specific to the specimen presented thereto.

25. An automated apparatus according to claim 24, wherein the filter magazine of the filter loading head is adapted to store at least two types of filters, and the controller causes one of said filter types to dispense in accordance with information specific to the specimen presented.

26. An automated apparatus according to claim 23, claim 24 or claim 25, wherein the specimen acquisition head is adapted to stir the specimen in any container presented to it, the controller actuating the specimen acquisition head to stir the specimen immediately prior to the aspirating operation.

27. An automated apparatus according to claim 26, wherein the specimen acquisition head stirs the specimen more slowly than the stirring head.

28. An automated apparatus according to claim 23, further comprising a slide presentation station in proximity to the specimen acquisition head, wherein the specimen acquisition head is movable relative to the processing path and is adapted to acquire and remove the filter from the separation chamber after aspiration of the liquid specimen and press the filter against a slide to transfer the particulate matter sample to the slide, and the controller allows the conveyor to advance after the filter is removed by the specimen acquisition head.

29. An automated apparatus according to claim 23, claim 24 or claim 25, wherein each container has a removable cover and is loaded onto the conveyor with the cover in place, and said plurality of operating heads further comprises an uncapping head along the processing path upstream of the stirring head having a gripper adapted to grip and remove the cover from a container presented thereto.

30. An automated apparatus according to claim 29, wherein said plurality of operating heads further comprises a container recapping head along the processing path downstream of the specimen acquisition head and adapted to apply a sealing cap to an uncapped container presented thereto.

31. An automated apparatus according to claim 30, further comprising a specimen container loading and unloading station having a pick-and-place arm adapted to grasp a processed and recapped container and remove it from its support on the conveyor, and grasp an unprocessed specimen container and place it on a vacant support on the conveyor.

32. An automated apparatus according to claim 31, wherein the controller causes the pick-and-place arm to remove a recapped container from a support on the conveyor and load an unprocessed specimen container onto the same support on the conveyor while the conveyor is immobilized.

33. An automated method for individually processing multiple specimens of particulate matter-containing liquid in respective containers, each container having a removable cover, the method comprising:

transporting the containers seriatim along a processing path to present them to a plurality of operating stations spaced so that the operating stations can operate simultaneously on different specimens, the plurality of operating stations comprising, in sequence:

an uncapping station at which the cover of a container presented thereto is removed,

a mixing station at which the specimen in a container presented thereto is mixed,

a filter loading station at which a filter is placed into the particulate matter separation chamber adjacent the top of a container presented thereto, and

a specimen acquisition station at which the previously stirred particulate matter-containing liquid is aspirated from the container and passes through the filter so as to deposit a particulate matter sample on a surface of the filter; and

actuating each of the operating stations in response to presentation of a container thereto so as to carry out the respective operation of each operating station independently.

34. An automated method according to claim 33, further comprising a container recapping station, downstream of the specimen acquisition station, at which a container presented thereto is recapped.

35. An automated method according to claim 33, wherein the specimen acquisition station re-mixes the particulate matter-containing liquid before aspirating it from the container.

36. An automated method according to claim 33 or claim 35, wherein a slide presentation station is located in proximity to the processing path and the specimen acquisition station, the method further comprising pressing seriatim each filter through which aspirated liquid has passed against a respective slide to transfer the particulate matter sample to the slide.

37. An automated method according to claim 36, further comprising a container recapping station, downstream of the specimen acquisition station, at which a container presented thereto is recapped.

38. An automated apparatus for individually processing multiple specimens of particulate matter-containing liquid in respective containers, each container having a removable cover, the apparatus comprising:

a conveyor that supports and advances containers seriatim along a processing path;

a plurality of operating stations along the processing path, the operating stations comprising, in sequence:

an uncapping station having a gripper adapted to grip and remove the cover of any container presented thereto;

a stirring station having a rotatable gripper adapted to engage and spin a stirrer in any container presented thereto;

a filter loading station having a filter magazine and a pusher adapted to dispense a filter from the magazine into a particulate matter separation chamber adjacent the top of any container presented thereto;

a specimen acquisition station having a suction head adapted to seal against the particulate matter separation chamber presented thereto and aspirate the previously stirred particulate matter-containing liquid from the container and pass

the same through the filter in the separation chamber so as to collect a particulate matter sample on a surface of the filter; and

a container recapping station having a movable head that applies a sealing cap to any container presented thereto; and

a controller governing operation of the operating stations and movement of the conveyor, the controller responding to presentation of a container to each operating head to cause such operating head to operate independently on the specimen in the container presented thereto.

39. An automated apparatus according to claim 38, wherein the suction head is rotatable to enable re-stirring of the particulate matter-containing liquid before aspirating it from the container.

40. An automated apparatus according to claim 38 or claim 39, further comprising a slide presentation station in proximity to the processing path and the specimen acquisition station, wherein the suction head is movable relative to the processing path and is adapted to acquire and remove the filter from the separation chamber after aspiration of the liquid specimen and press the filter against a slide to transfer the particulate matter sample to the slide.

41. An automated apparatus according to claim 40, wherein the controller allows the conveyor to advance after the filter is removed by the suction head.

42. An automated method for individually processing multiple fluid specimens of biological material in respective containers, the method comprising:

transporting the containers seriatim along a processing path to present them to a preprocessing apparatus and subsequently to a specimen acquisition apparatus, the preprocessing apparatus adapted to preprocess the specimen fluid in any container presented to it, and the specimen acquisition apparatus adapted to remove preprocessed specimen fluid from any container presented to it for subsequent analytical testing or evaluation;

actuating the preprocessing apparatus in response to presentation of a container thereto so as to carry out the preprocessing operation independently; and

actuating the specimen acquisition apparatus in response to presentation of a container thereto so as to carry out the fluid removal operation independently.

43. An automated method according to claim 42, wherein the preprocessing apparatus disperses particulate components of the specimen fluid.

44. An automated method according to claim 43, wherein the specimen acquisition apparatus collects a cytology sample.

45. An automated method according to claim 43, wherein the specimen acquisition apparatus filters the removed specimen fluid.

46. An automated method according to claim 45, wherein the specimen acquisition apparatus collects a cytology sample.

47. An automated method according to claim 46, wherein the specimen acquisition apparatus places the cytology sample on a slide.

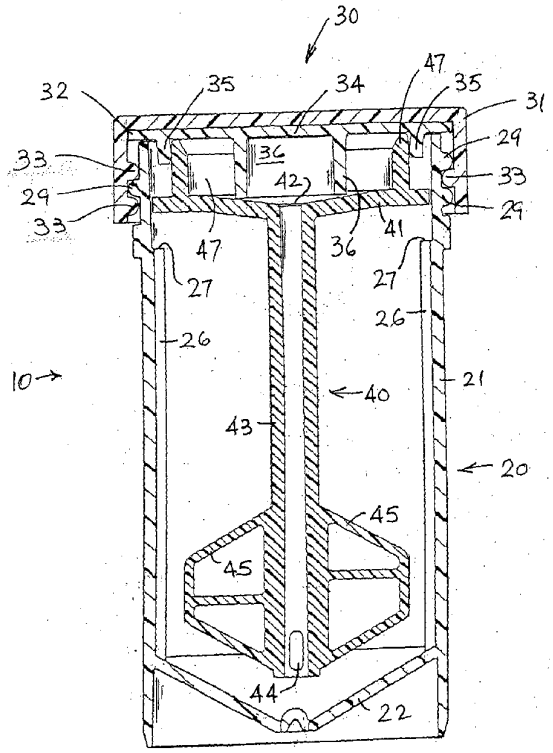
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FIG. 1

FIG. 2b

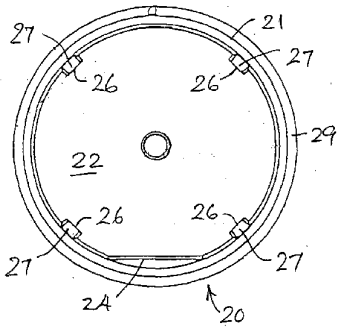
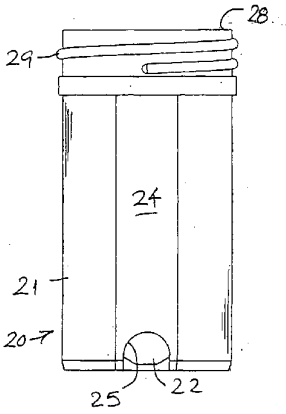


FIG. 2a



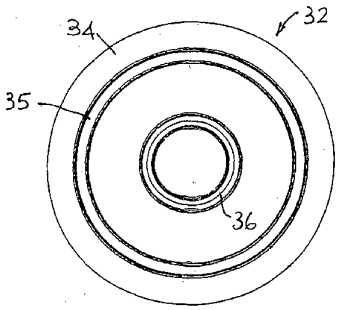


FIG. 4

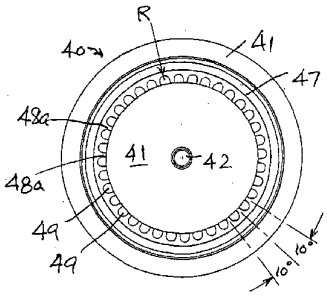


FIG. 3

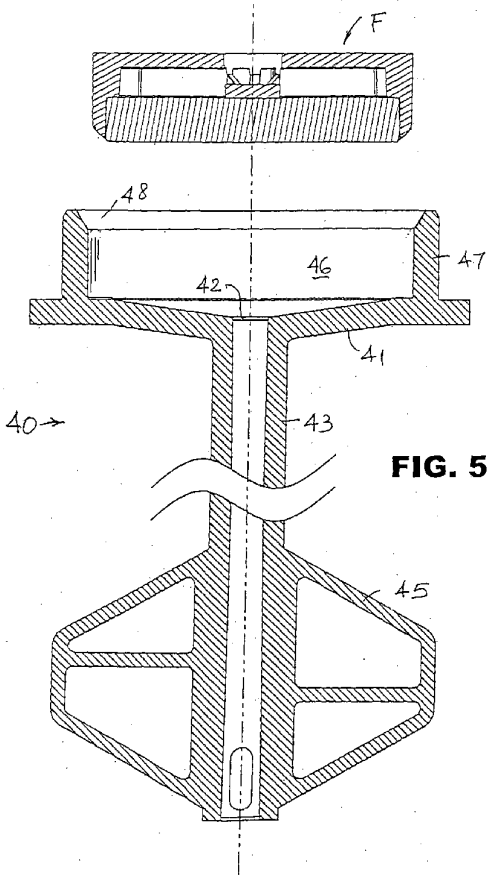
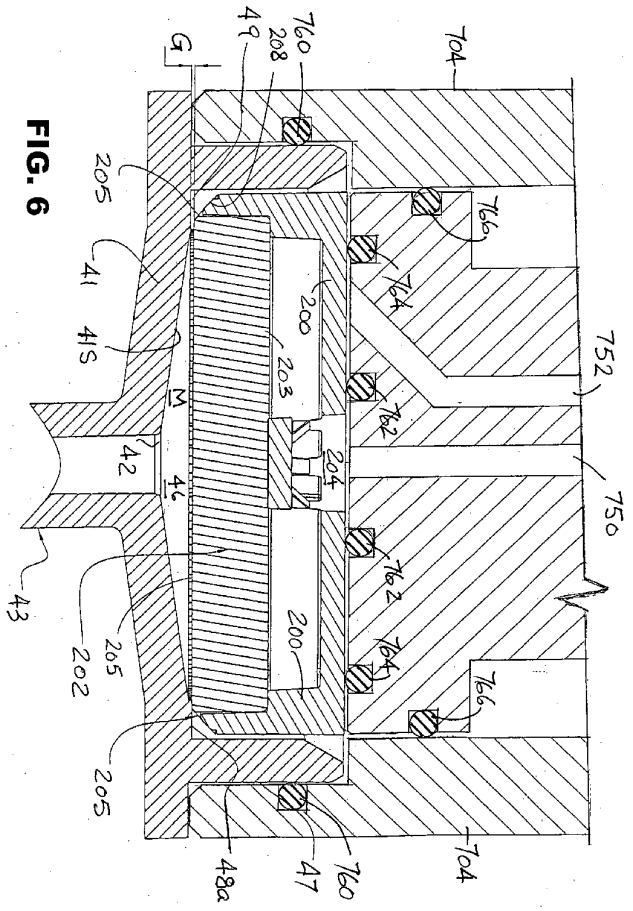


FIG. 5


G
49
760
208
704
205
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41S
M
42
46
43
202
205
205
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766
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200
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766

FIG. 6

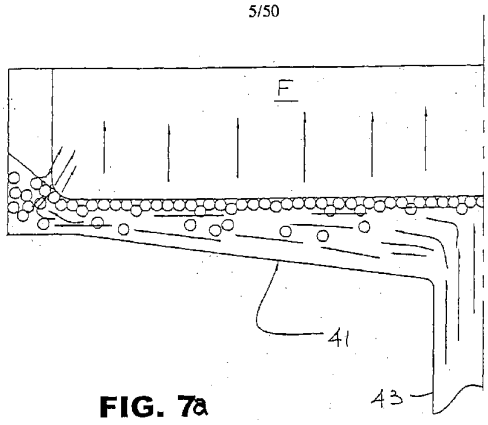


FIG. 7a

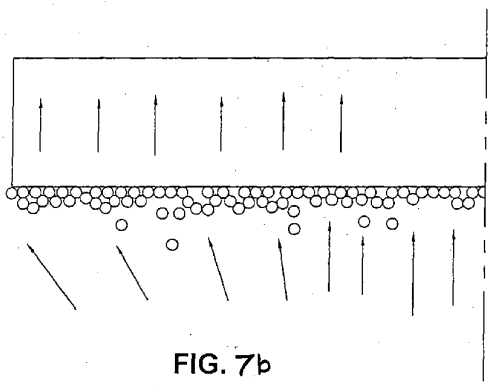
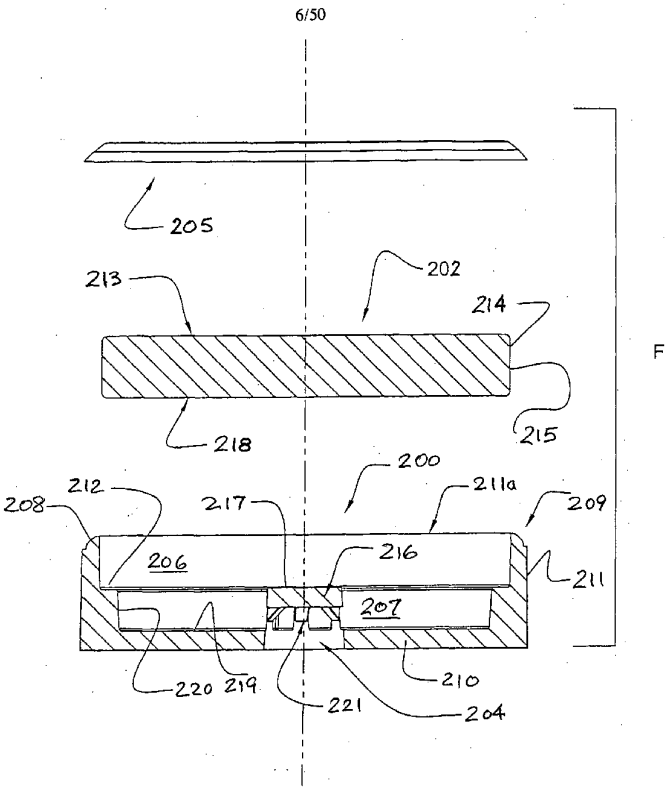


FIG. 7b
(PRIOR ART)


205
213
202
214
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211a
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204

FIG. 8

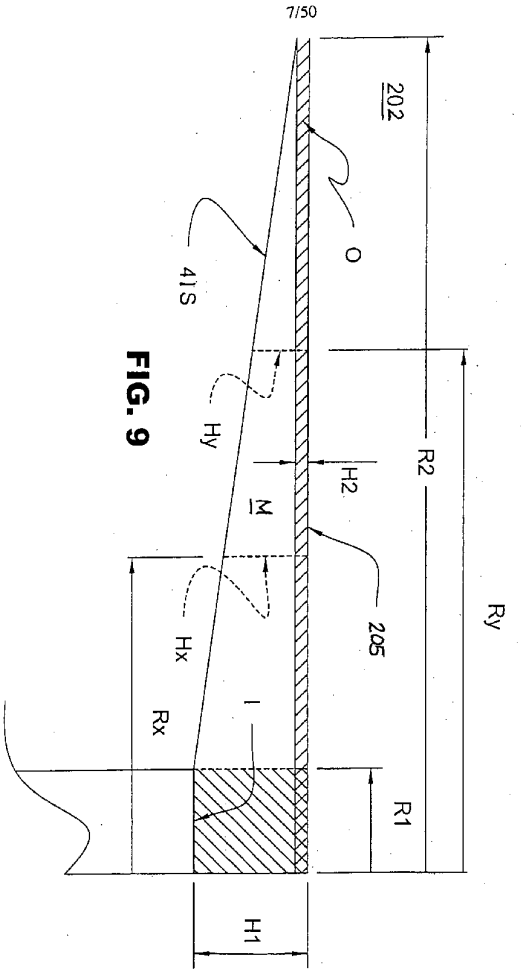


FIG. 9

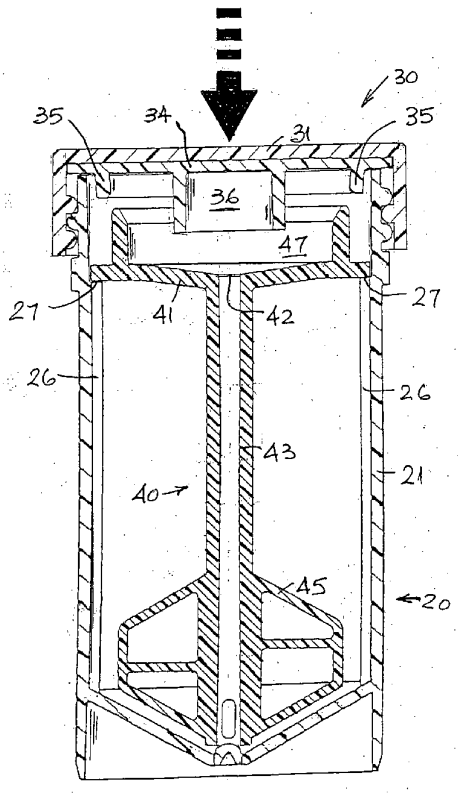


FIG. 10

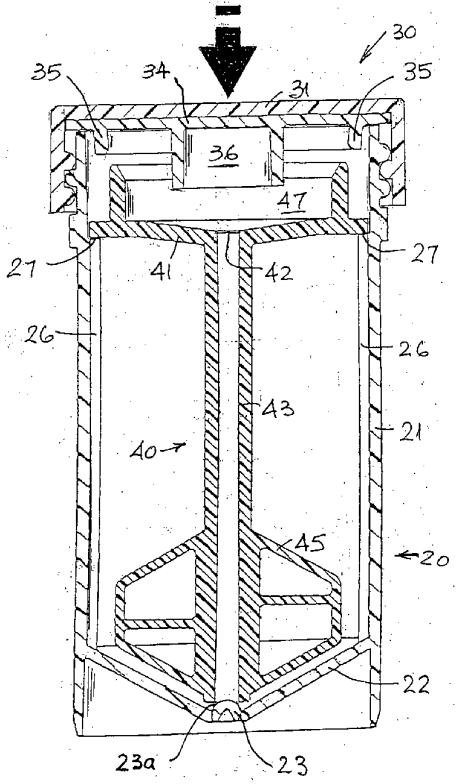


FIG. 10a

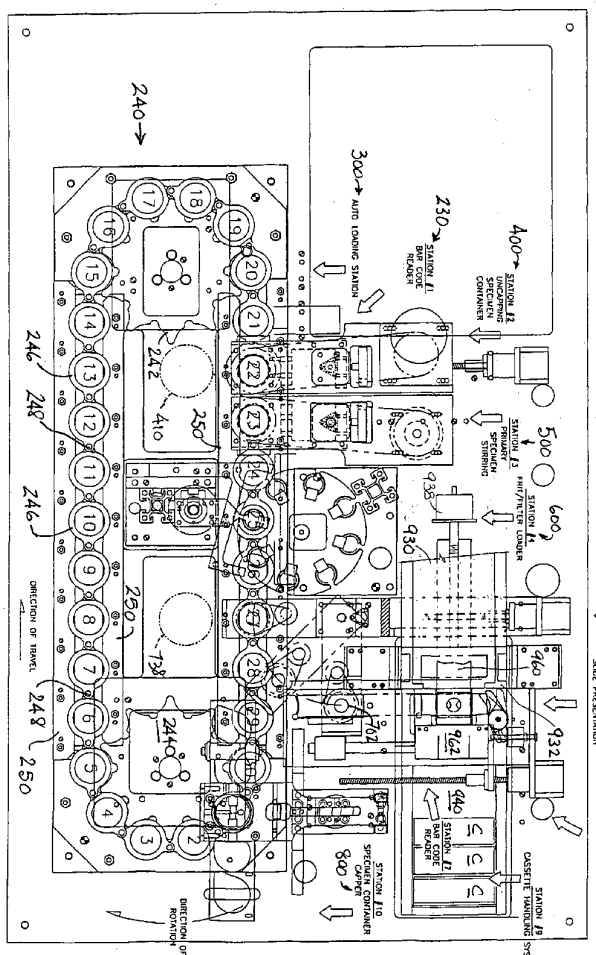

240
300
AUTO. LOADING STATION
230
STATION #1 BAR CODE READER
400
STATION #2 UNCAPPING SPECIMEN CONTAINER
500
STATION #3 SPECIMEN STIRRING
600
STATION #4 FRIT/FILTER LOADER
700
STATION #5 SPECIMEN ACQUISITION
900
STATION #8 SLIDE MANDLING, UNLOAD & RELOAD
800
STATION #10 SPECIMEN CONTAINER CAPPER
STATION #9 CASSETTE HANDLING SYSTEMS
246
248
242
410
250
DIRECTION OF TRAVEL
DIRECTION OF ROTATION

FIG. 11

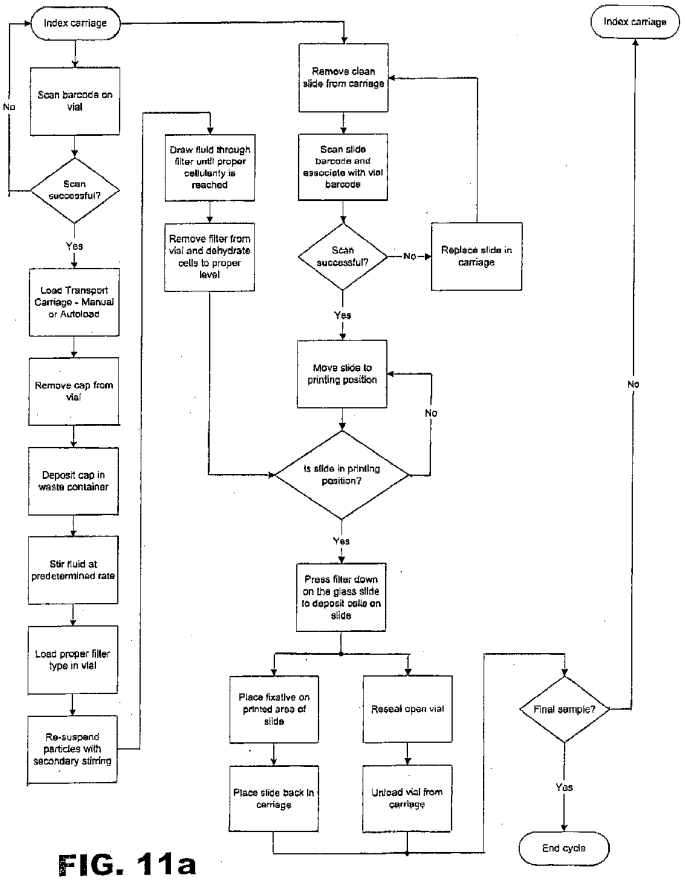

Index carriage
Scan barcode on vial
No
Scan successful?
Yes
Load Transport Carriage - Manual or Autoload
Remove cap from vial
Deposit cap in waste container
Stir fluid at predetermined rate
Load proper filter type in vial
Re-suspend particles with secondary stirring
Draw fluid through filter until proper cellularity is reached
Remove filter from vial and dehydrate cells to proper level
Remove clean slide from carriage
Scan slide barcode and associate with vial barcode
Scan successful?
No
Replace slide in carriage
Yes
Move slide to printing position
No
Is slide in printing position?
Yes
Press filter down on the glass slide to deposit cells on slide
Place fixative on primed area of slide
Reseal open vial
Place slide back in carriage
Unload vial from carriage
Index carriage
Final sample?
No
Yes
End cycle

FIG. 11a

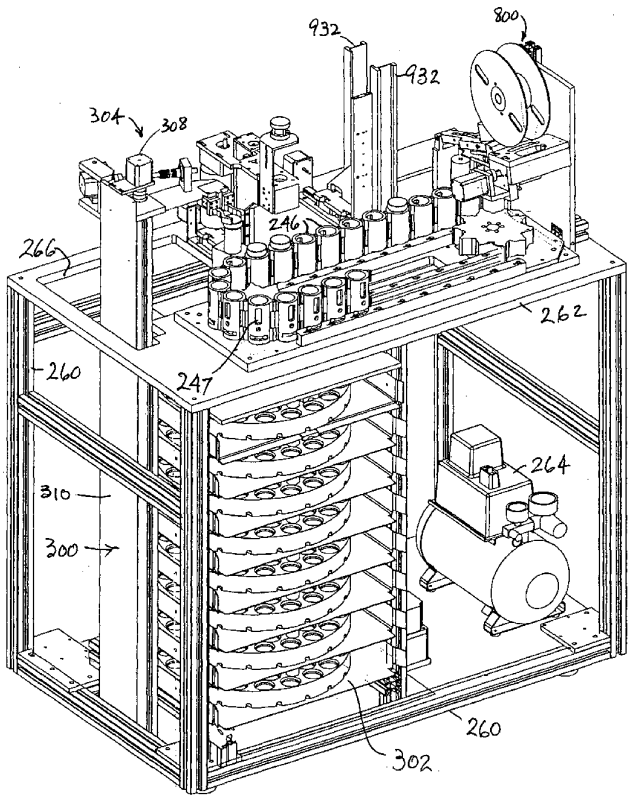
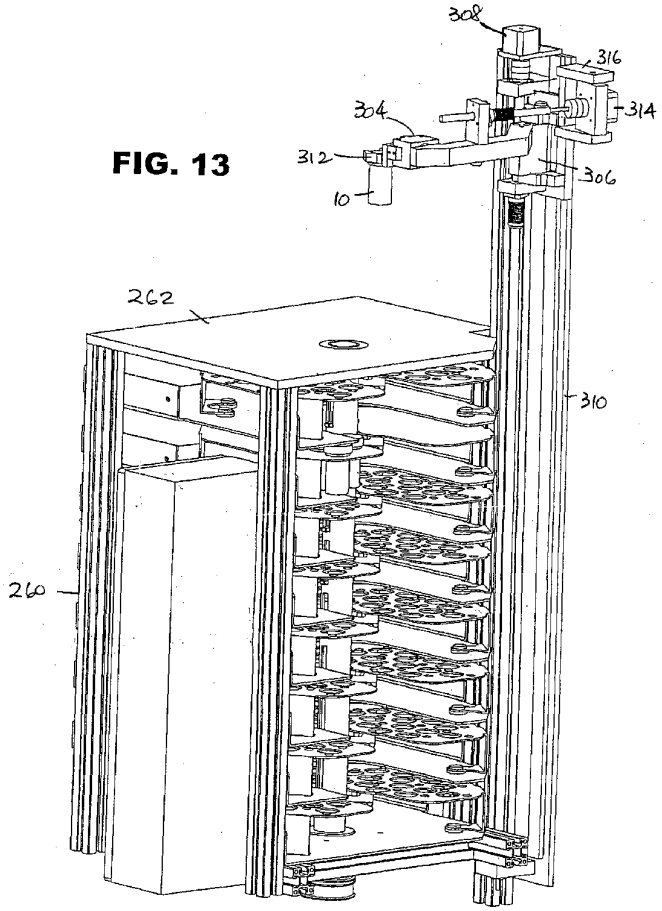


FIG. 12

FIG. 13



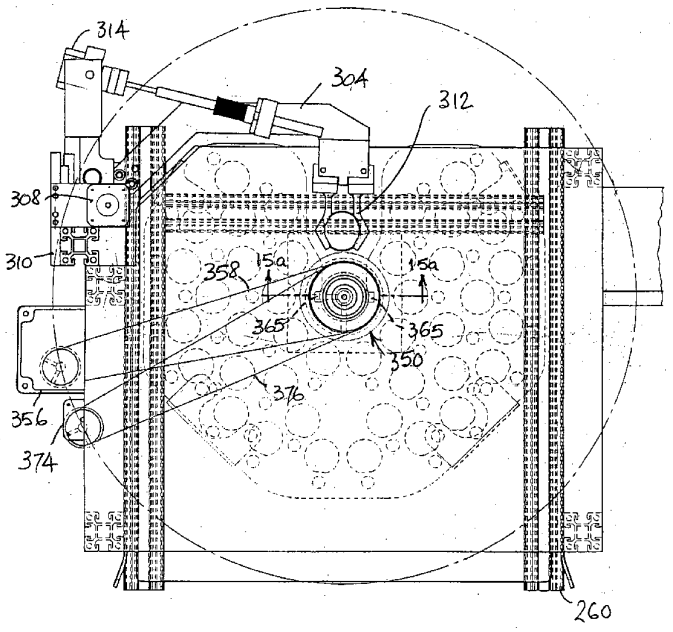


FIG. 14

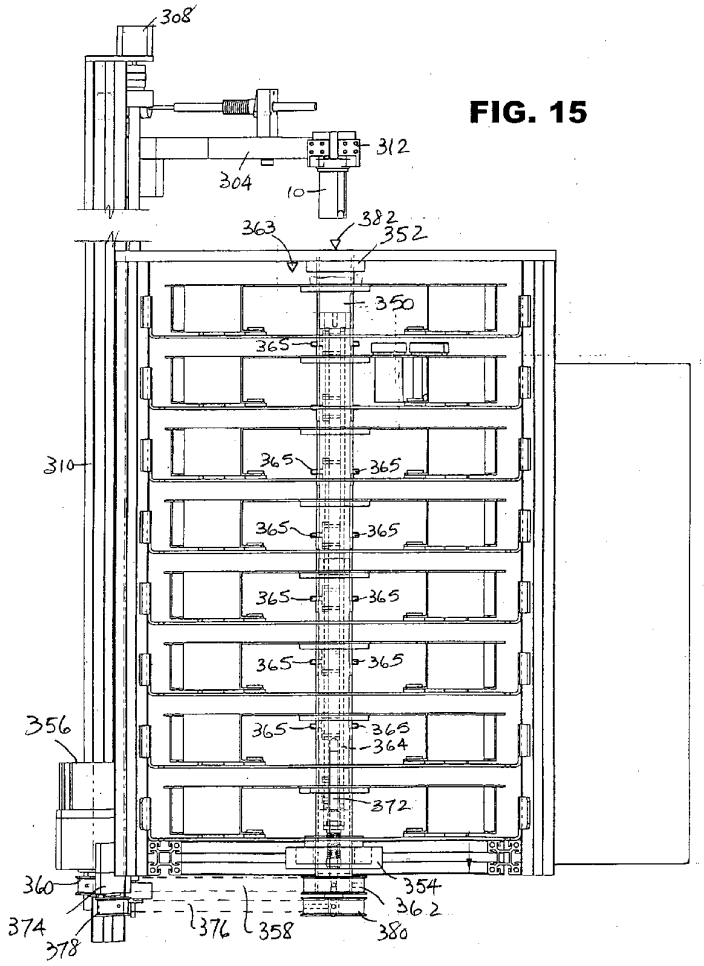

308
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FIG. 15

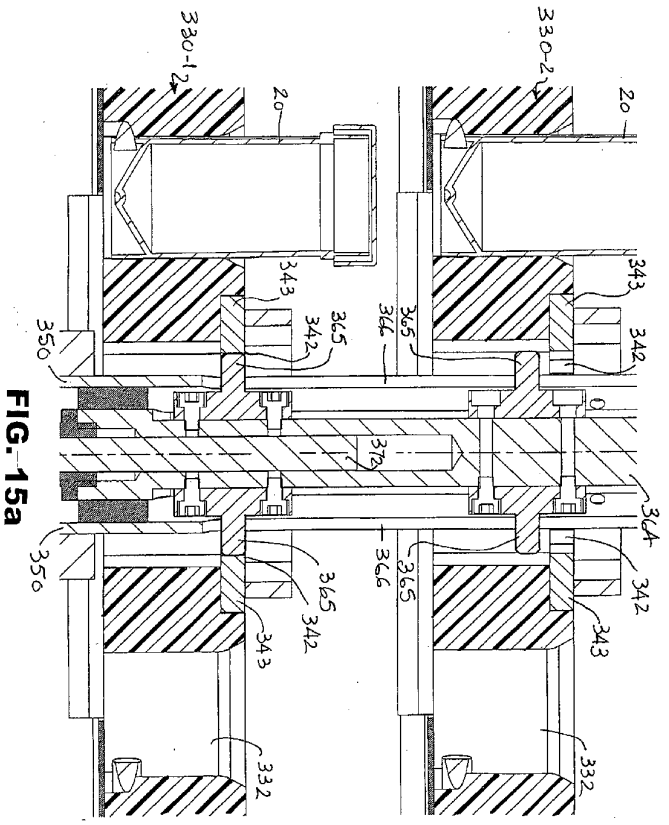


FIG. 15a

FIG. 18

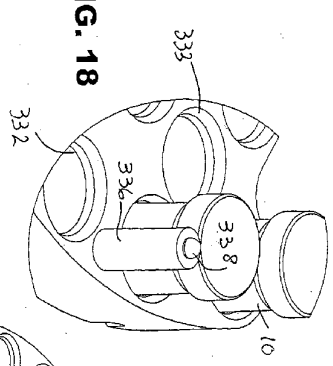


FIG. 17

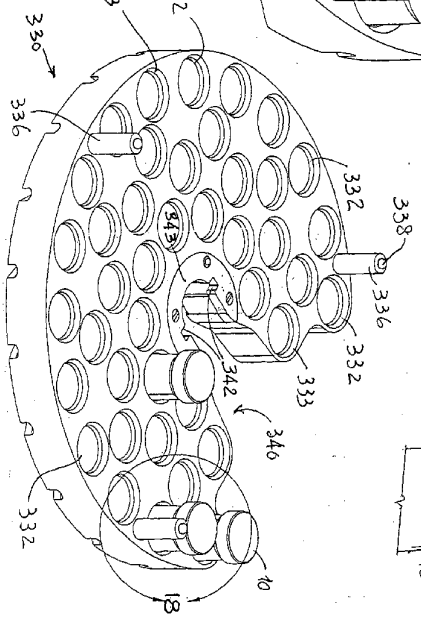
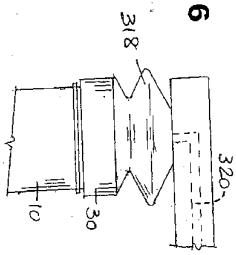


FIG. 16



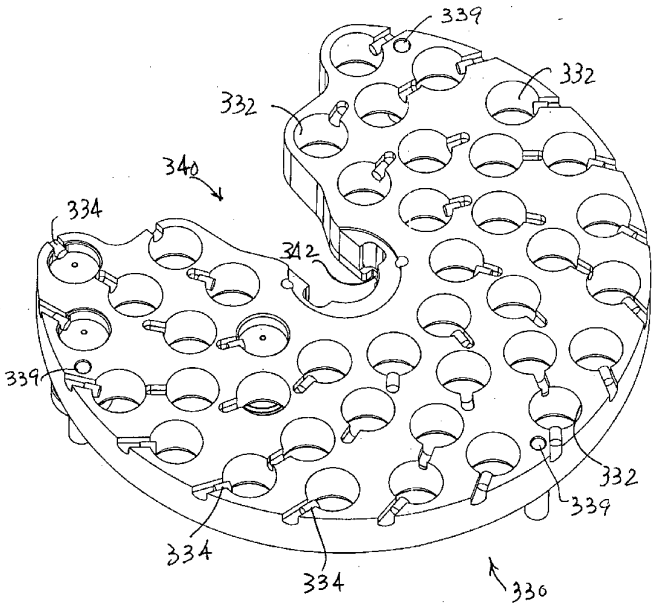


FIG. 19

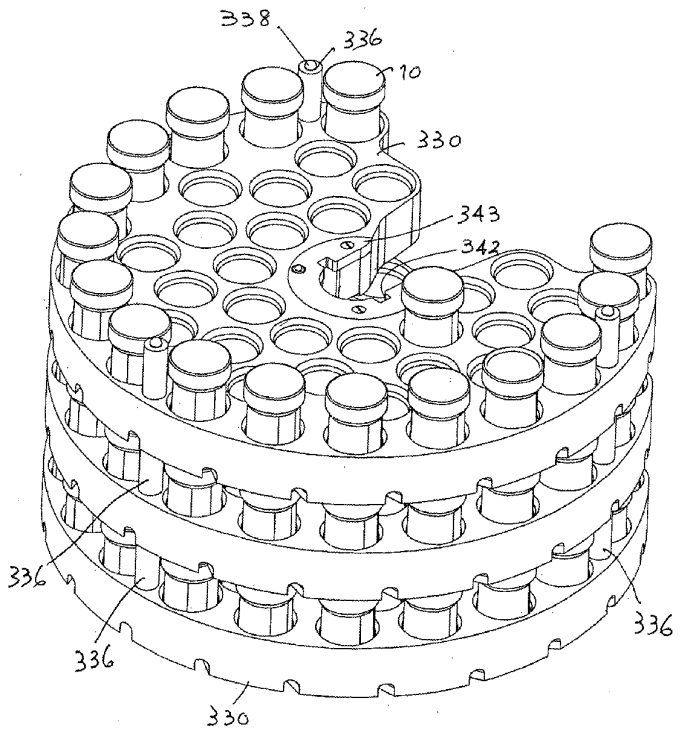


FIG. 20

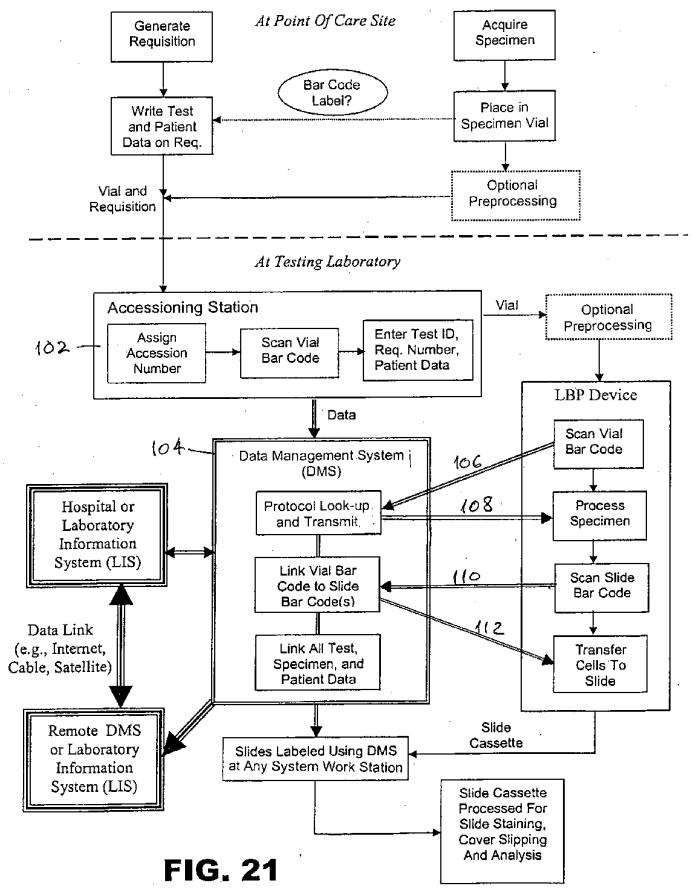
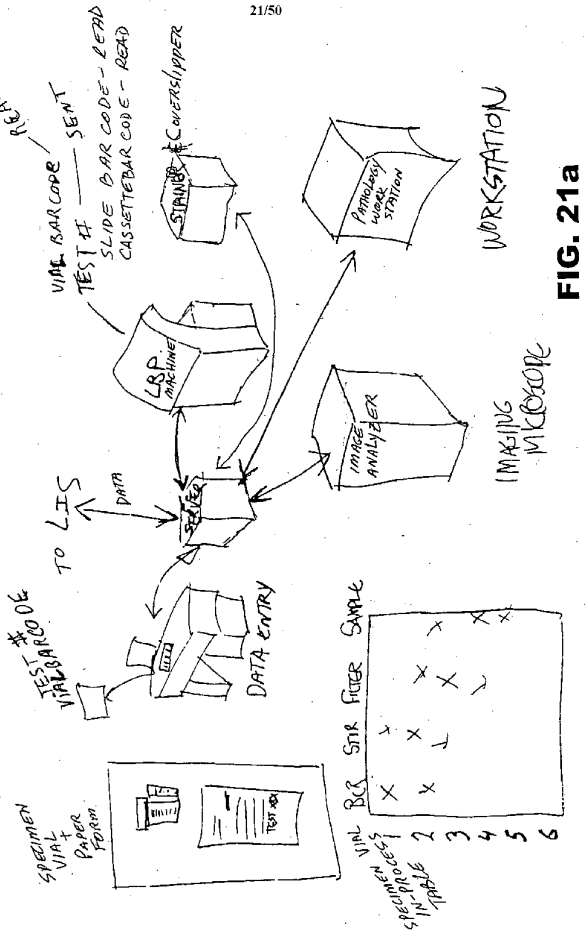

Generate Requisition
At Point Of Care Site
Acquire Specimen
Bar Code Label?
Write Test and Patient Data on Req.
Place in Specimen Vial
Vial and Requisition
Optional Preprocessing
At Testing Laboratory
Accessioning Station
102
Assign Accession Number
Scan Vial Bar Code
Enter Test ID, Req. Number, Patient Data
Vial
Optional Preprocessing
LBP Device
Data
104
Data Management System (DMS)
106
Scan Vial Bar Code
Hospital or Laboratory Information System (LIS)
Protocol Look-up and Transmit
108
Process Specimen
Link Vial Bar Code to Slide Bar Code(s)
110
Scan Slide Bar Code
Data Link (e.g., Internet, Cable, Satellite)
112
Link All Test, Specimen, and Patient Data
Transfer Cells To Slide
Remote DMS or Laboratory Information System (LIS)
Slide Cassette
Slides Labeled Using DMS at Any System Work Station
Slide Cassette Processed For Slide Staining, Cover Slipping And Analysis

FIG. 21


READ
VIAL BARCODE
TEST # —— SENT
SLIDE BAR CODE - LEAD
CASSETTEBAR CODE - READ
STAINER
COVERSLIPPER
PATHOLOGY WORK STATION
WORKSTATION
LBP MACHINE
IMAGE ANALYZER
IMAGING MICROSCOPE
TO LIS
DATA
SERVER
TEST #BARCODE
VIALBARCODE
DATA ENTRY
SPECIMEN VIAL PAPER FORM
TEST #
VIAL BCR SMR FICHER SAMPLE
SPECIMEN TYPE IN-HOUSE TEST
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3
4
5
6

FIG. 21a

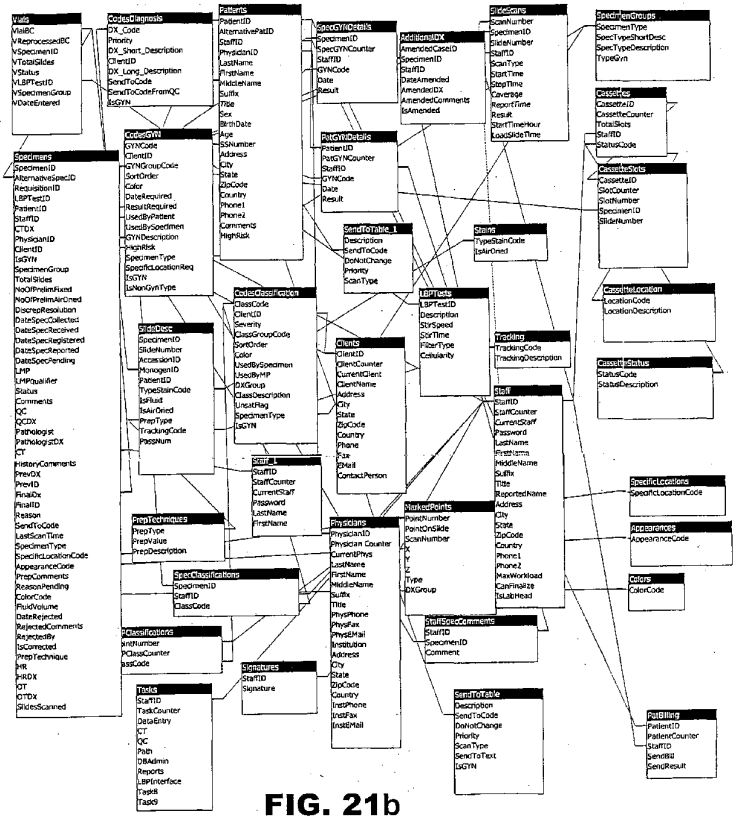

Visits
VisitID
VReprocessedIBC
VSpecimenID
VTotalSlides
VStatus
VLBPTestID
VSpecimenGroup
VDateEntered
CodesDiagnosis
DX_Code
Priority
DX_Short_Description
ClientID
DX_Long_Description
SendToCode
SendToCodeFromQC
IsGYN
Patients
PatientID
AlternativePatID
StaffID
PhysicianID
LastName
FirstName
MiddleName
Suffix
Title
Sex
BirthDate
Age
SSNumber
Address
City
State
ZipCode
Country
Phone1
Phone2
Comments
HighRisk
SpecGYNDetails
SpecimenID
SpecGYNCounter
StaffID
GYNCode
Date
Result
AdditionalDX
AmendedCaseID
SpecimenID
StaffID
DateAmended
AmendedDX
AmendedComments
IsAmended
SlideScans
ScanNumber
SpecimenID
SlideNumber
StaffID
ScanType
StartTime
StopTime
Coverage
ReportTime
Result
StartTimeHour
LoadSlideTime
SpecimenGroups
SpecimenType
SpecTypeShortDesc
SpecTypeDescription
TypeGyn
CassetteSizes
CassetteID
CassetteCounter
TotalSlots
StaffID
StatusCode
CassetteSlots
CassetteID
SlotCounter
SlotNumber
SpecimenID
SlideNumber
CodesGYN
GYNCode
ClientID
GYNGroupCode
SortOrder
Color
DateRequired
ResultRequired
UsedByPatient
UsedBySpecimen
GYNDescription
HighRisk
SpecimenType
SpecificLocationReq
IsGYN
IsNonGynType
PatGYNDetails
PatientID
PatGYNCounter
StaffID
GYNCode
Date
Result
SendToTable_1
Description
SendToCode
DoNotChange
Priority
ScanType
Stains
TypeStainCode
IsNrOned
Specimens
SpecimenID
AlternativeSpecID
RequisitionID
LBPTestID
PatientID
StaffID
CTDX
PhysicianID
ClientID
IsGYN
SpecimenGroup
TotalSlides
NoOfPrelimFixed
NoOfPrelimAirDried
DiscrepResolution
DateSpecCollected
DateSpecReceived
DateSpecRegistered
DateSpecReported
DateSpecPending
LMP
LMPqualifier
Status
Comments
QC
QCDX
Pathologist
PathologistDX
CT
HistoryComments
PrevDX
PrevID
FinalDx
FinalID
Reason
SendToCode
LastScanTime
SpecimenType
SpecificLocationCode
AppearanceCode
PrepComments
ReasonPending
ColorCode
FluidVolume
DateRejected
RejectedComments
RejectedBy
IsCorrected
PrepTechnique
HR
HxDX
QT
IOTDX
SlidesScanned
CodesClassification
ClassCode
ClientID
Severity
ClassGroupCode
SortOrder
Color
UsedBySpecimen
DXGroup
ClassDescription
UnsatFlag
SpecimenType
IsGYN
SlideDisc
SpecimenID
SlideNumber
AccessionID
MonogenID
PatientID
TypeStainCode
IsRuled
IsAirDried
PrepType
TrackingCode
PassNum
Clients
ClientID
ClientCounter
CurrentClient
ClientName
Address
City
State
ZipCode
Country
Phone
Fax
EMail
ContactPerson
LBPTests
LBPTestID
Description
StrSized
StrTime
FilterType
Cellularity
Tracking
TrackingCode
TrackingDescription
CassetteLocation
LocationCode
LocationDescription
CassetteStatus
StatusCode
StatusDescription
Staff
StaffID
StaffCounter
CurrentStaff
Password
LastName
FirstName
MiddleName
Suffix
Title
ReportedName
Address
City
State
ZipCode
Country
Phone1
Phone2
HasWorkload
CanFinalize
IsLabHead
Staff_1
StaffID
StaffCounter
CurrentStaff
Password
LastName
FirstName
PrepTechniques
PrepType
PrepValue
PrepDescription
SpecClassifications
SpecimenID
StaffID
ClassCode
Classifications
UnitNumber
PClassCounter
ClassCode
Signatures
StaffID
Signature
Tasks
StaffID
TaskCounter
DataEntry
CT
QC
Path
DBAdmin
Reports
LBPInterface
Task6
Task5
PhysicianS
PhysicianID
Physician Counter
CurrentPhys
LastName
FirstName
MiddleName
Suffix
Title
PhysPhone
PhysFax
PhysEMail
Institution
Address
City
State
ZipCode
Country
InstPhone
InstFax
InstEMail
StainedPoints
PointNumber
PointOnSlide
ScanNumber
X
Y
Z
Type
IDXGroup
StainCodeComments
StaffID
SpecimenID
Comment
SendToTable
Description
SendToCode
DoNotChange
Priority
ScanType
SendToText
IsGYN
SpecificLocations
SpecificLocationCode
Appearances
AppearanceCode
Colors
ColorCode
PatBilling
PatientID
PatientCounter
StaffID
SendBill
SendResult

FIG. 21b

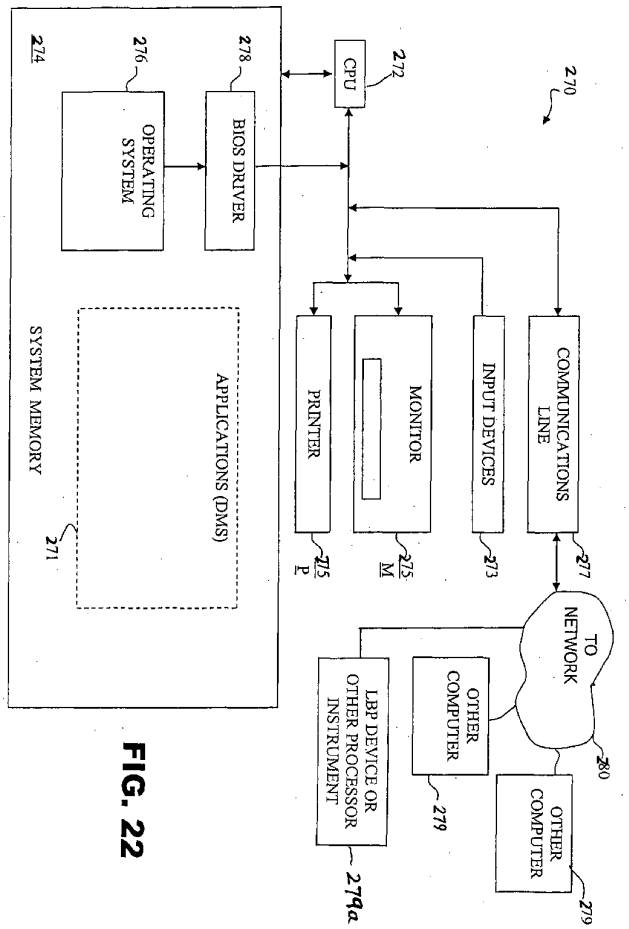

270
CPU
272
274
276
OPERATING SYSTEM
278
BIOS DRIVER
SYSTEM MEMORY
271
APPLICATIONS (DMS)
PRINTER
275 P
MONITOR
275 M
INPUT DEVICES
273
COMMUNICATIONS LINE
277
TO NETWORK
280
OTHER COMPUTER
279
OTHER COMPUTER
279
LBP DEVICE OR OTHER PROCESSOR INSTRUMENT
279a

FIG. 22

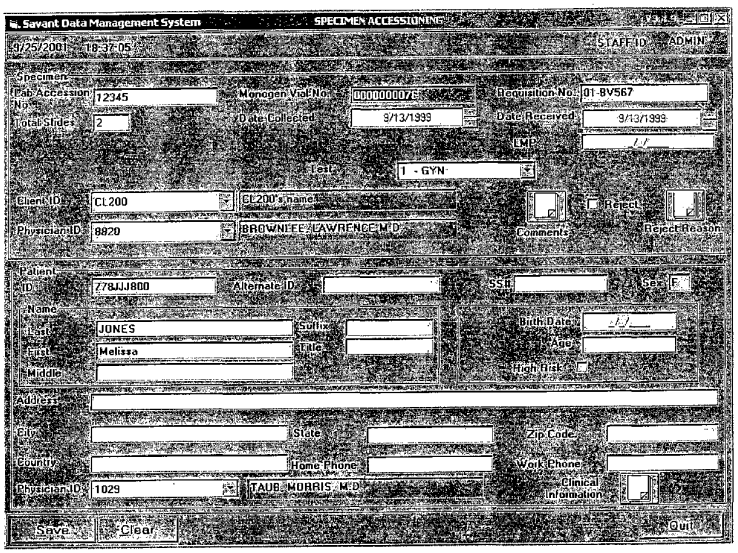

Savant Data Management System
SPECIMEN ACCESSIONING
9/25/2001 18:37:05
STAFF ID ADMIN
Specimen
Lab Accession No 12345
Total Slides 2
Monogen Vial No 00000007E
Date Collected 9/13/1999
Registration No 01-BV567
Date Received 9/13/1999
LMP
Test 1 - GYN
Client ID CL200
CL200's name
Physician ID 8820
BROWNFIELD,LAWRENCE,M.D.
Comments
Reject
Reject Reason
Patient
ID Z78JJJ800
Alternate ID
SS#
Sex F
Name
Last JONES
First Melissa
Middle
Suffix
Title
Birth Date
Area
High Risk
Address
City
State
Zip Code
County
Home Phone
Work Phone
Physician ID 1029
TAUB, MORRIS, M.D.
Clinical Information
Save
Clear
Quit

FIG. 23

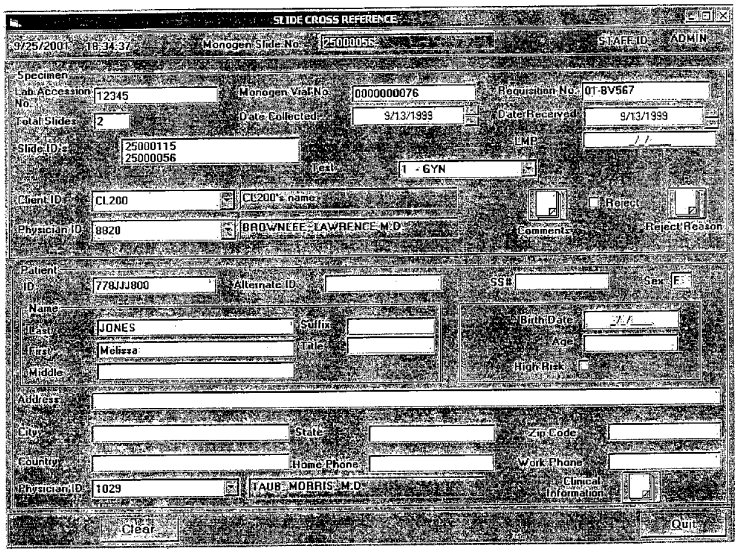
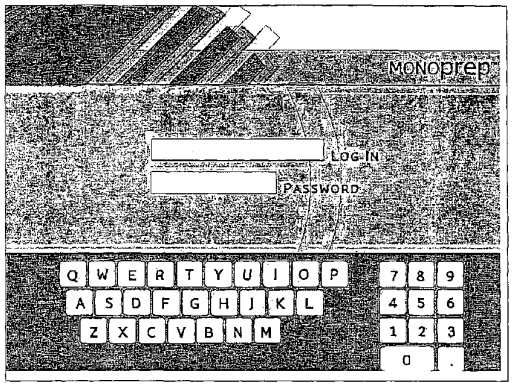

SLIDE CROSS REFERENCE
9/25/2001 18:34:37
Monogen Slide No:
25000056
STAFF ID: ADMIN
Specimen
Lab Accession No:
12345
Monogen Visit No:
0000000076
Requisition No:
01-BV567
Total Slides:
2
Date Collected:
9/13/1999
Date Received:
9/13/1999
LMP:
Slide ID:
25000115
25000056
Test:
1 - GYN
Client ID:
CL200
CL200's name:
Reject:
Physician ID:
8820
BROWNEFF-LAWRENCE M.D.
Comments:
Reject Reason
Patient
ID:
778JJJ800
Alternate ID:
SS#
Sex:
F
Name
Last:
JONES
Suffix:
Birth Date:
First:
Melissa
Title:
Age:
Middle:
High Risk:
Address:
City:
State:
Zip Code:
Country:
Home Phone:
Work Phone:
Physician ID:
1029
TAUB MORRIS M.D.
Clinical Information:
Clear
Quit

FIG. 24


MONOprep
LOG-IN
PASSWORD
Q W E R T Y U I O P
A S D F G H J K L
Z X C V B N M
7 8 9
4 5 6
1 2 3
0 .

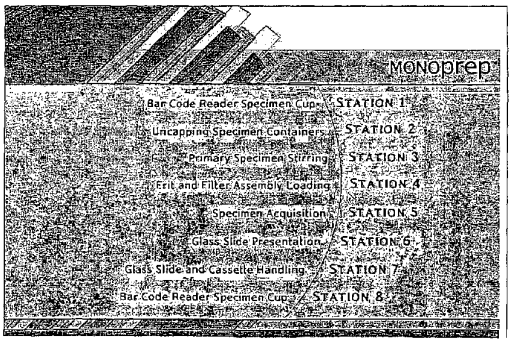

MONOprep
Bar Code Reader Specimen Cups
STATION 1
Uncapping Specimen Containers
STATION 2
Primary Specimen Stirring
STATION 3
Frit and Filter Assembly Loading
STATION 4
Specimen Acquisition
STATION 5
Glass Slide Presentation
STATION 6
Glass Slide and Cassette Handling
STATION 7
Bar Code Reader Specimen Cups
STATION 8

FIG. 25

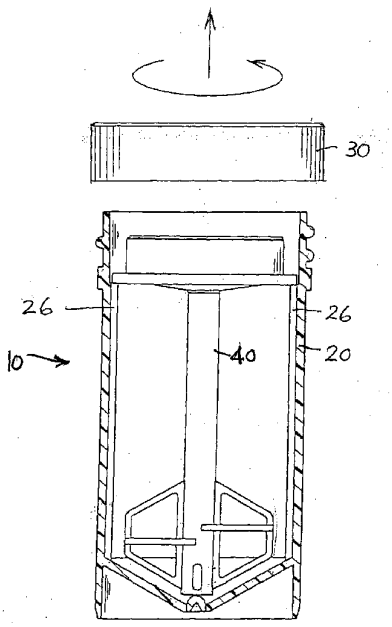
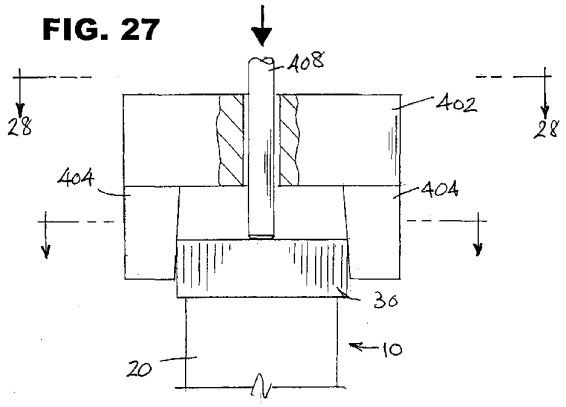


FIG. 26

FIG. 27


408
402
28
28
404
404
30
10
20

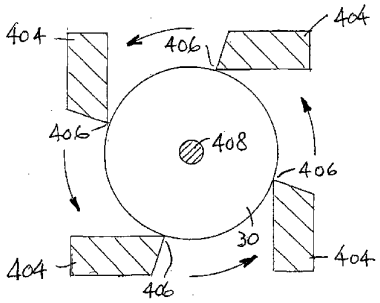

404
406
404
406
408
406
30
404
404
406

FIG. 28

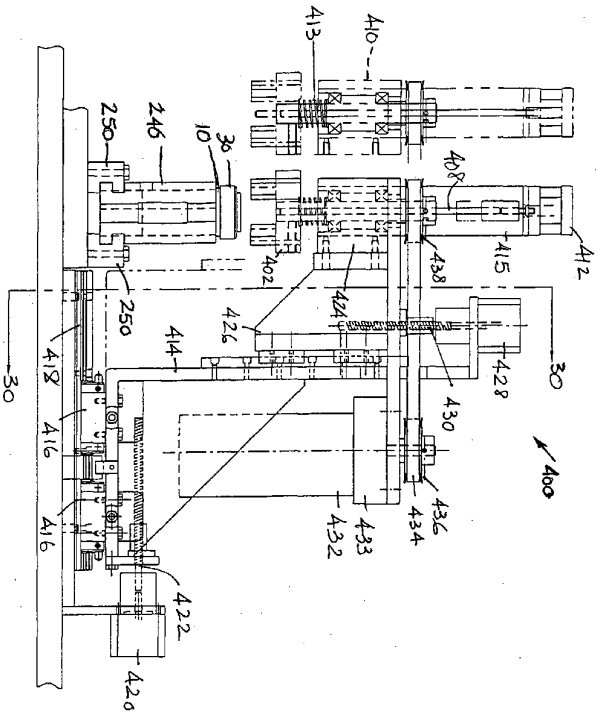

413
410
250
246
10
30
408
412
415
438
402
424
426
414
428
30
412
416
430
400
436
434
432
433
416
422
420

FIG. 29

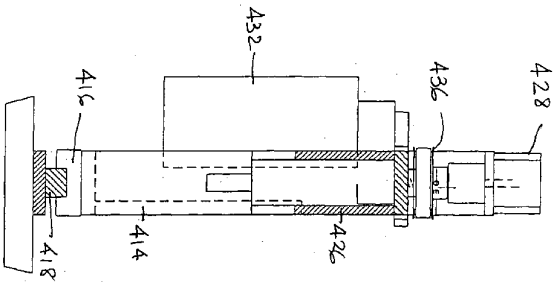


FIG. 30

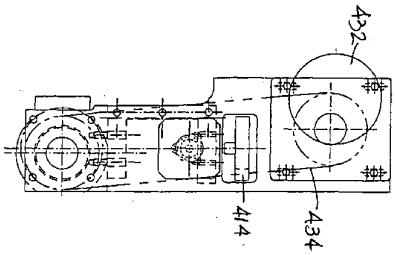


FIG. 31

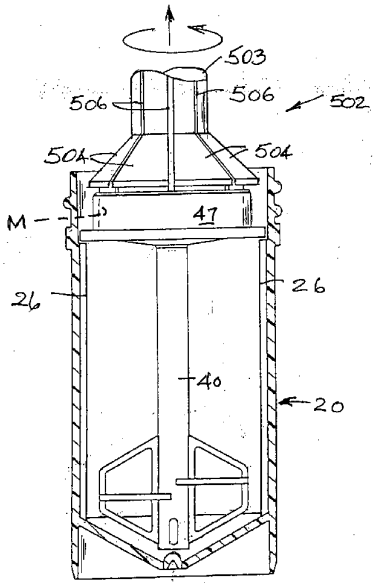


FIG. 32

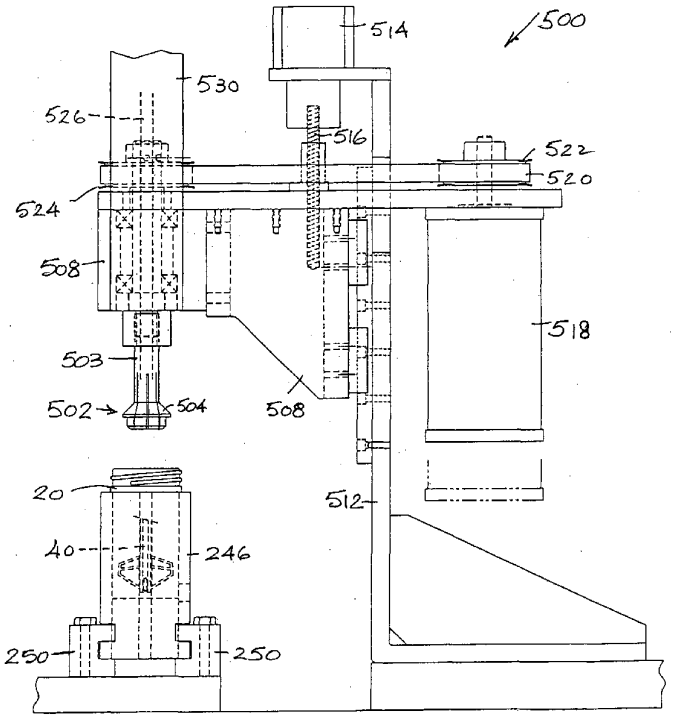

514
500
530
526
516
522
520
524
508
518
503
502
504
508
20
512
40
246
250
250

FIG. 33

FIG. 34

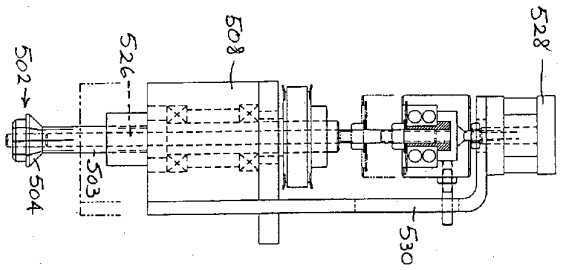
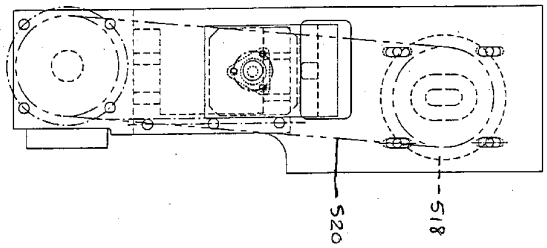


FIG. 35



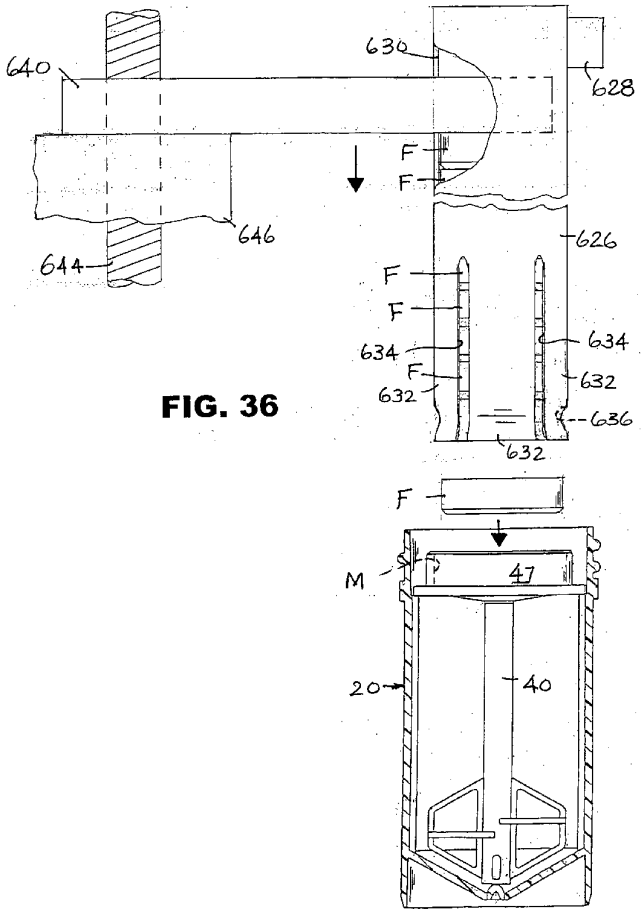


FIG. 36

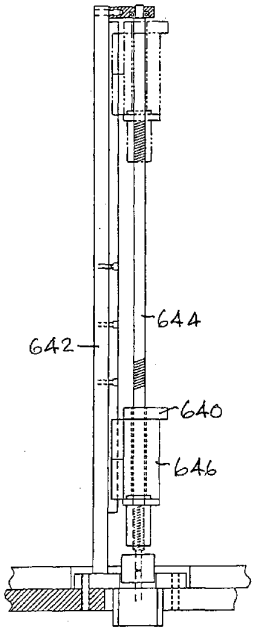


FIG. 38

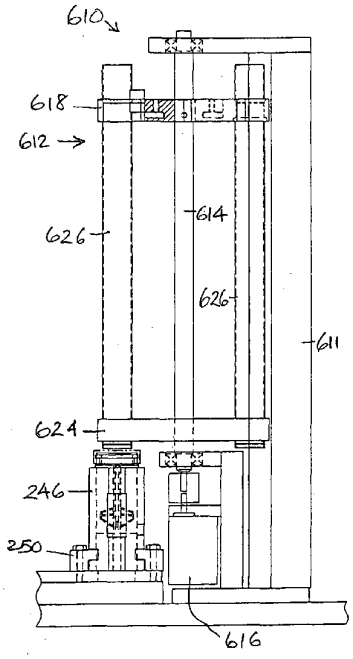


FIG. 37

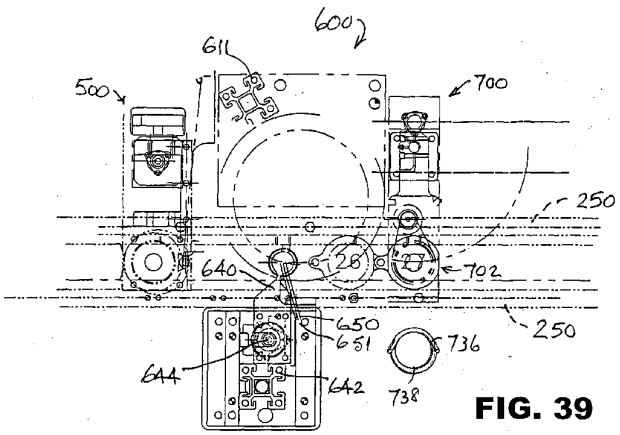

600
611
500
700
250
640
28
702
650
651
736
250
644
642
738

FIG. 39

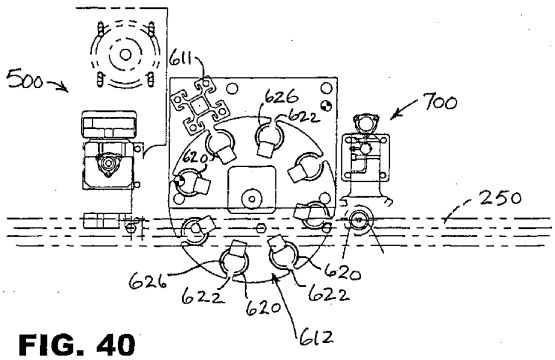

611
500
626
622
700
620
250
626
622
620
622
620
612

FIG. 40

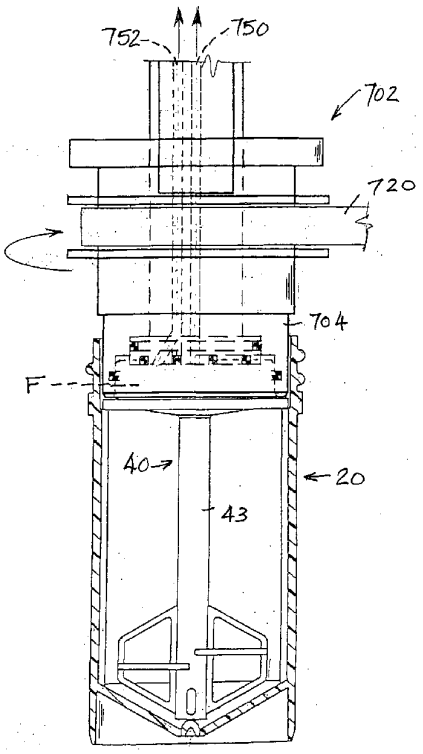


FIG. 41

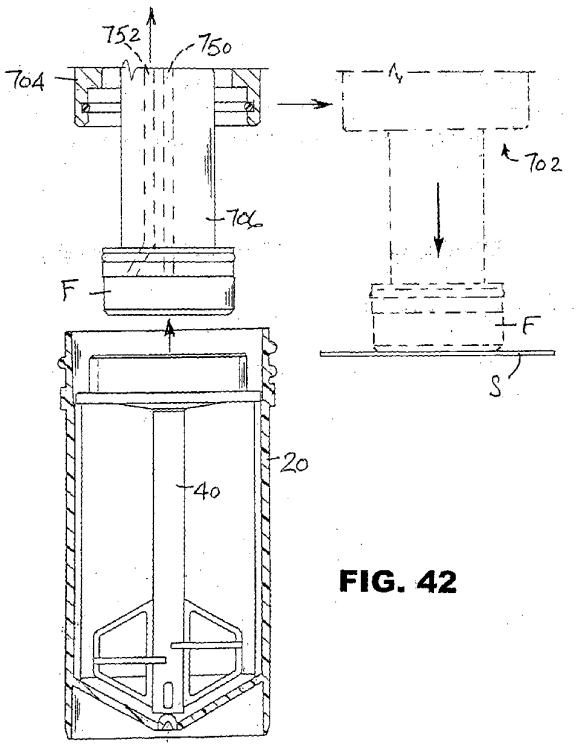


FIG. 42

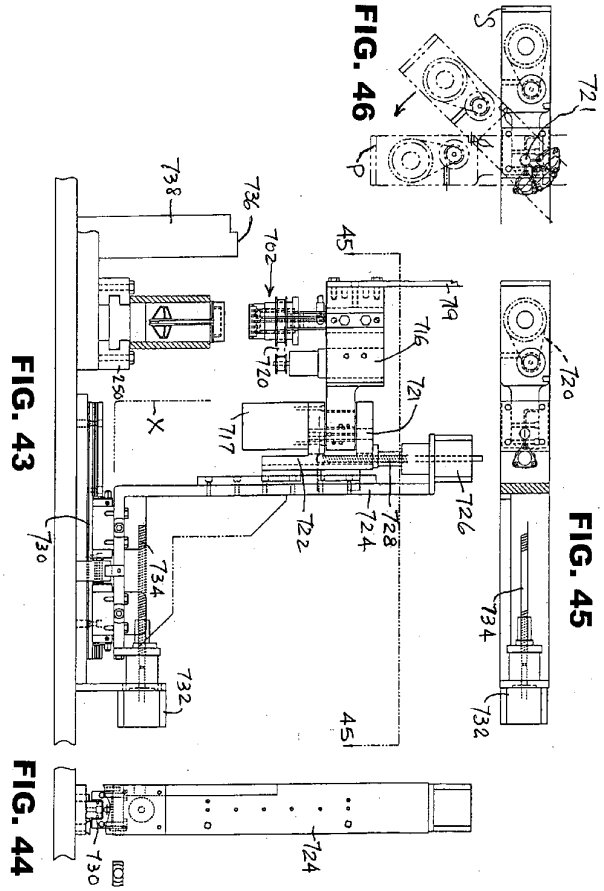


FIG. 43

FIG. 44

FIG. 45

FIG. 46

BUBBLE FLOW METER

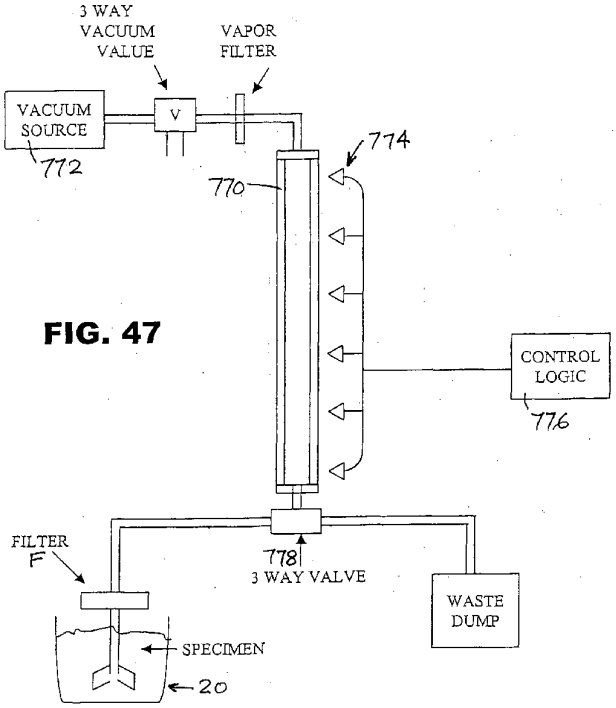


FIG. 47

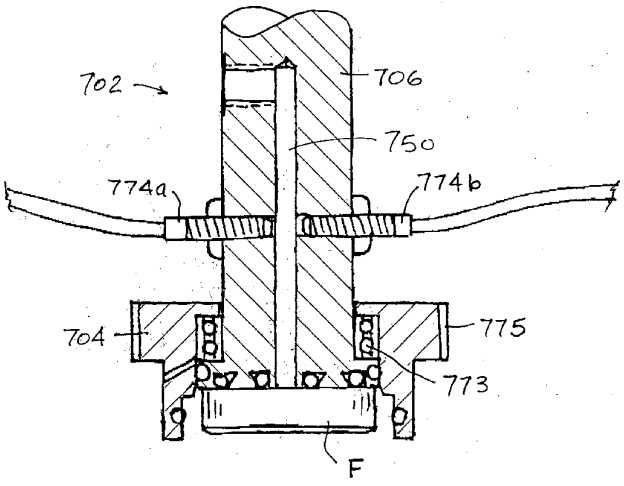


FIG. 47a

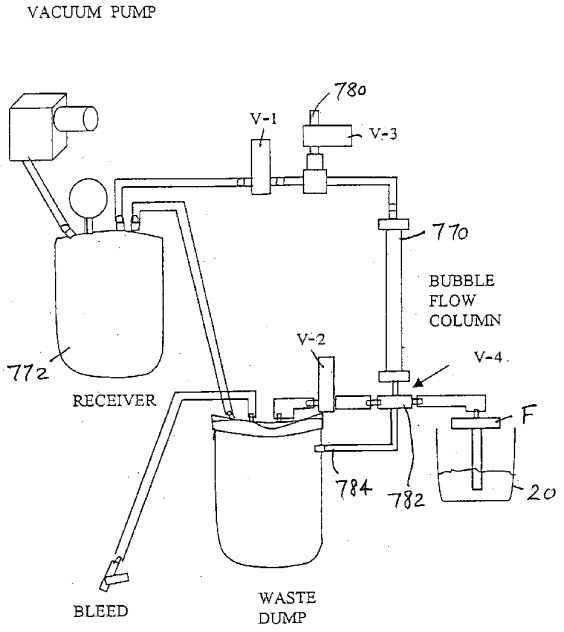

VACUUM PUMP
780
V-1
V-3
770
BUBBLE
FLOW
COLUMN
V-2
V-4
772
RECEIVER
F
784
782
20
BLEED
WASTE
DUMP

FIG. 48

FLOW SENSOR OPERATION

SEQUENCE OF OPERATIONS

	V-1	V-2	V-3	V-4
#1				
MEASURED PULL	ON	OFF	OFF	OFF
#2				
TAMP PRINT	OFF	ON	OFF	OFF
#3				
PURGE	OFF	OFF	ON	ON

FIG. 49

FIG. 50

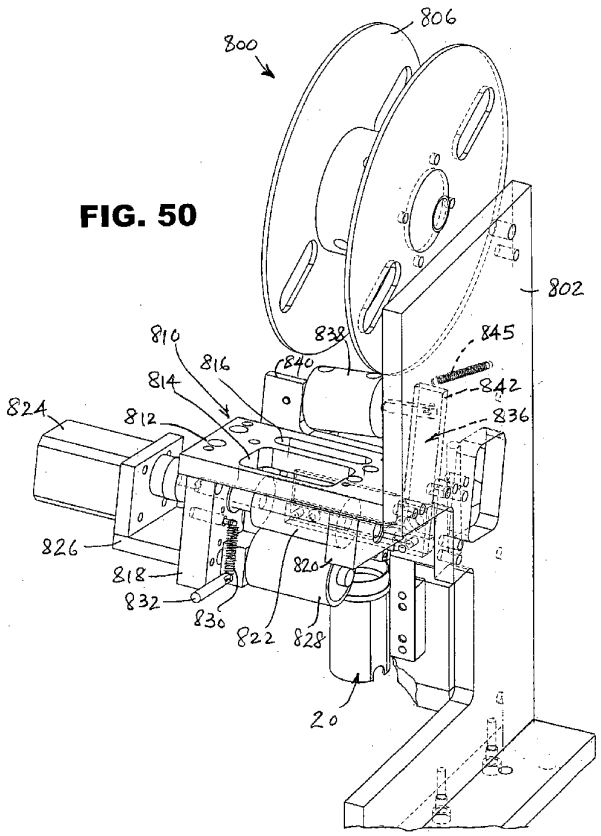
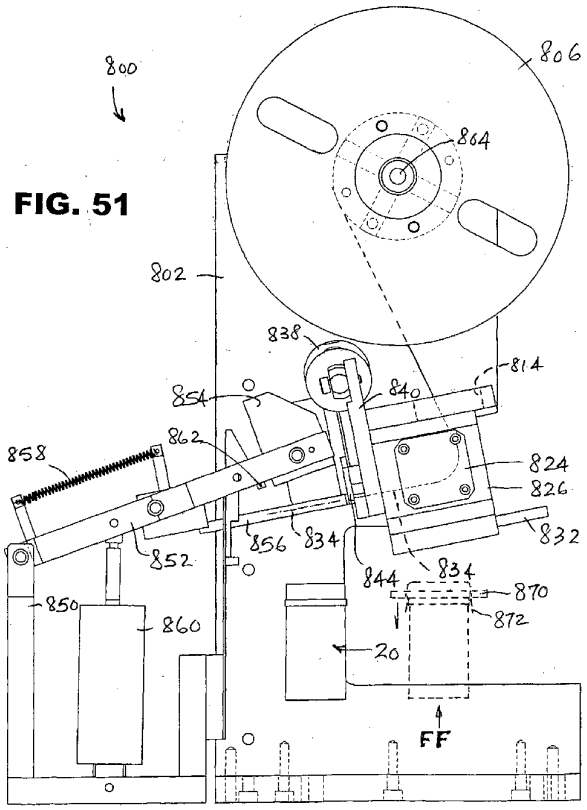

800
806
802
838
845
840
842
836
810
816
814
812
824
826
818
832
830
822
828
820
20

FIG. 51


800
806
864
802
838
814
854
840
858
862
824
826
856
834
832
852
844
834
870
850
860
872
20
FF

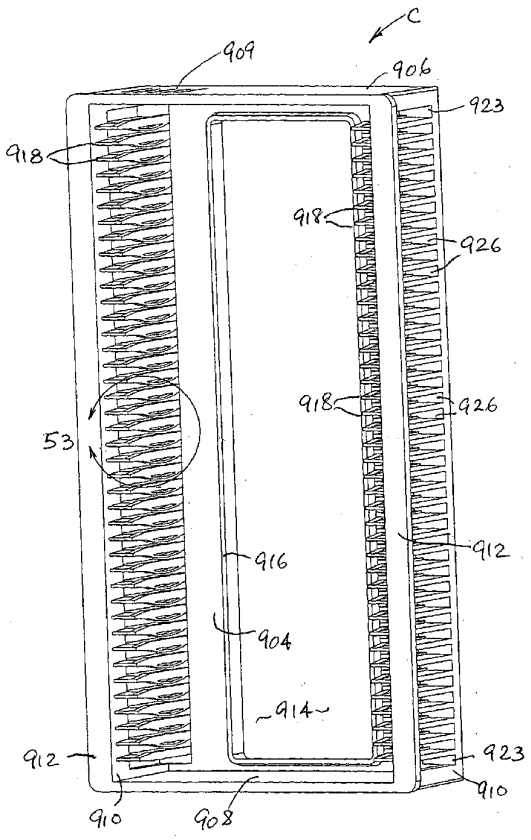

C
909
906
923
918
918
926
918
926
53
916
912
904
914
912
923
910
910
908

FIG. 52

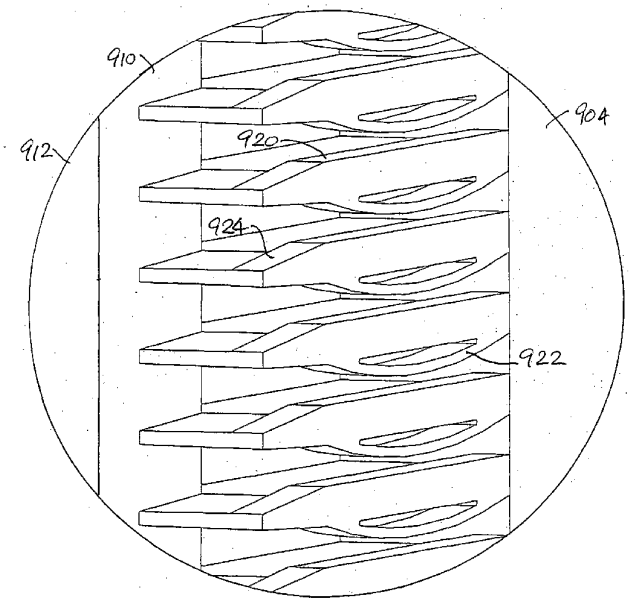


FIG. 53

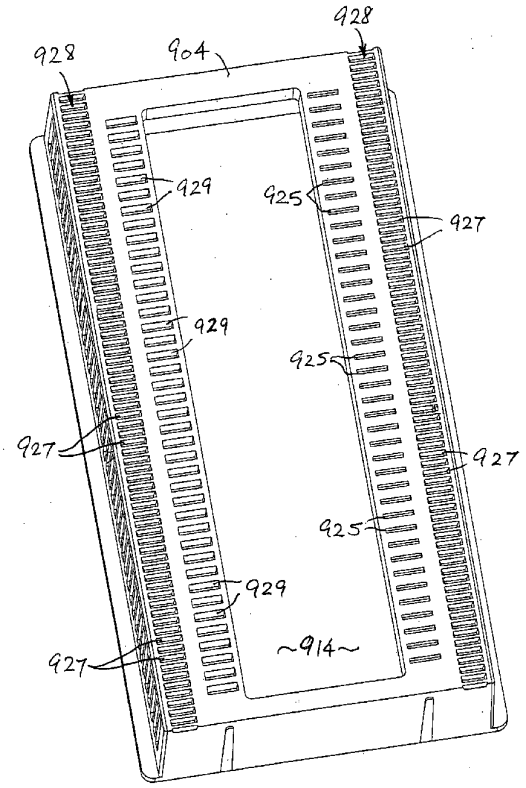


FIG. 54

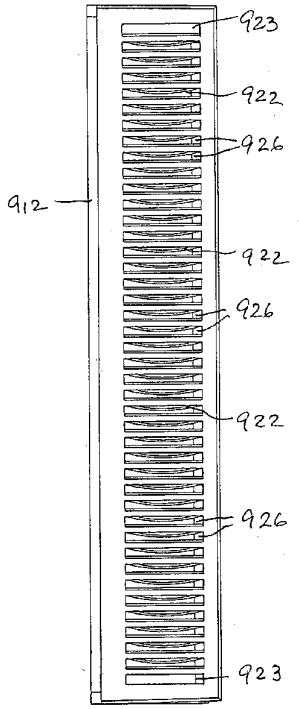


FIG. 55

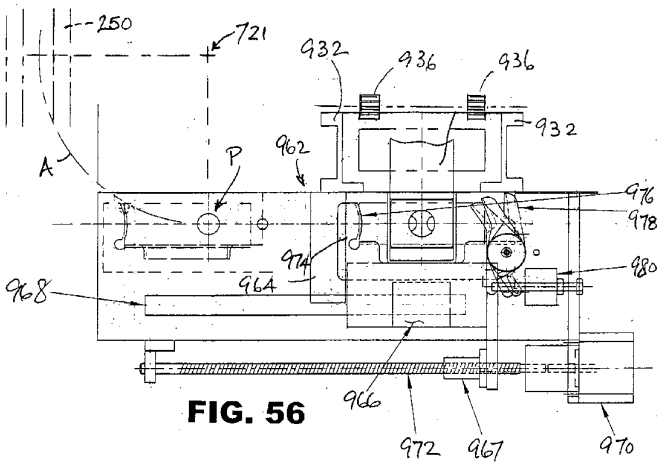

250
721
932
936
936
932
A
P
962
976
978
974
980
964
968
966
972
967
970

FIG. 56

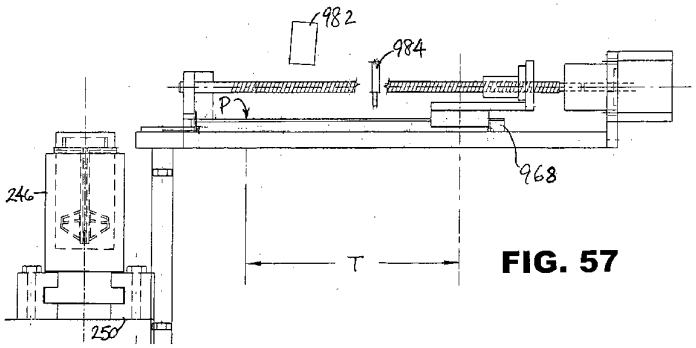

982
984
P
968
246
T
250

FIG. 57

【国際公開パンフレット（コレクトバージョン）】

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International Bureau

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PCT

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(51) International Patent Classification[7]: G01N 1/28, 35/02, 33/483

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(22) International Filing Date: 21 October 2002 (21.10.2002)

(25) Filing Language: English

(26) Publication Language: English

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60/372,080	15 April 2002 (15.04.2002)	US
60/373,658	19 April 2002 (19.04.2002)	US

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(72) Inventors; and

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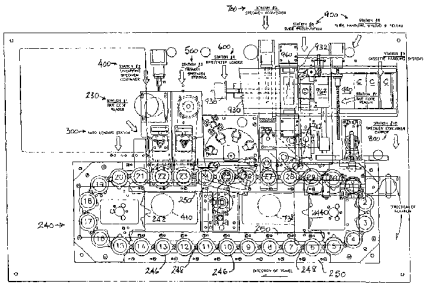
(54) Title: AUTOMATED SYSTEM AND METHOD FOR PROCESSING MULTIPLE LIQUID-BASED SPECIMENS



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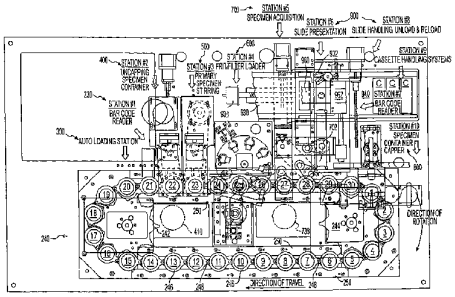

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AUTOMATED SYSTEM AND METHOD FOR PROCESSING MULTIPLE LIQUID-BASED SPECIMENS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of commonly owned U.S. provisional application Nos. 60/330,092, filed October 19, 2001, 60/372,080, filed April 15, 2002, and 60/373,658, filed April 19, 2002, all of which are incorporated herein by reference. This application also is related to commonly owned U.S. non-provisional application No. 10/122,151, filed April 15, 2002, which is also incorporated herein by reference.

TECHNICAL FIELD

The present disclosure is directed to apparatus and methods for collecting and processing specimens of particulate matter-containing liquid, e.g., biological fluid, including collecting and depositing onto a microscope slide or other surface a uniform layer of particulates therefrom (e.g., cells) suitable for examination (e.g., use in cytology protocols).

BACKGROUND ART

Diagnostic cytology, particularly in the area of clinical pathology, bases cytological interpretations and diagnoses on examination of cells and other microscopic objects. The accuracy of the screening process and diagnosis, and the preparation of optimally interpretable samples from specimens typically depends upon adequate specimen and sample preparation. In this regard the ideal sample would consist of a monolayer of substantially evenly spaced cells, which enables cytotechnologists, cytopathologists, other medical professionals, and automated screening and diagnostic equipment to view or image the cells more clearly so that abnormalities can be identified more readily, more accurately and more reproducibly. Newer methodologies such as immunocytochemistry and cytometric image analysis require preparation apparatus and methods that are safe, effective, accurate, precise, reproducible, inexpensive, efficient, fast and convenient.

Cytological examination of a sample begins with obtaining specimens including a sample of cells from the patient, which can typically be done by scraping, swabbing or brushing an area, as in the case of cervical specimens, or by collecting body fluids, such as those obtained from the chest cavity, bladder, or spinal column, or by fine needle aspiration or fine needle biopsy. In a conventional manual cytological preparation, the cells in the fluid are then transferred directly or by centrifugation-based processing steps

onto a glass microscope slide for viewing. In a typical automated cytological preparation, a filter assembly is placed in the liquid suspension and the filter assembly both disperses the cells and captures the cells on the filter. The filter is then removed and placed in contact with a microscope slide. In all of these endeavors, a limiting factor in the sample preparation protocol is adequately separating solid matter from its fluid carrier, and in easily and efficiently collecting and concentrating the solid matter in a form readily accessible to examination under a microscope.

Currently, biological specimens are collected for cytological examinations using special containers. These containers usually contain a preservative and transport solution for preserving the cytology specimen during shipment from the collection site to the diagnostic cytology laboratory. Further, cytology specimens collected from the body cavities using a swab, spatula or brush are also preserved in special containers with fixatives (e.g., alcohol or acetone fixatives) prior to transferring cells onto the slide or membrane for staining or examination. Specimen containers are known that allow a liquid-based biological specimen to be processed directly in the container so as to obtain a substantially uniform layer of cells on a collection site (in a filter housing defining a particulate matter separation chamber) that is associated with the container itself. See, for example, U.S. patent Nos. 5,301,685; 5,471,994; 6,296,764; and 6,309,362, of Raouf A. Guirguis, all of which are incorporated herein by reference.

The filtration techniques taught in these patents in practice have yielded fairly good results in terms of obtaining close to a monolayer of cells on slides, but there is room for improvement. Further, the types of specimen containers disclosed in these patents require specially configured apertured covers and adapters therefor that are designed to mate with the filter housing, and with suction equipment (e.g., a syringe or a mechanized vacuum source) used to aspirate liquid from the container and draw it through the filter. In addition, extraction of the filter so that it can be pressed against a microscope slide to transfer collected cells to the slide requires disassembly of the cooperating parts of the cover and/or adapters associated therewith. If the processing is done by automated equipment, special handling devices are required to carry out such disassembly. All of this complexity adds time, and material and labor cost to the processing required prior to the actual cytology examination.

In general, automated equipment thus far developed for processing liquid-based specimens have not performed with sufficient consistency, reliability, speed and automation to satisfy current and projected needs in cancer screening and other cytology-

based medical, analytical, screening and diagnostic procedures. The vial-based automated processing system disclosed herein provides a safe, elegant and effective solution to these problems.

SUMMARY DISCLOSURE OF THE INVENTION

The specimen vial disclosed herein houses a complete processing assembly, typically one for mixing the liquid-based specimen therein and for holding a filter on which a uniform layer of cells can be collected from the specimen. It is expected that the specimen vial would be prepackaged with a liquid preservative solution, as is commonplace, and sent to the point-of-care site for specimen collection.

The processing assembly is coupled to a simple cover for the vial by means of a simple and inexpensive releasable coupling. When the cover is removed at the point-of-care site (physician's office, clinic, hospital, etc.), the processing assembly remains with the cover to allow medical personnel easy access to the container interior for insertion of a biological specimen into the vial. The cover, along with the attached processing assembly, is then replaced to seal the vial. The vial may then be sent to a laboratory for processing.

When the vial is manipulated in a simple way while still closed, the processing assembly detaches from the cover and remains in the vial for access by automated or manual laboratory equipment when the cover is subsequently removed. In a preferred embodiment, a downward force on the center of the cover is all that is required to detach the processing assembly from the cover. In contrast with the prior art specimen vials discussed above, the vial of the present invention requires no further interaction with the cover, which can be removed by a simple uncapping device and is discarded to avoid contamination. Ribs inside the vial support the processing assembly in the proper position for access during processing. This self-contained vial and processing assembly arrangement minimizes human operator exposure to biohazards, such as tuberculosis or other pathogens in sputum or in other specimens types, such as urine, spinal tap fluid, gastric washings, fine-needle aspirates, and gynecological samples.

The automated specimen processing apparatus disclosed herein is referred to as the "LBP" device (for liquid-based preparation), and is designed to produce slides of high quality and consistency. The LBP device also can be interfaced with a device for detecting and/or quantifying multiple morphologic, cytochemical, and/or molecular changes at the cellular level.

During the past two years or so, a review of the literature and reanalysis of existing data have led to the identification of a panel of molecular diagnostic reagents that are

capable of detecting and characterizing lung cancer, which is the most common cancer, with high sensitivity and specificity. See, for instance, commonly owned U.S. patent application Nos. 10/095,297 and 10/095,298, both filed March 12, 2002, and No. 10/241,753, filed September 12, 2002. Here, the cells can be reacted with antibodies and or nucleic-acid "probes" that identify a pattern of changes that is consistent with a diagnosis of cancer. The molecular system can utilize algorithms fine tuned for that tumor heterogeneity.

Identifying molecular changes at the cellular level is one of the ways cancer can be detected early and at a more curable stage. Such molecular diagnostic devices can be used for early detection and diagnosis with the necessary sensitivity and specificity to justify their use as population-based screens for individuals who are at-risk for developing cancer. Such a molecular diagnostic device also can be used to characterize the tumor, thereby permitting the oncologist to stratify his/her patients, to customize therapy, and to monitor patients in order to assess therapeutic efficacy and disease regression, progression or recurrence. The availability of such tests will also foster the development of new and more effective therapeutic approaches for the treatment of early stage disease.

Such molecular diagnostics are designed to balance cost and test performance. While screening tests must exhibit high sensitivity and specificity, cost is always a critical factor, as the tests are typically directed to performing on a large number of individuals who, while at-risk, do not typically have symptomatic evidence of the disease. In this respect, the present LBP device can be interfaced with a molecular diagnostic device to develop a system for automatically diagnosing cancer, with a minimum or no human intervention. Alternatively, the present LBP device can be interfaced with a pathology work station, where medical professionals can observe individual slides prepared by the LBP device. The resulting diagnosing system, regardless whether an automated device or a manual observation device is interfaced, can be interfaced with an integrated data management system based on specialized software and a computer operating system to manage data entry and exchange of information, and network with the laboratory and hospital information systems.

The present LBP device transports multiple specimen vials of the novel type mentioned above sequentially through various processing stations and produces fixed specimens on slides, each slide being bar-coded and linked through a data management system to the vial and the patient from which it came. Fresh slides are automatically removed one at a time from a cassette, and each is returned to the same cassette after a

specimen is fixed thereon. Multiple slide cassettes can be loaded into the LBP device, and the device will automatically draw fresh slides from the next cassette after all of the slides of the preceding one have been used. The slide cassettes preferably are configured for liquid immersion and interfacing with automated staining equipment that will stain the specimens without having to remove the slides from the cassette. In this regard the cassettes preferably have slots that allow for liquid drainage, and slots or other means that cooperate with the hooks normally used in the staining equipment to suspend other types of slide holders. The same slide cassettes are also configured to interface with automated diagnostic equipment and other devices that are part of an integrated system.

While specimen vials can be loaded into the transport manually, the full benefits of automation can be realized by using an optional vial handling system that automatically loads specimen vials for processing, and removes each one after its processing is complete. In one example of such a handling system the vials initially are loaded manually into special space-saving trays that hold up to forty-one vials each. Up to eight trays can be loaded into the LBP device, and the device will process all of them sequentially, removing one at a time from a tray and returning processed (and resealed) vials to a tray. The trays also can be used for storing and retrieving processed vials.

Each vial is transported through the LBP device on a computer-controlled conveyor, in its own receptacle. (In the example disclosed the conveyor has thirty receptacles.) The vials and the receptacles are keyed so that the vials proceed along the processing path in the proper orientation, and cannot rotate independently of its respective receptacle. They first pass a bar code reader (at a data acquisition station), where the vial bar code is read, and then proceed stepwise through the following processing stations of the LBP device: an uncapping station including a cap disposal operation; a primary mixing or dispersal station; a filter loading station; a specimen acquisition and filter disposal station; a cell deposition station; and a re-capping station. There is also a slide presentation station, at which a fresh microscope slide is presented to the specimen acquisition station for transfer of the specimen to the slide. Each of the stations operates independently on the vial presented to it by the conveyor, but the conveyor will not advance until all of the operating stations have completed their respective tasks.

The vial uncapping station has a rotary gripper that unscrews the cover from the vial, and discards it. Before doing so, however, the uncapping head presses on the center of the cover to detach the internal processing assembly from the cover. The primary mixing station has an expanding collet that grips the processing assembly, lifts it slightly

and moves (e.g., spins) it in accordance with a specimen-specific stirring protocol (speed and duration). The filter loading station dispenses a specimen-specific filter type into a particulate matter separation chamber (manifold) at the top of the processing assembly. The specimen acquisition station has a suction head that seals to the filter at the top of the processing assembly and first moves the processing assembly slowly to re-suspend particulate matter in the liquid-based specimen. Then the suction head draws a vacuum on the filter to aspirate the liquid-based specimen from the vial and past the filter, leaving a monolayer of cells on the bottom surface of the filter. Thereafter the monolayer specimen is transferred to a fresh slide, and the vial moves to the re-capping station, where a foil seal is applied to the vial.

An improved filter system ensures that the highest quality monolayer specimens are produced. Specimen liquid flows through the filter as well as substantially across the front surface of the filter. Specifically, the specimen liquid is made to have a secondary flow component across the filter surface. The secondary flow is designed to flow radially outwardly or have a substantial radial component, which creates a shearing action that flushes or washes clusters of relatively weakly adhering particulates so that a more uniformly distributed and thinner layer can be formed on the front surface of the filter. In this respect, the present system includes a peripheral outlet through which specimen liquid can flow from the area adjacent the front surface of the filter.

The filter assembly preferably has a holder, a frit seated in the holder, and a membrane filter positioned over and in contact with the outer surface of the frit. The frit can extend beyond the end of the holder. The membrane filter can be attached to the holder. The sidewall portion extending beyond the holder forms an area through which the specimen liquid can flow, creating a secondary flow. The holder can be configured so that the frit is slightly bowed outwardly at the center so that when pressure is applied to a slide during the specimen transferring step, the central portion of the frit flattens to more evenly contact the membrane filter to the slide for more effective transfer.

The manifold at the upper end of the processing assembly seats the filter assembly with the membrane filter side facing down. The manifold preferably has a substantially conically configured bottom wall that rises from the central inlet (which communicates with the depending suction tube portion of the processing assembly). The filter assembly and the conically configured bottom wall form a manifold chamber that has a slight gap at its periphery, forming a peripheral outlet, by virtue of raised members or standoffs that act

as spacers. The standoffs can have channels between them through which the specimen liquid can flow out of the manifold chamber.

Various preferred materials and possible alternatives are specified herein for several components of the system. It is to be understood that material choices are not limited to the specific materials mentioned, and that the choice of an alternate material is governed by many factors, among them functionality, molding accuracy, durability, chemical resistance, shelf life, cost, availability, and/or optical clarity (e.g., to address user requirements or marketing issues).

In its most basic aspect the invention claimed herein is directed to an automated method and automated apparatus for individually processing multiple specimens of particulate matter-containing liquid in respective containers. The containers are transported seriatim along a processing path to present them to, at least, a preprocessing apparatus adapted to preprocess the specimen fluid in any container presented to it, and then to a specimen acquisition apparatus adapted to remove preprocessed specimen fluid from any container presented to it for subsequent analytical testing or evaluation. Each apparatus is actuated in response to presentation of a container thereto so as to carry out its respective operation independently. The specimens may contain biological material.

The preprocessing apparatus may act on the specimen to disperse particulate components of the specimen fluid, e.g., by mixing, while the specimen acquisition apparatus may collect a sample of the particulates, e.g., on a filter. In the case of filtration, a filter loading head upstream of the specimen acquisition apparatus dispenses a filter into a container-borne particulate matter separation chamber, the filter loading head operating independently of the other apparatus in response to any container presented thereto. The filter-borne sample may be transferred to a slide.

According to other aspects of the invention, the method may involve additional operations, including container uncapping prior to specimen preprocessing, and recapping of containers after processing is complete. The apparatus similarly may include additional heads or other devices for performing these operations. Each operation is carried out independently in response to presentation of container to the respective operating station.

BRIEF DESCRIPTION OF THE DRAWING FIGURES

Preferred embodiments of the disclosed system and the invention, including the best mode for carrying out the invention, are described in detail below, purely by way of example, with reference to the accompanying drawing, in which:

Fig. 1 is a vertical sectional view through a specimen vial for use with the LBP device, showing the processing assembly (stirrer) in the vial coupled to the cover;

Fig. 2a is a front elevational view of the container portion of the vial;

Fig. 2b is a top plan view of the container, shown with the stirrer removed;

Fig. 3 is a top plan view of the stirrer;

Fig. 4 is a bottom plan view of the liner that fits within the cover;

Fig. 5 is an exploded vertical sectional view of the stirrer and a filter assembly adapted for use in the stirrer;

Fig. 6 is a vertical sectional view of the upper portion of the stirrer, showing the filter assembly in place in the particulate matter separation chamber;

Fig. 7a is a partial schematic view of the arrangement depicted in Fig. 6, showing the flow of liquid and particulate matter separated therefrom;

Fig. 7b is a view similar to Fig. 7a, showing liquid flow in a prior art filter system;

Fig. 8 is an exploded, cross-sectional view of the filter assembly;

Fig. 9 is a schematic illustration of the dimensional configuration of the flow manifold;

Fig. 10 is a vertical sectional view of the specimen vial similar to Fig. 1, but showing the stirrer detached from the cover;

Fig. 10a is a partial vertical sectional view similar to Fig. 10, showing a modification of the stirrer;

Fig. 11 is a top plan view of the LBP device;

Fig. 11a is a schematic diagram of the operating sequence of the LBP device;

Fig. 12 is a front perspective view of the LBP device, with certain parts removed for clarity;

Fig. 13 is a rear perspective view of a portion of the LBP device, showing the auto loader/unloader mechanism;

Fig. 14 is a top plan view of the auto loader/unloader mechanism;

Fig. 15 is a front elevational view of the auto loader/unloader mechanism;

Fig. 15a is a detail sectional view taken along line 15a-15a in Fig. 14;

Fig. 16 is an elevational view of an alternative embodiment of a gripper for the auto loader/unloader mechanism;

Fig. 17 is a perspective view of a specimen vial tray used in the auto loader/unloader mechanism;

Fig. 18 is an enlarged detail view taken at encircling line 18 in Fig. 17;

Fig. 19 is a bottom perspective view of the specimen vial tray of Fig. 17;

Fig. 20 is a perspective view of three stacked specimen vial trays;

Fig. 21 is a block diagram showing specimen vial handling and data flow;

Fig. 21a is a pictorial diagram showing an overall laboratory system incorporating the LBP device;

Fig. 21b is a relational database table;

Fig. 22 is a block diagram showing a computer or work station;

Fig. 23 is a facsimile of a computer screen;

Fig. 24 is a facsimile of another computer screen;

Fig. 25 is a facsimile of two computer screens;

Fig. 26 is a vertical sectional view of a specimen vial being uncapped;

Fig. 27 is a front elevational view, partly in section, of a specimen vial engaged by the uncapping head of the LBP device;

Fig. 28 is a top plan view of the uncapping head, taken along line 28-28 in Fig. 27;

Fig. 29 is a side elevational view of the uncapping station of the LBP device;

Fig. 30 is a sectional view taken along line 30-30 in Fig. 29;

Fig. 31 is a top plan view of the uncapping station of Fig. 29;

Fig. 32 is a vertical sectional view of a specimen container showing engagement by the primary stirring head;

Fig. 33 is a side elevational view of the primary stirring station of the LBP device;

Fig. 34 is a front elevational view of the primary stirring station;

Fig. 35 is a top plan view of the primary stirring station;

Fig. 36 is a vertical sectional view of a specimen container during filter loading;

Fig. 37 is a side elevational view of the magazine portion of the filter loading station of the LBP device;

Fig. 38 is a front elevational view of the pusher portion of the filter loading station;

Fig. 39 is a top plan view of the pusher portion of the filter loading station;

Fig. 40 is a top plan view of the magazine portion of the filter loading station;

Fig. 41 is a vertical sectional view of a specimen container during specimen acquisition;

Fig. 42 is a vertical sectional view of a specimen container during specimen transfer to a slide;

Fig. 43 is a side elevational view of the specimen acquisition station of the LBP device;

Fig. 44 is a front elevational view of the lower portion of the specimen acquisition station;

Fig. 45 is a top plan view of the specimen acquisition station, partly in section, taken along line 45-45 in Fig. 43;

Fig. 46 is a top plan view of the specimen acquisition station;

Fig. 47 is a schematic of a bubble flow meter used in the specimen acquisition station;

Fig. 47a is a schematic of a modification of the flow meter of Fig. 47;

Fig. 48 is a schematic of a vacuum system used in the specimen acquisition station;

Fig. 49 is an operation chart for the vacuum system of Fig. 48;

Fig. 50 is a front perspective view of the re-capping station of the LBP device;

Fig. 51 is a side elevational view of the re-capping station;

Fig. 52 is a front perspective view of a slide cassette used in the LBP device;

Fig. 53 is a detail perspective view of the slide cassette taken from Fig. 52;

Fig. 54 is a rear perspective view of the slide cassette;

Fig. 55 is a side elevational view of the slide cassette;

Fig. 56 is a top plan view of the slide presentation system of the LBP device; and

Fig. 57 is a side elevational view of the slide presentation system.

DETAILED DESCRIPTION OF BEST MODE

A full description of this vial-based specimen handling and processing system must begin with the vial itself, which consists of a container, a cover and a processing assembly (stirrer) in the vial.

SPECIMEN VIAL

Referring to Figs. 1, 2a and 2b, the vial 10 comprises a container 20, a cover 30 and a processing assembly 40. Processing assembly 40 is designed to carry out several functions, among them mixing, and for this preferred rotary embodiment will be referred to as a stirrer for the sake of convenience. Container 20 preferably is molded of a translucent plastic, preferably polypropylene, and has a substantially cylindrical wall 21, surrounding its longitudinal axis, joined to a conical bottom wall 22. Possible alternative plastics include ABS and polycyclohexylenedimethylene terephthalate, glycol (commercially available from Eastman Kodak Co. under the name EASTAR® DN004). A small portion 24 of wall 21 preferably is flat, the outer surface of the flat portion adapted to receive indicia, e.g., a bar code label, containing information concerning the specimen placed in the vial. Although only one flat portion is shown, the container could be

configured without a flat portion, or with two or more flat portions, each adapted to receive indicia. Alternatively, the indicia could be located on a curved portion of wall 21. The bottom end of flat portion 24 has an arcuate notch 25 which acts to keep the container in a proper orientation when handled by the LBP device, which as noted is designed to cradle the container and move it through various processing stations. A differently shaped notch (e.g., V-shaped) can be used as long as the notch properly mates with the LBP device. Other suitable mating structures can be used instead.

Four longitudinal ribs 26 project inwardly from wall 21. The upper ends 27 of ribs 26 form rests for the stirrer 40 when it is detached from cover 30 (see Fig. 10). The top of container 20 has an opening 28 and a standard right-hand helical thread 29 that preferably extends for one and one half turns and mates with a similar thread on cover 30. Other types of cover-to-container coupling may be used, such as a bayonet coupling, snap-fit arrangement, etc.

Cover 30 comprises a commercially available simple molded plastic threaded cap 31, and a novel liner 32 retained in the cap. Cap 30 preferably is molded of polypropylene, but ABS and EASTAR® DN004, among others, are alternative plastic material choices. Cap 31 has a flat solid top, and an externally knurled depending flange with an internal helical thread 33 that mates with thread 29 on container 20. Referring to Fig. 4, liner 32 is molded of plastic material, preferably polyethylene, and has a substantially flat base 34 sized to fit snugly within cap 31, behind thread 33, so that the liner is not readily separated from the cap. As seen in Fig. 1, liner base 34 serves as a gasket-type seal between the cap 31 and the rim of the container wall 21.

Liner base 34 has a coupler in the form of an annular projection 35 that preferably is slightly conical in shape, preferably forming an angle of about 5° to its central axis. In other words, the inner diameter of annular coupler 35 is greater at its proximal end, where it joins liner base 34, than at its distal end. Liner base 34 also has a central annular boss 36 that projects further from base 34 than annular coupler 35 so as to interact with stirrer 40, as described below. While the use of a separate liner mated to a standard cap is preferred, the cover could be integrally molded in one piece to include the annular coupler 35 and the central annular boss 36. Such a one-piece cover (or even the two-piece cover described above) could instead be configured to act as a plug-type seal by projecting into and sealing against the inside of the rim of container wall 21.

Referring to Figs. 1, 3 and 5, stirrer 40 is molded of plastic, preferably polypropylene, and has a circular base or bottom wall 41, sloped at its center, with a central inlet port 42; a central depending suction tube 43 with two diametrically opposed suction ports 44 near the bottom of the tube; and a dispersing (mixing) element in the form of laterally extending vanes 45. The upper portion of the stirrer 40 has a cup-shaped particulate matter separation chamber or manifold 46 defined by base 41 and an upstanding annular wall 47. The upper edges of wall 47 are beveled, the inner edge 48 preferably being beveled to a greater degree to facilitate placement of a filter assembly F in manifold 46, as described below. Possible alternative plastic material for the stirrer include ABS and EASTAR® DN004.

Annular wall 47 serves as a coupler for releasably coupling the stirrer 40 to cap liner 32, and is therefore dimensioned to fit snugly within annular coupler 35 (see Fig. 1). Specifically, there is a friction or press fit between couplers 35 and 47 such that normal handling of the closed vial, and normal handling of cover 30 when removed from container 20 (e.g., to place a biological specimen in the container) will not cause separation of the stirrer from the cover. Coupler 47 is dimensioned relative to coupler 35 so that there is a very slight initial diametrical interference, preferably about 0.31 mm. Coupler 47 is stiffer than coupler 35, so assembly of the stirrer to the cover involves slight deformation principally of coupler 35, resulting in a frictional force that keeps the stirrer and the cover engaged. Application of an external force to the vial that overcomes this frictional retention force will cause stirrer 40 to detach from cover 30 and drop by gravity further into container 20 (see Fig. 10).

The external separation force preferably is applied to the central portion of cover 30 (see the arrow in Fig. 10), which deflects cap 31 and liner 32 inwardly. As illustrated in Fig. 1, central boss 36 on liner 32 is dimensioned such that its distal end just contacts or lies very close to base 41 of the stirrer. Thus, when the central portion of the cover is depressed, central boss 36 will deflect further than annular coupler 35 on liner 32 and push stirrer 40 out of engagement with coupler 35. Inward deflection of liner 32 also causes coupler 35 to spread outwardly, thereby lessening the retention force and facilitating detachment of the stirrer. The separation force applied to cover 30 and required to detach the stirrer should be in the range of 5 to 30 lbs., preferably about 12 lbs.

Once detached from the cover 30, stirrer 40 comes to rest on the upper ends 27 of ribs 26. See Fig. 10. The particulate matter separation chamber (manifold) 46 thus is stably supported near the container opening and easily accessed by the LBP processing

heads, which will manipulate the stirrer so as to process the specimen directly in the container. At least three ribs 26 are required to form a stable support for the stirrer, but four are preferred because that number seems to promote more thorough dispersion of the particulate matter in the liquid during stirring. Should the stirrer inadvertently become detached from the cover at the point-of-care site, the physician or an assistant simply places the stirrer loosely in the vial so that it descends into the specimen and then screws the cover on as usual. This is not difficult because the ribs in the vial allow insertion of the stirrer in only one direction. Once the vial is closed with the specimen inside, the stirrer remains in the vial throughout processing and is sealed therein when the vial is re-capped.

A small percentage of patient specimens, as may be found in gynecological Pap test and other specimen types, contain large clusters of cells, artifacts, and /or cellular or noncellular debris. Some of these large objects, if collected and deposited on a slide, can obscure the visualization of diagnostic cells and, consequently, result in a less accurate interpretation or diagnosis of the slide sample. Since most of these features are not of diagnostic relevance, their elimination from the sample is, in general, desirable. To achieve this result, the side suction ports 44 in the stirrer suction tube 43 preferably are eliminated (see Fig. 10a) in favor of close control of the interface between the bottom of the suction tube 43 and the small projection 23 at the center of bottom wall 22 of the container 20. This interface effectively forms a metering valve whose geometry (orifice) 23a is created when the stirrer 40 rests on the ribs 26 of the container 20 (see Fig. 10). Proper sizing of the annular flow orifice 23a prevents large objects from entering the suction tube 43, while allowing the passage of smaller objects that may be diagnostically useful. While the orifice 23a has a thin passage section and a small metering area, clogging is not an issue due to its large diameter. The annular orifice 23a preferably has an outside diameter on the order of 0.105 in. and an inside diameter on the order of 0.071 in., yielding a passage width on the order of 0.017 in. This orifice size is optimized for gynecological specimens.

FILTER SYSTEM

Figs. 6 and 8 illustrate one embodiment of a filter assembly F according to the present invention. Figs. 3 and 6 illustrate one embodiment of a manifold 46 (in stirrer 40) according to the present invention. The filter system includes the filter assembly F and the manifold 46.

Referring to Figs. 6 and 8, the filter assembly F comprises a filter housing or holder 200, a porous frit 202, and a porous membrane filter 205. Fig. 8 shows these components more clearly in an exploded view. The holder 200 can be cup- or container-shaped, having a recess or cavity 206 for seating the frit 202 and a chamber 207 between the frit 202 and the holder 200. The frit 202 and the membrane filter 205 can be made of the materials disclosed in the Guirguis patents identified above, namely U.S. Patent Nos. 5,301,685 and 5,471,994, the disclosures of which are incorporated herein by reference.

In the present filter assembly F the membrane filter 205, the frit 202, and the holder 200 are assembled together as a unit. The frit 202, which has a cylindrical shape, is first seated in the holder 200. Then the membrane filter 205 is permanently affixed, adhered, joined, or fused to the holder 200. In the illustrated embodiment, the outer perimeter or edge of the membrane filter 205 is fused to the holder 200. In this regard, the holder 200 has a bevel or chamfer 208 formed around an outer circumferential corner 209. The chamfer 208 provides an angled surface to which the membrane filter 205 can be attached using a conventional bonding technique, such as ultrasonic welding. The holder 200 and the membrane filter 205 should be made of materials that will fuse together. Preferably both are made of polycarbonate, although an ABS holder will work with a polycarbonate membrane filter. Thermoplastic polyester could be used for the holder if the membrane filter is made of the same material. The frit 202 preferably is made of polyethylene.

Referring to Fig. 8, the holder 200 preferably is cylindrical and comprises a substantially cup-shaped body having a bottom wall or base 210 and a substantially upright cylindrical sidewall 211 extending therefrom and terminating in a rim 211a. The sidewall 211 has an annular shoulder 212 extending radially inwardly, toward the center. The shoulder 212 acts as a seat that accurately positions the frit 202. Frit 202 preferably is dimensioned so that the frit's outer or front face 213 is proud of (extends beyond) the rim 211a when the peripheral portion of the frit's rear face abuts the shoulder 212.

The inner diameter of the sidewall 211 can be dimensioned to frictionally engage and hold the frit 202 in place. In this respect, the frit's outer diameter can substantially correspond to the inner diameter of the sidewall 211 to mechanically, i.e., frictionally, hold the frit 202 in place. However, since the membrane filter 205 covers the frit 202, the frit need not be frictionally held to the holder. That is, the frit 202 can be loosely seated in the holder. Frictionally seating the frit 202 in the holder 200, however, maintains the frit 202 in place so that attachment of the member filter 205 can be done at a remote site. It

also simplifies and reduces the cost of mass production of filter assemblies because the holder 200 and the frit 202 can be joined to make a secure subassembly and stored for later attachment of the membrane filter 205.

After the frit 202 is seated in the holder 200, the membrane filter 205 is draped over the frit's outer face 213 and the exposed portion 214 of the frit's side wall 215 that extends beyond the holder 200, and is attached to the chamfer 208, as is better seen in Fig. 6. The frit's exposed outer sidewall portion 214 provides an annular surface area through which the specimen liquid can flow to provide a dual flow path, as schematically illustrated in Fig. 7a.

The filter assemblies F can be coded to denote different pore size and pore density (number of pores per unit cross-sectional area) as may be required for specific processing protocols. Color coding of filter assemblies is preferred, although any form of machine-detectable coding can be used, including distinguishing projections, such as small nipples, for tactile-based sensor recognition. The LBP device is provided with a sensor that can discriminate between these colors or other codes to ensure proper filter selection. The filter assemblies also can be provided in paper carriers for easy insertion into the LBP device.

Referring back to Fig. 8, the holder's bottom wall 210 has a central opening 204 through which vacuum can be applied to draw specimen liquid therethrough. The holder 200 further includes a central projection or protrusion 216 extending into the holder from the bottom wall 210. The central protrusion 216 is aligned with the opening 204 and positioned in the chamber 207, which is defined by the frit's inner face 218, the inner face 219 of the bottom wall 210 and the inner side 220 of the sidewall 211. The protrusion 216 is substantially hollow and has a plurality of side openings 221 that distribute vacuum to the chamber 207 and provide a substantially symmetrical flow through the chamber. The specimen liquid drawn through the membrane filter 205 and the frit 202 fills the chamber 207 and exits the chamber 207 through the side openings 221 and the central opening 204.

The protrusion 216 has an abutting surface 217 that faces and extends toward the holder's open face. The abutting surface 217 is configured to abut against the frit's rear face 218. In particular, the abutting surface 217 is slightly proud of the annular shoulder 212. That is, the abutting surface 217 lies slightly above or beyond the level of the annular shoulder 212 so that the frit's outer face 213 bows slightly outwardly when the frit is installed in the holder. For example, the abutting surface 217 can extend beyond the height of the annular shoulder 212 by about 0.002 inch. The resulting slight bow created

by the protrusion pushing out the central portion of the frit 202 ensures that the central part of the membrane filter 205 contacts the slide. The pressure applied to the slide during imprinting flattens the frit's front surface 213, ensuring full contact of the membrane filter 205 with the slide to more effectively transfer the collected particulates to the slide and minimizing any deposition artifacts. If this slightly bowed configuration is desired, the frit 202 preferably is securely seated in the holder 200, such as by friction as previously explained.

Due to the bowed frit configuration, the membrane filter 205 need not be taut. This simplifies the manufacturing process, reduces cost, and reduces the rejected part rate. Anything short of a major wrinkle can work effectively. As noted, the frit 202 preferably is slightly deformable, its compliance allowing it to flex and flatten against a glass slide post aspiration to transfer cells and other objects of interest from the filter to the slide. To accomplish this the frit should have an elasticity that allows it to be crushed flat by application of a force of 8 lbs. through a displacement of 0.0016 in. Good frit materials include sintered polyethylene and sintered polyester. The frit 202 may be a porous material, with spatially random pores, typically with pore sizes in the range of about 50-micrometer to 70-micrometer. A significant attribute of this material is that it is of low fluidic impedance relative to the material of the thin membrane filter 205 (which typically has pore sizes of about 5-micrometer to 8-micrometer). In other words, the pressure drop across the frit 202 is much less than the pressure drop across the membrane filter 205. Thus, fluid that passes through the filter flows freely through the frit. Alternatively, instead of having randomly positioned pores, the frit 202 may be made of a material or structure that has many parallel channels of small (e.g., 50-micrometer to 70-micrometer) inner diameters through which aspirated fluid and particulates may flow. Such a parallel-channel arrangement would behave as an inner fluid-pervious medium with an apparent low fluidic impedance. In fact, any material or device with the proper low fluidic impedance and deformability/resilience characteristics may be used in the specimen acquisition station, whether it has pores or not.

It has been found that flowing the specimen liquid substantially or mostly in an axial direction, i.e., perpendicular to the membrane filter, can accumulate layers or clusters of particulates, as schematically illustrated in Fig. 7b, particularly if the vacuum is applied through the membrane filter for a longer period than necessary. This can happen even with the Guirguis dual flow design, which provides some secondary flow components that are radially directed. See, for example, Figs. 4 and 12 of Guirguis' U.S. Patent Nos.

5,471,994 and 5,301,685. It seems that the secondary flow generated by that configuration is insufficient to create an effective flushing, or shearing action across the membrane filter. An earlier Guirguis patent, namely U.S. Patent No. 5,137,031, discloses a funnel- or cone-shaped manifold. In that arrangement, however, there is no secondary radial outflow at its periphery. As there is no flow other than directly through the filter itself, there is no substantial radial flow component. Accordingly, the specimen liquid only flows substantially perpendicularly to the membrane filter.

Referring to Fig. 6, the inner diameter of the upright wall 47 of the manifold 46 at the top of stirrer 40 is dimensioned to be slightly larger than the outer diameter of the filter assembly F, namely the holder's sidewall 211, so that the manifold 46 can receive and seat the filter assembly F, with the membrane filter 205 facing down, as illustrated. The filter assembly F can be loosely seated in the manifold 46. When the filter assembly F is seated in the manifold 46, the outer peripheral edge of the membrane filter 205 rests on the bottom wall 41. The bottom wall 41 is configured to have a well or recess that forms a manifold chamber M when the filter assembly F is seated in the manifold 46. The chamber M is thus bounded by the outer surface of the membrane filter 205 and the upper surface 41S of the bottom wall 41.

The present dual flow arrangement solves the problem of particulate build-up or accumulation on the face of the membrane filter. This arrangement causes a shearing force or action across the front face of the membrane filter that is sufficient to flush the particulates aside and keep them from building up or layering. Built-up or layered particulates have a weaker bond to the layer underneath them as they build up, because the suction power decreases as the pores of the membrane filter 205 become covered with particulates. A shearing force is created by imparting a tangential or substantially radial flow component to the specimen liquid across the front face of the membrane filter 205. This flow component is substantially parallel to the front face of the membrane filter, i.e., it is perpendicular to the built-up direction of the layers, and flushes the particulates radially outwardly, away from the front face of the membrane filter.

To provide a secondary or radial flow path, the manifold 46 is configured to provide a small spacing or gap G (see Fig. 6) at the periphery of the manifold chamber M, between the front face of the membrane filter 205 and the upper surface 41S of the bottom wall 41, to allow flushed particulates to exit the manifold chamber M, away from the front face of the membrane filter. The gap G must be large enough to prevent the particulates from clogging it. That is, if the gap G is made too small for the particulates being filtered,

the gap G can get clogged, cutting off the secondary flow. The minimum size of the gap ultimately depends on the particulate size, the viscosity of the specimen liquid, and the temperature of the specimen liquid. It has been determined that the gap G should be at least 0.004 in. to prevent clogging by cellular particulates.

Referring to Figs. 3 and 6, to create the gap G, which forms an outflow nozzle, the bottom wall 41 of manifold 46 includes a plurality of spaced standoffs or raised ribs 48a around the periphery of the manifold 46. The spaces 49 between the ribs 48a provide a passage for specimen liquid to exit the chamber M. In the illustrated preferred embodiment, the manifold 46 has an inner diameter of 23.4 mm, and has thirty-six ribs 48a, evenly spaced at 10°. The ribs are 0.150 mm high and arcuately blend into the surrounding shoulder with a radius R of 0.63 mm, as illustrated. Of course, the present invention contemplates other configurations of spaced ribs or standoffs, which are intended to precisely space the filter assembly from the bottom wall 41 so that a precise outflow area is created. Depending on the number and thickness of ribs or standoffs, the total outflow area can be reduced as much as 50% as compared to the inlet area.

It has been observed in the Guirguis type filter arrangement referred to above that specimen liquid traveling radially outwardly loses velocity. The present dual flow filter system compensates for the velocity slowdown by providing a shallow, substantially conical surface across which the specimen liquid flows. This surface forms a substantially conical distribution manifold chamber M confronting the membrane filter 205. The chamber M according to the present invention has an annular radial outlet O, through spaces 49, having an area that is about equal to or smaller than the maximum area of the central inlet I. Referring to Fig. 9, the "face" area of the radially directed annular flow passage is cylindrical and is defined (bounded) at any given radius R_1, R_x, R_y, ..., R_2 by the front surface of the membrane filter 205 and the conical surface 41S of the manifold. As the specimen liquid travels outwardly, the radius increases while the manifold height decreases. The manifold chamber M can be configured so that the height H_1, H_x, H_y, ..., H_2 decreases at a rate which maintains the face area of the annular passage substantially uniform from the inlet I to the outer perimeter outlet O of the manifold, yielding a substantially linear radial flow velocity across the face of the membrane filter 205.

In this regard, still referring to Fig. 9, the maximum theoretical radial flow area of a round manifold inlet I can be defined as the circumference ($2\pi R_1$) multiplied by the height of the manifold chamber H_1. In this instance, $2\pi R_1 H_1$ defines the total

circumferential area of the manifold inlet I. The maximum circumferential flow area of a round manifold outlet O can be defined as $2\pi R_2H_2$. If the outlet flow area is to equal the inlet flow area, then the inlet and outlet areas can be expressed as:

$$2\pi R_1H_1 = 2\pi R_2H_2$$

$$R_1H_1=R_2H_2$$

Using this expression, the heights, e.g., H_x, H_y, can be defined at their given radii, e.g., R_x, R_y from the inlet I to the outlet O. If the heights H_1, ..., H_x, ..., H_y, ...H_2 from the inlet to the outlet are plotted, the resulting surface 41S would be curved, not linear. However, it has been observed that a significantly curved lower manifold surface does not work as effectively as a linear surface 41S. Accordingly, the present preferred embodiment contemplates a linear or substantially or nearly linear surface 41S (which can be slightly curved) extending from the inlet to the outlet. Also, there is a minimum height H_2 of about 0.006 inch clearance for the specimen liquid to effectively flow. Based on this requirement, the minimum R_1 can be defined as $0.006R_2/H_1$ inches. With this configuration, as the specimen liquid is drawn through the filter, the specimen liquid traverses the front face of the membrane filter 205 in a direction that is substantially parallel to or approaching nearly parallel to the front face of the membrane filter, creating the desired shearing action.

Empirical study has revealed that for a linear conical surface 41S, the area of the outlet O preferably should be less than or equal to the maximum area of the inlet I. That is, R_1H_1 R_2H_2. For example, the exemplary manifold can have the following dimensions (all units here in mm): $R_1 = 1.24$, $H_1 = 1.32$, $R_2 = 10.00$, $H_2 = G = 0.15$. The maximum inlet area would thus be 3.27π mm^2 and the outlet area 3.00π mm^2, which is slightly less than the maximum inlet area, but greater than the average inlet area, which can be defined as 50% of the maximum inlet area (1.64π mm^2). Thus, the outlet area can fall between the maximum inlet area and the average inlet area. Another example can have the following dimensions (all units here in inches): $R_1 = 0.040$, $H_1 = 0.060$, $R_2 = 0.400$, $H_2 = 0.006$. The maximum inlet area would thus be 0.0048π in^2, which is equal to the outlet area.

In summary, the manifold chamber M that confronts the substantially flat membrane filter should have a shallow, funnel-shaped configuration and a peripheral outlet so as to create a substantial radial flow across the outer surface of the membrane filter. The radial flow creates a shearing action that washes or flushes away any

particulates that are relatively weakly attached so as to leave a very thin layer of particulates – a monolayer – on the surface of the membrane filter.

LBP DEVICE AND METHOD

Figs. 11-57 illustrate a preferred embodiment of an LBP device according to the present invention. The LBP device is an automated machine for preparing slides for viewing, imaging or optical analysis. The LBP device can use the above-described dual flow filtering system (Figs. 6, 7a, 9) to collect monolayers or thin layers of cells and transfer them onto slides.

Referring to Fig. 11, the illustrated embodiment of the LBP device can be compartmentalized into at least six discrete processing stations: data acquisition station (bar code reader) 230; uncapping station 400; primary stirring station 500; filter placement station 600; specimen acquisition station 700; and re-capping station 800. These six stations are structured for parallel processing, meaning that all these stations can operate simultaneously and independently of the other. The LBP device also includes a separate data reading station, a slide presentation station, a slide handling station, and a cassette handling station, all of which can be incorporated as an integrated system 900. The LBP device further includes a transport mechanism 240 for moving the specimen containers to the various operating stations. It can further incorporate an auto loading mechanism 300 that automatically loads and unloads specimen vials onto and from the transport mechanism. All stations are computer-controlled. Fig. 11a shows the operating sequence of the LBP device. This is the top-level table from which the operating software is structured.

Fig. 12 shows the basic structural elements of the LBP device, namely a frame 260 preferably made of extruded aluminum, preferably on casters (not shown) for mobility, and a machined aluminum base plate 262 supported by the frame and on which the main operating mechanisms are mounted. Beneath the base plate is a compressor 264 for supplying compressed air for powering some of the components; a vacuum pump (not shown) which provides a vacuum source for various components; stainless steel shelves for holding the vial trays used in the auto loading mechanism 300; and electrical components, including power supplies and controllers, and miscellaneous equipment. A compressor would not be required if electrically-powered actuators were used instead of air-powered actuators. A user interface, e.g. a touch-sensitive LCD display (not shown), is mounted to the left of the transport mechanism 240 and gives the technician control over machine operation beyond the normal automated processing protocols. See Fig. 25, which

shows examples of a log-in screen (top) and a navigation screen (bottom) as they might appear on the user interface. Of course, other screens would be presented to the user as he/she interacts with the user interface.

An "economy" version of the LBP device can take the form of a counter-top model for processing a more limited number of specimens at a time. In such a model certain components can be eliminated, such as frame 260 and auto loading mechanism 300, while other components can be scaled back, such as the capacity of filter placement station 600. External sources of vacuum and compressed air could be used to power such a device, while other components (power supplies, controllers, etc.) could be repositioned to one or more modules adjacent to or on a modified machine base plate. Various ways of implementing these modifications will be readily apparent to those skilled in the art.

TRANSPORT MECHANISM

Referring to Fig. 11, the transport mechanism 240 comprises an endless link-belt conveyor 242 driven by a stepper motor (not shown) around precision sprockets 242, 244. The conveyor has a plurality of receptacles or carriers 246, linked by pins 248, for receiving a corresponding number of specimen vials. The illustrated embodiment in Fig. 11 has 30 receptacles, numbered 1 through 30. Depending on the sample vial size and the length of the conveyor, the LBP device can use fewer than or greater than 30 receptacles, as desired or feasible, sufficiently long to permit all processing to be completed in a single line.

The receptacles 246 of the link-belt conveyor are guided between the sprockets by pairs of guide rails 250 forming tracks, and has a conventional position correction system (not shown) to accurately position the receptacles. The LBP device can track the position of each receptacle and step-drive or index them in a conventional manner. For instance, the LBP device can include linear position sensors, such as optical sensors or a photo-interrupter on each link, that can feed the position to a controller for registering carrier position and precisely indexing each carrier at each of the processing stations along the processing path. The manner of driving the conveyor for precise alignment and positioning is conventional and thus will not be described further.

The guide rails 250 that form tracks in Z and Y axes engage slots machined in the sides of the receptacles. See, for example, Figs. 29, 33, 37 and 43. The mechanical tracks and drive sprockets can be constructed of a self-lubricating plastic for operation without the need to add an external lubricant. The receptacles 246 each can have a window 247 (see Fig. 12) for allowing access to laser or optical scanning of the bar code on the

specimen containers. The conveyor can be hard-coated aluminum, ®-impregnated with PTFE7 for easy cleaning. The link pins 248 can be precision ground and hardened. The link pins can be axially fixed in location in the non-rotating link bore. Rotating link bores can be fitted with a suitable bearing material capable of operation without additional lubricant. For operator safety, the conveyor operation can be interlocked with the cover of the machine (not shown).

The receptacles 246 are also configured so that they receive or seat the specimen vials in a particular orientation. That is, the specimen vials and the receptacles are complementarily configured or keyed so that the vials can only be seated in the receptacles in a particular orientation. For example, the vials can be "D" shaped, namely having a flat side (see Figs. 2a, 2b), and the receptacles can be "D" shaped so that the flat sides align with each other. In this way the vials do not rotate relative to the receptacles, while allowing unrestricted vertical movement relative to the receptacles. In addition to the D shape, each vial can have a bottom notch 25 (see Fig. 2a), and the receptacles can have a mating peg or stud (not shown) that keys into the notch 25. While the illustrated notch and peg are arcuate, they can take on other mating shapes (e.g., V-shaped).

VIAL LOADING/UNLOADING MECHANISM

Figs. 12, 13 and 14 show the automated vial loading and unloading mechanism 300. A pivoted pick-and-place arm 304 is mounted on an elevator carriage 306 driven by a vertical (Y-axis) lead screw motor 308 atop a vertical standard 310. Arm 304 has a conventional electrically- or pneumatically-operated jaw-type gripper 312 adapted to grasp and move specimen vials 10 in three degrees of freedom. Arm motion in horizontal planes is afforded by lateral lead screw motor 314, which is pivotally mounted in a clevis-type bracket 316 to elevator carriage 306. Instead of a jaw-type gripper as shown, the pick-and-place arm can be equipped with a conventional pneumatically operated suction-head type gripper as shown in Fig. 15. Such a gripper has a silicone rubber bellows 318 which seals against the cover 30 of a vial when placed against the cover and subject to suction through a suction line 320. Whether mechanical or pneumatic, actuation of the gripper is accomplished through the programmed operation of the machine as is understood by those skilled in the art.

Referring to Figs. 17-20, specimen vials 10 are stored in special injection molded plastic vial trays 330 that slide into the machine on shelves 320 (see Fig. 12). To avoid confusion, it should be pointed out that Figs. 13-15 show a different form of tray (made of stamped steel), but the operation of the mechanism that rotates the trays, regardless of

their construction, is the same. The plastic vial trays 330 are the preferred form, and are preferably made of polypropylene. The term "tray" as used herein is not limited to the embodiments shown, and should be construed to cover any type of carrier, rimmed or rimless, that can support and move a generally planar array of discrete articles generally in the manner described herein.

Each tray 330 has forty-one circular recesses 332 sized and configured to receive specimen vials 10 only in one orientation. The upper edge of each recess 332 preferably has a beveled edge 333, which facilitates smooth insertion of vials. The recesses are arranged in a close-pack array of four concentric rows, preferably as follows. The outermost row has sixteen recesses; the next row in has eight recesses; the third row in has nine recesses; and the innermost row has eight recesses. The receptacles of adjacent rows are offset for closer spacing. The receptacles of the second row are radially aligned with the receptacles of the fourth (innermost) row. The receptacles of the outermost row are spaced at 18° on center. The receptacles of each of the other rows are spaced at 36° on center. Of course, other receptacle arrays could be used as long as they permit access of all vials by the pick-and-place arm 304. Each receptacle has a unique and addressable location, so that any vial can be accessed at will and in any sequence.

As noted above, orientation of specimen vials during the processing is critical, so the proper orientation of the stored vials in these trays ensures that the pick-and-place arm 304 will properly position each vial in a conveyor receptacle 246. Accordingly, each recess 332 has at its bottom (see Fig. 19) a fixed indexing peg 334 that is sized to fit into notch 25 in the vial. The pegs 334 are installed, e.g., by adhesive, in grooves 335 that are molded into the tray adjacent the bottoms of the recesses 332. Some of the pegs have been omitted from Fig. 19 for illustrative purposes.

The pegs 334 are arranged at specific angles with respect to the median plane of the tray 330 such that each vial removed from the tray is delivered to a transport receptacle with its notch aligned with the mating peg in that receptacle, and vice versa. Each of these angles is dictated by the rotational position of the tray 330 when a vial in a specific recess 332 is to be accessed by the pick-and-place arm 304, and the angular rotation of the pick-and-place arm from the point of vial pick-up to the point of vial placement in the conveyor receptacle 246. The determination of these angles is considered to be within the abilities of one of ordinary skill in the art.

The tray 330 also has three upstanding guide posts 336, each with a spring-loaded ball 338 at its tip, which cooperate with guides (not shown) above each shelf 302 and serve to guide the tray into the machine as it is inserted and ensure its proper orientation. The guide posts 336 also serve as stacking posts when the trays are stacked for storage (see Fig. 20), the balls 338 engaging dimples 339 (see Fig. 19) in the bottom of the superior tray.

The tray 330 also has a large flared notch 340 which is oriented toward the machine when the tray is inserted on a shelf 302. The innermost portion of the notch 340 has opposed keyways 342 which are adapted for engagement by floating keys, as described below. The keyways preferably are formed in a milled brass hub insert 343 that is recessed flush with the top of the tray and secured thereto by screws.

Referring to Figs. 14, 15 and 15a, a rotary outer spindle 350 is journaled at its top and its bottom in bearings 352, 354, respectively. Outer spindle 350 engages and rotates only one tray at a time so that the pick-and-place arm 304 can access vials therefrom by moving downwardly through an opening 266 in base plate 262 and past any idle trays via their homed notches 340. Fig. 14 shows the home positions of the trays in dashed lines, with their notches 340 aligned and embracing outer spindle 350. Spindle 350 is rotated in a precision manner from the bottom by a computer-controlled rotation stepper motor 356 and a timing belt 358 engaging timing gears 360, 362. A downwardly facing optical rotary position sensor 363 located over the aligned tray notches detects when and how far a tray is rotated from its home position and provides control feedback for rotation of stepper motor 356.

Within outer spindle 350 is an inner spindle 364 carrying eight pairs of opposed keys 365, one pair for each tray. The keys 365 project from outer spindle 350 through opposed slots 366 in the outer spindle (see Fig. 15a, which is a sectional view through the spindles and the center portions of the bottom two trays). The inner spindle 364 is moved vertically within the outer spindle 350 by an internal lead screw 372. Lead screw 372 is rotated by lead screw stepper motor 374 through a timing belt 376 and timing gears 378, 380. A key "home" sensor 382 (see Fig. 15) is located at the top of inner spindle 364 to provide a reference point, i.e., when the machine is turned on, it will "home" the inner spindle to the key home sensor 382 and then reference its movements from there.

The even vertical spacing of the pairs of keys can be seen in Fig. 15. This spacing, or pitch, differs from the pitch of the keyways 342 in a full complement of installed trays 330. Accordingly, which keyways are engaged by the keys depends on the vertical

position of inner spindle, and only one pair of keyways (tray) can be engaged at any time. The enlarged view of Fig. 15a shows that the keyways 342 of bottom tray 330-1 are engaged by keys 365, while the keyways of the tray above it, 330-2, are not engaged by any keys. Movement of inner spindle 364 by one-eighth the pitch difference disengages one tray and engages the immediately adjacent tray. The operation of the loading and unloading mechanism is unaffected by the absence of one or more trays from the tray slots, which are defined by shelves 302.

When a selected tray is to be accessed by the pick-and-place arm 304 (as determined by the computer controller), the lead screw motor 374 moves the inner spindle the appropriate distance so that the appropriate keys engage the keyways of the selected tray. The rotation motor 356 then rotates the keyed tray to the proper angular position so the arm 304 can access a particular recess 332. The superposed arrangement of the trays, the way in which a selected tray is accessed by the gripper 312 through the flared notches 340 of superior trays, and the close-pack spacing of the recesses 332 in each tray make for an extremely compact, high capacity and efficient vial handling system that is readily incorporated into the compact base of the LBP device.

In the embodiment shown, the LBP device can accommodate up to eight trays holding forty-one specimen vials each. One of the forty-one recesses can be reserved for a cleaning vial, which would contain a cleaning solution and be run through the LBP device to clean the various parts of the device that normally come into contact with specimen fluid. Alternatively, the forty-first vial could contain a typical control specimen for calibration purposes. Thus the LBP device can accommodate up to at least 320 vials containing specimens to be processed. The device is therefore capable of operating continuously unattended for a long duration – at least eight hours – so that specimen processing can be carried out even when laboratory personnel are not normally present, such as at night.

When the trays 330 are bar-coded or otherwise labeled with machine-readable identifying data, they can be used in an automated storage device that can access a particular tray on command. The tray-identifying data can be input into the integrated data management system so that the location of any specimen vial in tray storage can be readily ascertained.

A cost reduction in tray-based storage of specimen vials can be achieved by using a liner-type system in conjunction with trays 330. For example, vials can be supported and stored in thin sheet-like liners (not shown) that conform to trays 330 and slip readily

into recesses 332. The liners are stiff enough to be self-supporting when fully loaded, can be stacked, and can be housed in wheeled carts for ease of mobility.

DATA ACCESSIONING AND SPECIMEN MANAGEMENT

It is, of course, important to keep track of each specimen vial and the specimen slides produced from each vial. Accordingly, the LBP device typically communicates with the integrated data management system (DMS) 104 through an accessioning station 102 or other computer. Fig. 21 schematically illustrates specimen vial handling and the flow of data that is integrated into to operation of the LBP device. The communication link between the LBP device and the DMS can be made via ethernet or other protocol using a direct peer-to-peer connection, or through a server-based network.

The specimen processing operation begins with collecting or transferring data from the labeled specimen vial, e.g. via a bar code reader on a data entry terminal or accessioning station, to the DMS via either a direct connection or over a network. Specimen tracking data can include, for example, the patient's name, test identification (ID) number, patient data, and any special processing instructions. For example, the bar-coded specimen vial can be linked to the patient information initially by a paper requisition form and subsequently by an assigned, unique numerical ID in the database. In a preferred embodiment, the patient and test information including the vial bar code can be entered into the networked DMS database at the point-of-care site (e.g., physician's office), thereby eliminating entirely the need for a paper requisition form. U.S. patent No. 5,963,368 (incorporated herein by reference), which is assigned to AccuMed International, Inc. (now Molecular Diagnostics, Inc., or MDI) discloses a similar concept as applied to a computer-controlled instrument for analyzing biological specimens (a microscope) and storing data from each analysis. The '368 patent is exclusively licensed to MonoGen, Inc. (the owner of this application) in the field of liquid-based cytology in combination with or for use with non-fluorescence based image analysis devices, processes, systems and/or instruments. MonoGen's commercially available pathology work station and data management system implement the concept disclosed in the '368 patent.

Each specimen vial includes an identification (ID) symbol or label (e.g., bar code) and/or a stored information label or symbol such as a hologram or a memory chip or device. The present embodiment contemplates reading an ID label using an optical reader, such as a bar code reader, which provides the information to a DMS for sharing information between different work stations or instruments at the same or different locations, such as laboratories, doctors' offices, hospitals, or other patient care providers.

Fig. 21a depicts an overall laboratory system wherein the DMS is expanded to link specimen/patient data through a server to a variety of specimen processing devices and/or computerized work stations for fully integrated specimen management.

A separate bar code reader 230 (see Fig. 11) is mounted on the LBP machine itself, and scans all specimen vials prior to processing through a slit in each transport receptacle 246. Each of the transport receptacles 246 is tracked using this symbol or code, such as a bar code that can be read with a conventional optical reading device. The bar code readers used in the LBP device can be any commercially available type, such as Keyence BL-600, with a minimum BCR target code capability of Interleaved 2 of 5, Code 128c, or EAN-128. The bar code readers preferably are sealed in liquid-tight enclosures for operator protection. After reading, specimen vial/transport receptacle ID data are transmitted to the DMS of the host database or work station. The host database or local work station can then transmit back to the LBP device the specific processing protocol to be performed on that individual specimen.

Some of the most important functions of the data management system (DMS) include:

Obtaining data on the patient and the specimen during accessioning, and making this available to each instrument as required to set processing parameters and to provide medical data to the slide reviewer;

Maintaining chain of custody of specimens and slides to ensure data integrity;

Compiling data and printing required forms for regulatory, compliance, and laboratory management reports;

Generating medical reports and ensuring integrity using safeguarded digital electronic signatures;

Managing billing for instruments on "per use" charges;

Storing optimal processing protocols for each process and supplying to the instrument in accordance with the specimen type and/or user requirements; and

Facilitating remote diagnostics and repair, and providing user manuals and troubleshooting guides.

Fig. 21b shows an example of a relational database table that can be used to accomplish these tasks.

The DMS can provide paper-free data flow among the different stages of the cytology process, saving a significant amount of personnel time and cost, reducing transcription errors, improving accuracy, and eliminating the space required to store paper

records. By automating and managing data acquisition, storage and retrieval, each operation becomes more efficient, significantly reducing the turn-around time for specimens. Specimen quality is enhanced by automated calibration and cross-checking routines that identify potential problems early. Flexible foreign language support for worldwide sales assists laboratories in multicultural environments.

The DMS provides a common user interface that provides detailed information on the operation of each connected laboratory device and work station, and together with online user manuals and training aids eases use and minimizes training. The DMS handles the exchange of all relevant patient and specimen data with the users' own LIS (or other data management systems) through a provided software interface. Moreover, remote instrument diagnostic capabilities ensure maximum interruption-free operation. The reduction in paperwork, ready cross-compatibility with other instruments and existing computer networks, and integration with the central hospital or laboratory information system provides significant user benefits.

In typical operation, the laboratory: (1) receives a requisition from the healthcare provider along with the pre-bar-coded specimen vial, (2) assigns a unique ID number (accession number) to the specimen, and (3) based on information on the requisition, enters a specific LBP test ID to specify the process to be used. Fig. 23 shows an example of the accessioning (data entry) screen that is presented to the technician, into which the vial bar code, accession number and LBP process code are entered. When the specimen vial is loaded into the LBP device for processing, the LBP device automatically reads the bar code on the specimen vial and transmits the bar code number (106) to the DMS, which sends back the processing parameters for the selected test, and the number of slides to be produced. The LBP device returns an acknowledgment (108) and processes the specimen, making one or more slides as instructed via the DMS. Immediately before the LBP device imprints a specimen slide with material filtered from a specimen vial, the LBP device reads the bar code from the pre-bar-coded slide that is to receive the specimen sample. The LBP device sends each slide bar code (110) and its associated vial bar code to the DMS which updates the patient database with the slide bar code number, cross-references it to the correct vial number, and signals (112) the LBP device to proceed. The LBP device then imprints a cytological sample from the specimen onto one or more slides and readies the onboard data log for the next specimen to be processed. Fig. 24 shows an example of a DMS menu screen showing data items that are now linked in the DMS database, including the vial number, slide number(s) and patient data. The DMS can

produce a printable report listing slide ID numbers and associated vial ID numbers, patient data and processing protocols.

At a minimum the protocol variables include specimen mixing parameters (stirring speed and time) and filter selection. Typically, primary stirring speed can be varied from 500 rpm to 3,000 rpm selectable in 50 rpm steps. The stirring interval can be varied from 5 to 120 seconds, selectable in 5 second increments. Choice of filter type is based on average pore size diameter: either 5 micron (red housing), e.g. for non-gynecological specimens, such as sputum specimens, or 8 micron (white housing), e.g. for gynecological specimens, depending on the test protocol selected.

The LBP device is capable of processing mixed sample-runs (i.e., runs that may include vials containing various types of specimens) interchangeably and without the need for batch processing of same-type specimens. Specimen processing can include at least 100 different processing protocols resident within the DMS and accessible to users. Predefined procedure codes (test ID's) such as the following can be used to simplify operator input and specify which processing protocol is used:

1	breast cyst, L
2	breast cyst, R
3	bronchial brushing
4	bronchial washing
5	bronchoalveolar lavage
6	cerebrospinal fluid
7	colonic brushing/wash
8	esophageal brushing/wash
9	gastric brushing/wash
10	gingival (buccal) scrape
11	gyn PAP test
12	intestinal brushing/wash
13	nipple discharge, L
14	nipple discharge, R
15	ovarian cyst, L
16	ovarian cyst, R
17	pericardial effusion
18	peritoneal effusion
19	pleural effusion

20 rectal brushing/wash
21 sputum, induced
22 sputum, spontaneous
23 urine, catheterized
24 urine, voided

Each specimen is processed with a new filter to prevent the possibility of cross contamination. In the present embodiment, either of two or more different filter types can be specified for versatility in test selection (the device's eight filter tubes allow for up to eight different filter types). Processing parameters for each type of specimen preparation can be determined remotely and in advance, and communicated to the processing device using a bi-directional communication link utilizing the specimen vial bar code as the key identifier. The LBP device can utilize default (pre-loaded into the DMS) process protocols as well as laboratory-generated process protocols that users can add to the DMS.

An overfilled-vial sensor (not shown) can be positioned at or just downstream of the bar code reader 230 to detect whether an excessive amount of fluid is present in each translucent vial. Opening and processing an overfilled vial can result in hazardous spillage or ejection of biological fluid. Accordingly, if an overfilled vial is detected, the DMS will be so notified and the complete LBP processing protocol for that vial will be canceled, allowing the overfilled vial to proceed through the processing path unopened. Alternatively, an overfilled condition can be sensed at the conveyor holder 246 into which vials are loaded by the vial loading mechanism 300. If an overfilled vial is detected there, the DMS will be so notified and the loading mechanism will be instructed immediately to return the overfilled vial to its tray 330.

A similar approach can be used to deal with other anomalies detected as each vial is loaded into the conveyor. For example, a sensor (not shown) can be used to detect an unreadable bar code on the vial, or detect when a vial is improperly position in the holder 246. When any such condition is detected, the DMS will be so notified and the loading mechanism will be instructed immediately to return the overfilled vial to its tray 330.

Fig. 22 is a block diagram showing the components of a general purpose computer system or work station 270, which can be used to run the DMS. The computer system 270 typically includes a central processing unit (CPU) 272 and a system memory 274. The system memory 274 typically contains an operating system 276, a BIOS driver 278, and application programs 271, such as a DMS. In addition, the computer system 270 can

include input devices 273, such as mouse, keyboard, microphone, joystick, optical or bar code reader, etc., and output devices, such as a printer 275P, and a display monitor 275M.

The computer system or work station can be connected to an electronic network 280, such as a computer network. The computer network 280 can be a public network, such as the Internet or Metropolitan Area Network (MAN), or other private network, such as a corporate Local Area Network (LAN) or Wide Area Network (WAN), or a virtual private network. In this respect, the computer system 270 can include a communications interface 277, such as ethernet, USB, or Firewire, which can be used to communicate with the electronic network 280. Other computer systems 279, such as a remote host database, other types of work stations including automated analyzers, and computers or databases (e.g., LIS) of a hospital, laboratory, or other medical establishment, can also be linked to the electronic network 280. Other LBP devices, as well as other types of specimen processing instruments (e.g., automated slide stainers and coverslippers) 279a can also be connected to each other and the DMS via the network.

One skilled in the art would recognize that the above-described system includes typical components of a general purpose computer system connected to an electronic network. Many other similar configurations can be used to control the LBP device and its processes. Further, it should be recognized that the computer system and network disclosed herein can be programmed and configured by one skilled in the art to implement the methods, system, and software discussed herein, as well as provide requisite computer data and electronic signals to implement the present invention.

In addition, one skilled in the art would recognize that the "computer" implemented invention described further herein may include components that are not computers per se, but include devices such as Internet appliances and Programmable Logic Controllers (PLCs) that may be used to provide one or more of the functionalities discussed herein. Furthermore, while "electronic" networks are generically used to refer to the communications network connecting the processing sites of the present invention, one skilled in the art would recognize that such networks could be implemented using optical or other equivalent technologies. One skilled in the art would recognize that other system configurations and data structures can be provided to implement the functionality of the present invention. All such configurations and data structures are considered to be within the scope of the present invention. In this context, it is also to be understood that the present invention may utilize known security and information processing measures for transmission of electronic data across networks. Therefore, encryption, authentication,

verification, compression and other security and information processing measures for transmission of electronic data across both public and private networks are provided, where necessary, using techniques that are well known to those skilled in the art.

UNCAPPING STATION

One of the advantages of the present vial-based LBP device and system is that it minimizes operator exposure to the specimens, which can contain potential biohazards. Referring to Figs. 26-31, the LBP device has an uncapping mechanism 400 that first automatically separates the stirrer 40 in the vial from cover 30, and then removes and discards the cover – all without intervention by an operator. See Fig. 26, which shows the stirrer resting on vial ribs 26 after the cover 30 is removed.

A closed specimen vial 10 which has arrived at the uncapping station in its transport receptacle 246 is met by an uncapping head 402 which is lowered onto the cover 30 of the specimen vial. See Figs. 27 and 28. Uncapping head 402 has four tapered legs 404 that form a tapered gripping cavity having chisel-like inner edges 406 spaced and sized to progressively tighten onto cover 30 as head 402 is lowered. Once the cover is tightly engaged by the legs, a central spindle or plunger 408 is lowered into contact with the center of cover 30 and applies a downward force to the cover to cause the stirrer 40 to detach from the cover 30, as described above, and drop down in the vial onto ribs 26. Then the plunger is retracted and the uncapping head 402 is rotated counterclockwise (Fig. 28) to unscrew cover 30 and remove it from container 20. Thereafter the uncapping head with the removed cover in its grip moves laterally to the position shown in dashed lines 410 in Figs. 29 and 11, and plunger 408 is again lowered, this time to eject cover 30, which falls into a waste chute or bin (not shown) beneath the uncapping head. Alternatively, a movable waste chute can be brought beneath the uncapping head to catch the ejected cover, so that lateral movement of the uncapping head is not required. Covers are not reused to eliminate the possibility of cross-contamination.

The plunger 408 is driven by a pneumatic cylinder 412, mounted on an L-bracket 415 at the top of the uncapping head, that can apply a force on the cover of up to about 30 lbs. A coil spring 413 returns the plunger to its retracted position when cylinder 412 is deactivated. The head 402 is capable of applying an uncapping torque through the gripping legs of up to about 10 lb-ft, which is sufficient to loosen the cover. The gripping legs can be of the self-energizing type so that precise alignment with the cover or small variations in cover geometry do not frustrate their grip.

The uncapping mechanism has a mounting frame 414 supported on blocks 416 that slide laterally of the processing path on rails 418. A Y-axis stepper motor 420 and lead screw 422 effect lateral motion. The uncapping head 402 is rotatably mounted in a bearing block 424. Bearing block 424 is secured to a C-frame 426 that is vertically slidable on mounting frame 414. Vertical movement of C-frame 426 and, hence, uncapping head 402 is effected by Z-axis stepper motor 428 and lead screw 430. Lead screw 430 can be vertically compliant to accommodate upward movement of the cover 30 as it is unscrewed. However, it is preferred that stepper motor 428 be actuated during the uncapping sequence so that head 402 rises at about the same rate as, but no faster than, the unthreading cover. Uncapping head 402 is rotatably driven by uncapper motor 432 through a gear reduction unit 433, a timing belt 434 and timing pulleys 436, 438.

The uncapping head described above would also work with vials having a conventional "press and turn" bayonet-type coupling between the container and the cover. The downward force of the plunger 408 would be sufficient to release the internal anti-turn lock of the coupling, allowing the gripper to rotate and remove the cover. Vials having covers that do not require rotation for removal, e.g., a snap-on cover, would require a differently designed uncapping head, tailored to the type of cover connection involved.

Alternatives to the above-described plunger 408 can be employed at or upstream of the uncapping station for applying the required external force to the covered vial to effect separation of the stirrer from the cover. For example, a cam, lever arm or other movable mechanical element can contact and press down on the cover. Alternatively, an abrupt upward external force can be applied to the vial to yield an acceleration force that overcomes the frictional retention force between couplers 35 and 47, effectively pulling the stirrer out of engagement with the cover. This can be done by, e.g., moving the closed vial rapidly downwardly to rap the bottom of the container 20 against a rather hard surface, e.g., by mechanically and/or pneumatically thrusting the closed vial into the transport carrier 246 that will hold the vial during the subsequent processing steps, or by dropping the vial down a chute into the carrier a sufficient distance to dislodge the stirrer. Another way to exert an abrupt upward external force on the vial is to strike the bottom of the container 20 with a striking member. This can be accomplished by, e.g., cradling the container 20 and momentarily thrusting a striker against the bottom of the container, e.g. through a bottom opening in the vial carrier 246, by pneumatic and/or mechanical means. The design of these and other variants of suitable automated mechanisms for accomplishing these tasks is within the grasp of those skilled in the mechanical arts.

PREPROCESSING (PRIMARY STIRRING) STATION

After uncapping is completed, the transport mechanism indexes the specimen container to a station where preprocessing occurs. The preprocessing station is the location at which preprocessing operations, such as specimen dispersal within its container, are performed prior to the container and its specimen moving to the specimen acquisition station. The preprocessing station typically performs a dispersal operation. In the preferred embodiment, the dispersal operation is performed by a mechanical mixer, which rotates at a fixed speed and for a fixed duration within the specimen container. In this example, the mixer serves to disperse large particulates and microscopic particulates, such as human cells, within the liquid-based specimen by homogenizing the specimen. Alternatively, the specimen may contain subcellular sized objects such as molecules in crystalline or other conformational forms. In that case, a chemical agent may be introduced to the specimen at the preprocessing station to, for example, dissolve certain crystalline structures and allow the molecules to be dispersed throughout the liquid-based specimen through chemical diffusion processes without the need for mechanical agitation. In this example, the chemical preprocessing station introduces its dispersing agent through the preprocessing head.

In the illustrated preferred embodiment preprocessing occurs at the primary stirring station 500, which uses a specified or instructed stirring protocol to stir the specimen, if needed, using the stirrer 40 in the container, at a specified speed (rpm) for a specified duration. The stirring protocol chiefly depends on the specimen, as described above, and is normally intended to disaggregate any mucous material and disperse it and/or other particulate material in the specimen liquid.

Referring to Figs. 32-35, the primary stirring station 500 has a stirring head 502 in the form of an expanding steel collet. The collet is formed at the lower end of a shaft 503 which splits into six flexible fingers 504 defined by six equally spaced slits 506. Shaft 503 is rotatable in a bearing block 508 secured to a C-frame 510 that is vertically slidable on a mounting frame 512. Vertical movement of C-frame 510 and, hence, stirring head 502 is effected by a Z-axis stepper motor 514 and a lead screw 516. Stirring head 502 is rotatably driven by a stirring motor 518 through a timing belt 520 and timing pulleys 522, 524.

The inner surfaces of the collet fingers 504 taper uniformly inwardly toward the lower end of the collet. A central plunger 526, movable vertically by a pneumatic cylinder 528 atop a bracket 530, expands the fingers 504 outwardly when it descends and

encounters the narrowing passage defined by the tapering fingers. Thus the diameter of the lower end of the stirring head (collet) 502 increases when the plunger descends. This end is sized to fit loosely but closely within the annular wall 47 at the top of stirrer 40 when the collet is not expanded. When plunger 526 descends, the fingers 504 expand outwardly to wedge against the inside of wall 47, in manifold M, securely engaging the stirrer.

In operation, the stirring head 502 is first lowered so that the collet enters the manifold M. The dashed motor and bracket lines in Figs. 33 and 34 indicate this lowered position. Then plunger 526 descends to lock the stirring head to the stirrer. Then the stepper motor 514 is operated to slightly raise the stirring head and the attached stirrer 40. This vertical movement need only be very small, such as 0.050 in., just to free the stirrer from the ribs 26 and prevent interference with the container during stirring. Then DC stirring motor 518 is operated in accordance with the specimen-specific stirring protocol. Stirring speed can vary, and is usually in the range of about 500 rpm to about 3,000 rpm. The stirring time can vary from about 5 seconds to about 90 seconds. The base or bottom wall 41 of the stirrer acts as a slinger to thrust any liquid that may rise along the stirrer against the container wall, and prevents the escape of liquid from the container. Withdrawing the plunger 526 from the collet releases the stirrer 40 from the collet 502 so the specimen container can move on to the next station.

A contracting collet could be used instead of expanding collet 502. In that case, the collet fingers would fit around the outside of annular wall 47, and would be squeezed together to clamp around the wall by a descending sleeve that surrounds the fingers.

FILTER PLACEMENT STATION

At the filter placement station 600 an appropriate filter assembly F (see Fig. 5) is loaded into the open manifold M at the top of the stirrer 40. Filter assemblies can come in different filter configurations for automated machine recognition. For example, one set of filter assemblies can be colored red (5 micrometers), another set white (8 micrometers), each having different filtering properties, and a color sensor can detect which type of filter is before it and cause the proper filter to be loaded. The filter assemblies are dispensed by a pusher from a magazine having multiple filter tubes.

Figs. 36-40 show the structure and operation of the filter placement station. Referring to Figs. 37 and 40, a filter dispensing head 610 comprises a filter magazine in the form of a turret 612 rotatable on a spindle 614 by a stepper motor 616. Vertical post 611 provides the main support for the turret. Turret 612 has a top support plate 618 with

eight equally spaced holes 620 near its periphery, each hole opening through the edge of the plate 618 with a slot 622. A bottom guide plate 624 on spindle 614 has a similar arrangement of holes that are aligned with the holes and slots in the top support plate.

Eight steel filter tubes 626, each having an upper support shoulder 628, are supported vertically in holes 620 and the aligned holes beneath them, with shoulders 628 resting on the top of top plate 618. Each filter tube 626 has a full-length slot 630, and its bottom portion is split into four springy fingers 632 by slots 634. Just above the bottom end the fingers 632 curve inwardly, forming rounded inner shoulders 636 against which a filter assembly F rests. The filter tube is dimensioned such that the shoulders 636 keep up to a full stack of filter assemblies F from falling out of the tube, but deflect to allow a filter assembly to pass when the stack is pushed downwardly without damage to the filter assembly. Fingers 632 thus form a springy choke.

Fig. 39 shows the position of the filter magazine 612 in relation to the processing path and the adjacent processing stations, namely the primary stirring station 500 to the left, and the specimen acquisition station 700 to the right, all located on one side of the processing path as defined by guide rails 250. On the other side of the processing path opposite the filter magazine 612 is the assembly that supports and drives a pusher arm 640. This assembly comprises a support post 642 supporting a Z-axis lead screw 644 driven by a stepper motor (not shown) which moves a shuttle 646 that carries pusher arm 640. A filter sensor 650 positioned opposite bottom guide plate 624 monitors the passage (drop) of the lowest filter assembly F in the filter tube presented to (i.e., directly above) the specimen container. Sensor 650 also detects when the filter tube is empty. A second sensor 651 monitors filter type.

Filter assemblies of the same type are stacked in the proper orientation, with the membrane filter side (beveled edge) facing down, in each tube. For example, 54 filter assemblies can be housed in each tube; thus a total of 432 filter assemblies can be loaded into the magazine. Fifty-four filter assemblies can be prepackaged in a stack that is inserted into a filter tube with a wrapper tab projecting from slot 630, and unwrapped by pulling the tab outwardly. Alternatively, filter assemblies of the same type can be dumped onto a vibratory feeder, which can recognize their orientation by geometric configuration, and properly orient and feed the filter assemblies onto the tubes. Several of these feeders can be used, one for each type of filter assembly.

In operation, with the pusher arm 640 in its home (top) position, indicated by the dashed shuttle outline in Fig. 38, the filter magazine 612 is rotated by stepper motor 616

until sensor 650 detects the presence of the specified type of filter assembly in the filter tube before it. Shuttle 646 then moves downwardly with pusher arm 640 moving through slot 630 to press the stack of filter assemblies in that tube downwardly, until the lowest filter assembly drops from the tube into the manifold M in stirrer 40. When filter drop is sensed, the shuttle 646 with its pusher arm 640 stops its advance. In an alternative arrangement, a weight sensor can be used to monitor the weight of the filter stack, and detect by weight change when a filter assembly has dropped from the stack and when the filter tube is empty.

The use of eight filter tubes 626 in magazine 612 enables unattended processing of all of the specimens housed in the trays of the vial autoloader 300. For a counter-top model of the type described above, however, a single filter tube supported in a fixed position above the processing path would suffice for processing specimens that require the same type of filter.

SPECIMEN ACQUISITION AND CELL DEPOSITION STATION

Referring to Fig. 41, specimen acquisition station 700 has a suction head 702 that descends to engage the upper portion of the stirrer 40. Before drawing a vacuum on the specimen through the filter assembly F, the suction head grips, slightly lifts and rotates the stirrer 40, this time more slowly than at the primary stirring station (typically no more than 500 rpm for a 5 second interval), to re-suspend the particulate matter in the specimen liquid. The re-stir motor can be a Maxon 24 volt DC planetary gear-reduced type. Then suction is applied through suction line 750 to aspirate specimen liquid from the container 20 through suction tube 43, into the particulate matter separation chamber (manifold) 46 and through the filter assembly F, leaving a monolayer or thin layer of uniformly deposited cells on the bottom surface of the filter as described above. It may also be possible to rotate the stirrer slowly while the specimen liquid is being aspirated.

Fig. 6 shows how the suction head cooperates with the annular wall 47 of the stirrer manifold and the filter assembly F therein. The outer portion 704 of the suction head envelops the wall 47 and has an O-ring 760 that seals against the outside of wall 47. The inner portion 706 of the suction head has two concentric O-rings 762, 764 that seal against the top of filter holder 200. Suction applied through port 750 creates a vacuum around central opening 204 and within filter holder 200, which draws liquid into the manifold 46 and through the filter 202. An O-ring 766 is interposed between the inner and outer portions of the suction head.

Referring to Fig. 42, when aspiration of the specimen is complete, the suction head 702 is raised. The inner portion 706 of the suction head is extended at the same time by action of a pneumatic cylinder (not shown) mounted above the suction head. As the suction head 702 is raised, the outer portion 704 disengages from the stirrer 40, but the filter assembly F is retained on the inner portion 706 by application of a vacuum through suction line 752 to the annular space between O-rings 762 and 764. Thus the suction head 702 removes filter assembly F from the stirrer, and can continue to apply light suction via suction line 750 through the filter to effect a desired degree of moisture control of the cellular material on the filter.

The suction head 702 then moves laterally away from the transport conveyor by pivoting 90° about a vertical axis to the cell transfer position "P" shown in Fig. 46, to position the filter assembly F over a microscope slide S delivered from a slide cassette at slide presentation station 900. This pivoting movement of suction head 702 can also be seen in Figs. 11 and 39. The inner portion 706 of the suction head 702 then moves downwardly to press the filter against the slide S with a tamping force in the range of 4 to 8 lbs. and transfer the monolayer of cells thereto. The phantom lines in Fig. 42 show this change in position of suction head 702 and contact of the filter with slide S. Instead of being pivotally mounted, the suction head 702 could be mounted for rectilinear movement to and from a different deposition site where slides are presented, e.g., above the processing path.

Referring to Figs. 43-46, suction head 702 is rotatably mounted on a boom 716 that also carries the re-stirring motor 718, which rotates suction head 702 through a timing belt 720. Boom 716 is pivotally supported about a vertical axis 721 on a slide 722, which is vertically movable along frame support 724 by means of a Z-axis stepper motor 726 and a lead screw 728. Motor 726 thus moves the entire suction head vertically. Pivoting motion of boom 716 is effected by stepper a motor 717 operating through a gear train (not shown). Vertical motion of the inner portion 706 of the suction head is effected by a pneumatic cylinder and return spring (not shown) mounted above the suction head to an L-bracket 719, substantially identical to the arrangement 412, 413, 415 (see Fig. 29) used to move the plunger 408 of the uncapping head 402.

The frame support 724 is mounted on a slide 730 so as to be movable laterally of the transport path. A Y-axis stepper motor 732 and a lead screw 734 effect this movement. After the slide is printed the suction head is raised by the Z-axis motor, and

the Y-axis stepper motor 732 advances the entire assembly to the dashed line position "X" shown in Fig. 43. Then the suction head pivots back to its original orientation, transverse to the transport path (position "S" in Fig. 46). The Y-axis stepper motor 732 then pulls the entire assembly back toward its original position (solid lines in Fig. 43). As the suction head 702 moves (to the right as seen in Fig. 43), the still-retained filter assembly F is "scraped" off the suction head by the edge 736 of an open-top used filter (waste) tube 738 (see also Figs. 11 and 39). This leaves suction head 702 free to engage a fresh filter assembly.

The vacuum source that communicates with the suction head 702 pulls a slight vacuum, e.g., in the range of 3 in. to 10 in. Hg (adjustable by a regulator), through suction line 750 to aspirate specimen liquid and draw it through the filter assembly F. The separately regulated vacuum applied through suction line 752 for holding the filter assembly to the suction head 702 is higher, on the order of 20 in. Hg.

Formation of high-quality specimens on microscope slides depends critically on the deposition of a monolayer of cells of specified concentration (i.e., number of cells per unit area) on the surface of the filter that will contact the slide. That, in turn, depends critically on the aspiration rate and/or the aspirated flow volume. Since cell concentration on the filter surface is a function of the number of filter pores blocked by the solids suspended in the specimen liquid, the percent of flow reduction from the maximum open filter condition correlates to the blockage or amount of accumulation on the filter. Because of the nature of biological specimens, solid particle concentration is a significant variable in the process and must be taken into consideration. Also, it is important to identify the total volume of material filtered on a real time basis for other processing operations.

The specimen acquisition station thus further includes a deposition control system for controlling the liquid draw vacuum duration by monitoring the flow rate and/or aspirated volume. The monitored flow rate or aspirated volume can be used to signal vacuum cut-off and/or suction head retraction, which correlates to the specified concentration of cells collected on the membrane filter surface. If a specified concentration factor is not achieved before a specified volume of fluid is aspirated, the system can also issue a retract signal.

Different types of deposition control systems or modules can be used for these purposes. Fig. 47 schematically shows one such system, which has a meter in the form of a digital level detector positioned along a fluid column. This "bubble flow" system can

use sensors in the form of a plurality of LED emitters and corresponding number of photosensors, such as Omron sensor, EE-SPX613 GaAs infrared LED, placed along the length of the column. Any other type of sensors may be used. Alternatively, LED sensors such as the Omron sensors mentioned above can be used without corresponding emitters when they are positioned just at the edge of a glass tube. The meniscus edge of the liquid in the tube diffracts the light passing through the tube, and the sensor will detect the shifted light pattern when the rising meniscus edge reaches the sensor.

The fluid column is formed in a vertically extending transparent tube or cylinder 770, e.g., one made of Pyrex glass 9 mm in diameter by 1 mm thick. The aspirated specimen fluid is drawn from the specimen container through the membrane filter, and pulled into the glass cylinder 770 via suction line 750 and a 3-way valve 778, by means of a vacuum source 772 connected to the top of the cylinder. The sensors 774 are positioned evenly along the length of the cylinder 770, preferably at 1.5 ml capacity intervals, and are interfaced with a controller or microprocessor 776.

In operation, in the normal state, with no fluid in the tube 770, the sensor relay line is "low." Vacuum begins to draw fluid into the tube through the filter, and the controller marks the beginning of the draw sequence. When the fluid reaches the first sensor, the first sensor relay line goes "high." The controller marks the time it took for the fluid to reach the first sensor, indicating the nearly free-flow condition of the filter, and the relative viscosity of the fluid in the test. When an additional 1.5 ml of fluid is drawn into the tube, the second sensor relay line goes "high." The time interval for the first 1.5 ml of fluid (between the first and second sensors) is noted by the controller, and this becomes the reference time base. As each additional 1.5 ml of fluid is drawn into the system (and is detected by succeeding sensors), the time base for that increment is computed. When the incremental time base reaches an empirically derived percentage (e.g., 120%) of the original (reference) time base, the controller indicates that cell collection is completed, and a stop signal is transmitted, preferably to retract the suction head 702 from the manifold in the specimen container. The empirically derived figure mentioned above is variable with the protocol and directly controls the cellularity of the specimen sample.

The best approximation of the free-flow condition of the filter is obtained if the time it takes for the fluid to reach the first sensor 774 is kept to a practical minimum. This can be accomplished by incorporating the first sensor into the suction head itself, as schematically illustrated in Fig. 47a. In this embodiment, inner portion 706 of the suction head carries an emitter 774a and an opposed sensor 774b, which detects the leading edge

of the fluid column very close to the filter assembly F. The outer portion 704, which has teeth 775 engaged by timing belt 720 (not shown), is rotatable about the inner portion 706 (note interposed bearing 773) to rotate the stirrer (not shown) and stir the specimen prior to aspiration.

During the specimen drawing operation, the controller records the cumulative or total aspirated volume. If the cumulative volume reaches a predetermined level before reaching the predetermined flow rate reduction from the reference flow, the controller will also issue a stop signal and a flag indicating that the stop signal issued not as a result of desired reduced flow, but by reaching the maximum liquid draw limit. A slide formed under the flagged condition will likely form a hypo-cellular condition. The controller can imprint the slide and indicate to the DMS that a hypo-cellular condition likely exists. Accordingly, if the flagged condition exists, the controller issues a signal to purge the liquid in the cylinder 770 and initiate a second draw. The cylinder is purged of all liquid after each sample is taken.

Referring to Fig. 48, the deposition control system can have a purge value so that when the draw cycle is completed, the stop signal generated by the controller 776 will open the purge valve to vent the vacuum supply line to the atmosphere and divert the liquid remaining in the cylinder 770 into a waste container. The cylinder 770 can be maintained under a negative pressure. The system is then ready for the next cycle. Specifically, the system can have a 2-way solenoid valve V-3 in the suction line with one port 780 open to the atmosphere. The bottom of the cylinder 770 is connected to a valve manifold 782 with two solenoid valves V-2, V-4. The solenoid valves can be Lee LF series designed for use in vacuum systems, 2-way valve LFVA 2450110H, viton seal, 24 volt and 3-way valve, LFRX 0500300B, viton seal, 24 volt. The 2-way valve V-4 can port the specimen liquid to the bubble flow cylinder 770, or to vacuum by-pass 784. The 2-way valve V-2 can control the filter dehydration vacuum source. Fig. 49 illustrates the valve logic.

The deposition control system can use an analog level indicator instead of the digital sensors 774. The analog level indicator senses capacitance of the aspirated liquid. The difference is only in the method of sensing the volume and fill rate of the liquid in the cylinder 770. Here two spaced electrodes are used, one around the outside of the cylinder 770 and the other positioned down the center of the cylinder the cylinder, separated from the aspirated liquid by a dielectric. A high frequency, such as 10 kHz, low voltage current is applied across the electrodes. Capacitance in this system is measured by a bridge

circuit, which provides an analog indication of capacitance in the circuit. As fluid fills the column, capacitance in the circuit increases. A 10X differential in direct capacitance is easily obtained with this system. Capacitance is indicated on a real time basis and can be sampled frequently enough to provide control of the sampling system. This arrangement, like the first two, uses a computer or microprocessor and a bubble flow technology to measure the flow rate and the total fluid volume in real time. The predetermined volume increment for these arrangements can be in the range of about 0.1 ml to 5.0 ml, and preferably is in the range of about 1.0 to 2.0 ml.

A different system can use an ultrasonic indicator for measuring fluid movement through a tube. The ultrasonic system uses ultrasonic wave propagation through a moving liquid. In this regard, the third system employs an ultrasonic emitter and detector clamped across the liquid draw tube (suction line 750) operating on the distal end of the filter assembly F. This system provides a digital indication of fluid flow in the tube, the total volume aspirated through the tube being calculated by a flow interval calculation. It measures phase shift from the ultrasonic wave generator source to a detector for measuring flow speed.

Another way to measure aspirated fluid volume and control the duration of the specimen draw is to detect the change in the weight of the specimen vial. This can be accomplished by using a sensor that makes a high-precision measurement of the weight or mass of the vial containing the specimen that is being aspirated. Vial weight or mass is repeatedly measured at a high frequency such that the rate of change of the weight or mass of the vial is accurately determined. Specimen aspiration is completed when the rate of change in weight or mass has diminished by a predetermined amount or percentage from the initial rate. The weight sensor can be, e.g., a load cell in each conveyor receptacle 246, or a single load cell beneath the conveyor at the specimen acquisition head that rises to engage the container above it. In either case, the specimen acquisition head can be raised slightly during aspiration to unload the container so that the load cell can measure only the combined weight of the container and the remaining specimen.

Although specimen acquisition preferably is accomplished through aspiration (using a vacuum), it can also be accomplished by pressurizing the container 20 through an appropriate head that seals against the top of the container and forces specimen liquid up through tube 43 and through the filter assembly by means of positive pneumatic pressure. The fluid volume control schemes and mechanisms described above would also work in conjunction with such a pressurized specimen acquisition system.

The cell concentration can be selected from low to high by defining flow control cut-off. For a typical low cellularity result, the cut-off can be 80% of the 120% reference discussed above, and for high cellularity the cut-off can be set at 60% of the reference, selectable in 5% increments. The number of slides per specimen can range from one to three. Some of the typical default protocols are as follows:

GYN: 1,000 RPM stir, 30 second interval, 8-micrometer filter, 60% - high cellularity, one slide.

Urine: 1,000 RPM stir, 20 second interval, 5-micrometer filter, 70% - medium cellularity, one slide.

Lung sputum: 3,000 RPM stir, 120 second interval, 5-micrometer filter, 80% - high cellularity, two slides.

RE-CAPPING STATION

After completing the specimen processing cycle, the specimen container is resealed with the stirrer still inside the container. It is preferred to use a thin, polypropylene-coated aluminum foil to form the new cap, which is available in roll form. The foil is drawn across the open end of the specimen container, thermally bonded to the container at a seal temperature of about 365° F applied for about 3 seconds with a seal force of 3 pounds, and cut from the roll. Of course, any other type of re-capping material can be used as long as it is compatible with the vial material and creates a safe and reliable seal. For example, a foil backed with a thermosetting resin adhesive could be used; a sticky-backed foil could be used that does not require heat to effect a seal; or a plastic seal material can be bonded to the container ultrasonically. To enhance unattended operation, an automatic threader could be included for threading a new roll of sealing material into the re-capping mechanism. Cutting caps from a roll can be eliminated if roll-mounted pre-die-cut closures having peel-off tabs are fed to the re-capping mechanism.

Referring to Figs. 50 and 52, the re-capping mechanism 800 has a side support plate 802 secured to the machine base plate. The side support plate carries a main frame 810 having a top plate 812 with slots 814, 816, and two side plates 818, 820. A driver capstan 822 is journaled in side plates 818, 820. A foil advance motor 824, mounted on a bracket 826, drives the capstan. A pressure roller 828 is pivotally mounted to the main frame 810 and resiliently engages the capstan under the influence of a spring 830. Capstan 822 and pressure roller 828 define between them a throat through which the foil runs, and have resilient surfaces which grip the foil for positive feed. A handle 832 allows

the throat to be opened manually to allow the end of the foil to be fed into the throat after first passing through slot 814. A spindle 804, carried side support plate 802, supports a replaceable roll of foil.

Fig. 51 shows the foil path 834 through the throat. An L-shaped cutter 836 is pivoted at its elbow to the rear of main frame 810. One end of a single-acting pneumatic cutter actuator cylinder 838 is mounted on a bracket 840, and the other end of the cylinder is linked to the upper leg 842 of cutter 836. The lower leg of the cutter has a blade 844 that normally rests above the foil path downstream of the throat, held in that position by a spring 845 linked between the upper leg 842 and the support plate 802.

A rear post 850 pivotally supports an arm 852 that extends forwardly toward main frame 810. Arm 852 carries a heated platen 854 and a foil guide fork 856 having two tines that extend toward the throat and are spaced apart so as to allow the platen 854 to pass between them. Arm 852 is kept elevated, in the rest position shown in Fig. 51, by a spring 858. During the re-capping operation a single-acting pneumatic cylinder 860 pulls down on the arm 852 to lower the platen 854 and the guide fork 856. Note the position of a container 20 in a transport receptacle (not shown) beneath the platen 854.

In operation, the foil advance motor turns the capstan 822 to feed a measured length of foil past the cutter blade 844, into the fork 856, and to the position shown by the dashed line in Fig. 51. A photocell 862 detects the leading edge of the foil and signals the motor to stop. Then cylinder 838 is actuated to cut the foil, and cylinder 860 is actuated to pull arm 852 down to the seal position. The cut length of foil is sandwiched between the platen 854 and the container 20, and the container is sealed. After about three seconds cylinder 860 is deactivated and the arm 852 rises, returning to its rest position. A vacuum assist (not shown) optionally may be used to help hold the cut length of foil in position on the platen prior to sealing.

The foil caps applied by the re-capping mechanism are approximately square in shape. The corners of the foil caps can protrude from the vials and interfere with other re-capped vials that are returned to the trays 330. Accordingly, a foil folding ring 870 (seen in phantom lines in Fig. 51) preferably is provided which acts to fold the edges and corners of each foil cap down along the side of the container. The foil folding ring 870 preferably is mounted to act on the vial in the transport position immediately downstream of the re-capping mechanism, i.e., position "FF" in Fig. 51, and may be mounted on the re-capping mechanism itself, e.g., to main frame 810, so that actuation of cylinder 860 serves simultaneously to apply a foil cap to one container and fold the edges and corners of the

foil cap of the preceding (downstream) container. Alternatively, the foil folding ring or an equivalent foil folding mechanism can be mounted further downstream of the re-capping mechanism so as to act independently thereof.

Foil folding ring 870 is a metal ring having an inner diameter that is slightly larger than the outside diameter of the threaded portion of the container 20. The ring 870 is mounted on an arm (not shown) that moves downwardly when actuated to lower the ring 870 over the upper end of the container. As the ring encircles the container, it folds the overhanging portions 872 of the foil cap against the side of the container. When the ring rises after folding the foil, the container is held in position in its transport receptacle by a pin (not shown) that is mounted on a leaf spring (not shown) and is situated in the center of the ring 870. The leaf spring is carried by the arm that holds the ring, so the pin resiliently presses down against the center of the foil cap until the arm and the ring retract fully.

The foil seals applied to the processed containers are easily punctured by a syringe or a pipette to obtain further liquid specimen samples. The seals are very durable, however, withstanding rough handling and preventing leakage in low ambient pressure conditions, e.g., in aircraft flying as high as 40,000 ft. Further, the appearance of the foil seal makes it readily distinguishable from the cover of an unprocessed vial, making handling by low-skilled operators virtually foolproof. To avoid the potential of puncturing the foil seal inadvertently, the re-sealed container can be capped with an unused screw-on cover of a distinct color.

SLIDE HANDLING AND PRESENTATION

The LBP device can use 30 and 40 slide plastic magazines (cassettes), which can accept standard 25 mm x 75 mm x 1 mm and 1 x 3 x 0.040 in. slides. Metric and inch based slides can be used interchangeably. Figs. 52-55 show a 40-slide cassette C suitable for use in the LBP device. The slide cassette is in some respects similar to that disclosed in U.S. patent No. 5,690,892 (incorporated herein by reference), but is specially adapted for use in other devices as well, such as an automated stainer, an automated image analyzer, and a pathology work station, so that the slides do not have to be unloaded and reloaded into different magazines for use in those devices. Machine-readable indicia on the cassette, such as a bar code or an embedded microchip, provides cassette information that can be linked by the DMS to the bar codes on the slides in the cassette so that the location and status of any cassette and any slide in that cassette can be tracked in a laboratory system. The cassettes are stackable for compact storage and easy retrieval.

Specifically, the slide cassette is molded of plastic and has a generally rectangular shape with an open front 902, a rear wall 904, a top wall 906, a bottom wall 908 and side walls 910. The top wall 906 bears bar-coded information 909. A guide flange 912 extends laterally outwardly from each side wall. Rear wall 904 has a rectangular central opening 914 through which a slide shuttle can pass (see below) to extract and return one slide at a time. An inwardly projecting ridge 916 around the central opening acts as a stop against which the slides abut when they are inserted into the cassette. The preferred material for the cassette is ABS plastic; alternative choices include polyurethane, thermoplastic polyester, and polypropylene. The open front face is sized to accommodate the rear of another like cassette so as to be stackable.

The slides are supported on shelves 918 at each side of the cassette. In the illustrated embodiment there are 41 pairs of left and right shelves, and each pair (except for the top pair) supports one slide that spans the space between the shelves. Referring to the detailed view in Fig. 53, each shelf (except for the top and bottom shelves) has a raised top ledge 920 on which the slide rests and an underside beam spring 922 for applying a force to pinch and thereby frictionally restrain the slide against the top ledge directly beneath it. This arrangement keeps the slides from falling out of the cassette, even when the cassette is held face down, yet enables each slide to be moved out of and back into the cassette by the slide presentation apparatus, described below, without blocking, scratching or interfering with the slide-mounted specimens. Each shelf 918 also has a lead-in ramp 924 which guides the slide during insertion into the cassette. Each shelf 918 (including spring 922) preferably is integrally molded into the cassette and is attached to both the rear wall 904 and a side wall 910. However, separately fabricated springs, plastic or metal, may be inserted between the shelves instead.

Each side wall is provided with multiple drainage ports 926 which allow fluid to drain from the cassette after removal from a staining bath. The last (top and bottom) drainage ports 923 on each side also cooperate with a hanger assembly of a stainer for moving the cassette from one staining bath to another. During the staining operation the cassette is oriented generally on its side, hung from the last two drainage ports on the upper side. An all-plastic construction makes the cassette compatible with acid baths and all types of staining bath compositions.

Referring to Fig. 54, rear wall 904 has two rows of apertures 927 that form two integrally molded gear racks 928, which are adapted to engage pinion gears 936 (see below) for moving the cassette longitudinally so that each slide can be accessed by the

slide shuttle. Two spaced parallel racks and two pinion gears enhance the smoothness and accurate positioning of the cassette, as compared to a single rack and single pinion. Also integral with the rear wall is a row of 40 cassette position sensing slots 929 extending through the rear wall and coincident with the positions of the slides to allow for optical sensing of each slide. Further, rear wall 904 has a row of 40 blind recesses 925 (these do not extend completely through the rear wall) that allow for accurate sensing of cassette position when it is driven via the gear racks 928.

The molded cassette preferably is supplied wrapped in sealed plastic for cleanliness, with slides installed. It is therefore well suited for shipping, relatively low in cost, disposable yet reusable. It has a high storage capacity and is stackable with others, thus providing high density storage for specimen samples.

Slide cassettes populated with slides are manually loaded into the LBP device in an elevated in-feed track 930 (see Fig. 11) located behind the filter loading station 600 and the specimen acquisition station 700. No latching is required to enter cassettes into the system. Up to ten unprocessed cassettes can be loaded in the LBP device at any one time, but only in a single orientation. The cassettes can be marked with a top indicator, and will not be accepted if they are installed backwards or upside down. The cassettes are loaded with their open fronts facing to the right as seen in Fig. 11, with the lead cassette between vertical rails 932.

The lead cassette moves down incrementally whenever a new slide is to be withdrawn from the cassette for specimen printing. This is accomplished by a stepper motor (not shown) driving pinion gears 936 that engages the racks 928 on the back of the cassette C (see Fig. 54). When all slides in the cassette have been processed, the cassette descends all the way to outfeed track 940, and a stepper motor/lead screw pusher 938 moves the cassette to the right into outfeed track 940, and then retracts. Then the next cassette in the infeed track 930 is advanced by a motor/lead screw pusher (not shown) to the front position between vertical rails 932, where it is engaged by the pinion gears 936 and moved downwardly until the first (lowest) slide comes into position for extraction. Each of the feed tracks can have a home sensor, which can be Omron self-contained shutter type, and a cassette full sensor, which can be Keyence fiber optic.

Figs. 11, 56 and 57 show the slide presentation system, which uses a slide shuttle feed system 960, e.g. AM Part No. 5000-1, for extracting one slide at a time from the cassette along the X-axis and placing it on a Y-axis handler, which moves the slide to the pressing (print) position. The aforementioned U.S. patent No. 5,690,892 discloses a

similar slide cassette and shuttle arrangement used in a pathology work station (microscope). The Y-axis handler 962 has a slide platen 964 secured to a follower 966, 967. The handler is driven by a stepper motor 970 and a lead screw 972, guided along a rail 968. A slide is held to the platen under a fixed shoulder 974 (against a spring 976) and a pivoted arm 978 which is spring-biased in the counterclockwise direction as seen in Fig. 56.

When the handler 962 moves to the left, arm 978 moves off an adjustable stop 980 and rotates over the slide. The full Y-axis slide travel (shown as "T" in Fig. 57) brings the center of the slide to the print position "P" (note the dashed line position of the slide and the handler in Fig. 56). On its way to the print position the bar code number on the slide is acquired by a bar code reader 982 and transmitted to the host data base. When the print position is reached the suction head 702, which has pivoted along arc "A" about axis 721, lowers the filter assembly F into contact with the slide, as described above, depositing (printing) the specimen on the slide. Vacuum on the filter is maintained throughout the printing cycle to prevent over–hydration of the sample and unintentional dripping.

After printing the slide moves back to the right, pausing under a fixative dispensing head 984. Here a solenoid-driven pump (not shown), such as Lee LPL X 050AA, 24V, 20 microliter per pulse, yielding 12 microliters per pulse (maximum of 2 pulse/second), applies fixative to the specimen. The total volume can be determined by the number of solenoid cycles. The total fixative volume dispensed is programmable in 20 microliter increments. It can have a flexible connection to a dispensing sapphire jet nozzle with a 0.030 in. orifice. The liquid can be gravity-fed from a reservoir to the pump. The reservoir can be a tank and can have a "fluid low" sensor connected to the operating system. More than one fixative dispenser can be employed to provide alternative fixatives as determined by processing protocols.

After the specimen is fixed, the completed slide moves all the way to the right, where it is transferred by the slide shuttle mechanism back to its original position in the cassette. When the cassette is fully processed, the entire cassette is ejected into the outfeed track 940, as described above.

A COMPLETE LABORATORY SYSTEM

The present LBP device does not require that specimens be pre-processed before loading, and can automate every step of the slide preparation process. Moreover, the device does not require the operator to open any of the specimen containers – an important

operator safety feature. The LBP device can automatically prepare high quality cytology slides from all specimen types, including mucous-containing GYN and non-GYN specimens, using the integral high-speed, high-shear mixing station that facilitates mucous disaggregation. The incorporated dual-flow filter system allows production of slides with optimal cell separation, cell concentration, cell dispersion, and optimal preservation of antigens, DNA, and morphologic characteristics to enhance the performance of subsequent testing. The slide cassettes, containing up to 40 slides each, will be utilized in the follow-on laboratory processing devices to avoid the labor-intensive need to transfer slides to different racks before continuing with slide processing. Data on the patient, the specimen, the vial, the cassette and the slide can be transferred automatically to the LIS over the user's network, via a DMS software interface.

The present LBP device can provide eight hours of unattended operation. Thus, if the operator re-loads the device before leaving for the day, a single-shift laboratory can produce two shifts of output per day without added personnel or equipment costs. The total throughput can exceed 160,000 slides per year, at a per-test cost significantly below that of the current leading LBP system.

The LBP device also has the capability to process specimens for current and future molecular diagnostic tests including quantitative DNA analyses, and tests utilizing markers & probes. Features built into the device include the capacity to employ multiple fixative dispensers in order to provide non-routine fixatives that may be required for special molecular diagnostic tests.

The complete laboratory system, illustrated, e.g., in Fig. 21a, includes a pathology review station, a computer-aided microscopy work station used by pathologists to review specimen slides and sign out cytology cases. As with all components of the laboratory system, the pathology review stations are networked to the DMS and thereby to all other devices on the system, for rapid access to patient data and specimen processing information. The pathology review station accepts slide cassettes for automated loading and review of specimen slides. Computerized, fully automated image analyzers will perform quantitative analyses of DNA and molecular diagnostic tests, receiving their operating instructions and reporting their results via specimen bar codes using the integral DMS. See, for example, AccuMed/MDI U.S. patent Nos. 5,963,368; 6,091,842; and 6,148,096, which are incorporated herein by reference.

The laboratory system will also include, for example, slide autostainers and autocoverslippers (and/or combination automated stainer/coverslipper devices) controlled

via the DMS that utilize the same slide cassette as the present LBP device. Cassettes containing processed slides can be utilized directly in these additional devices without the need to unload slides and reload them into separate racks.

The inter-connectivity and high degree of automation of the processing and analytical devices making up the laboratory system will enable high-quality, high-throughput specimen processing and analysis at relatively low cost.

INDUSTRIAL APPLICABILITY

The above disclosure presents a safe, effective, accurate, precise, reproducible, inexpensive, efficient, fast and convenient vial-based system and method for collecting, handling and processing liquid-based cellular specimens, providing fully integrated specimen and information management in a complete diagnostic cytology laboratory system.

CLAIMS

1. An automated method for individually processing multiple specimens of particulate matter-containing liquid in respective containers, the method comprising:

transporting the containers seriatim along a processing path to present them to a mixing head and subsequently to a specimen acquisition head, the mixing head adapted to mix the specimen in any container presented to it, and the specimen acquisition head adapted to aspirate previously mixed particulate matter-containing liquid from any container presented to it and pass the aspirated liquid through a respective filter so as to collect a particulate matter sample on a surface of the filter;

actuating the mixing head in response to presentation of a container thereto so as to carry out the mixing operation independently; and

actuating the specimen acquisition head in response to presentation of a container thereto so as to carry out the aspirating operation independently.

2. An automated method according to claim 1, wherein operation of the mixing head is carried out in accordance with a protocol specific to the specimen presented thereto, and operation of the specimen acquisition head is carried out in accordance with a protocol specific to the specimen presented thereto.

3. An automated method according to claim 1 or claim 2, further comprising pressing seriatim each filter through which aspirated liquid has passed against a respective slide positioned in proximity to the processing path to transfer the particulate matter sample to the slide.

4. An automated method according to claim 1 or claim 2, wherein the specimen acquisition head is adapted to mix the specimen in each container presented to it, the method including actuating the specimen acquisition head to mix the specimen immediately prior to the aspirating operation.

5. An automated method according to claim 4, wherein the specimen acquisition head mixes the specimen more slowly than the mixing head.

6. An automated method according to claim 5, further comprising pressing seriatim each filter through which aspirated liquid has passed against a respective slide positioned in proximity to the processing path to transfer the particulate matter sample to the slide.

7. An automated method for individually processing multiple specimens of particulate matter-containing liquid in respective containers, each container having therein a mixer with an upper particulate matter separation chamber adapted to receive a filter and a depending aspiration tube communicating with the separation chamber, the method comprising:

transporting the containers seriatim along a processing path to a plurality of operating heads spaced so that the operating heads can operate simultaneously on different specimens, the plurality of operating heads comprising:

a mixing head adapted to engage and move the mixer in any container presented to the mixing head to mix the specimen therein,

a filter loading head downstream of the mixing head having a filter magazine and adapted to dispense a filter into any particulate matter separation chamber presented to the filter loading head, and

a specimen acquisition head downstream of the filter loading head adapted to seal against the particulate matter separation chamber presented and apply suction thereto to aspirate previously mixed particulate matter-containing liquid from the container and pass the aspirated liquid through the filter in the separation chamber so as to collect a particulate matter sample on a surface of the filter; and

actuating each of the operating heads in response to presentation of a container thereto so as to carry out the respective operation of each operating head independently.

8. An automated method according to claim 7, wherein operation of the mixing head is carried out in accordance with a protocol specific to the specimen presented thereto, and operation of the specimen acquisition head is carried out in accordance with a protocol specific to the specimen presented thereto.

9. An automated method according to claim 7 or claim 8, further comprising pressing seriatim each filter through which aspirated liquid has passed against a respective slide positioned in proximity to the processing path to transfer the particulate matter sample to the slide.

10. An automated method according to claim 7, wherein the filter magazine of the filter loading head is adapted to store at least two types of filters, and the filter type dispensed into the particulate matter separation chamber is governed by information specific to the specimen presented.

11. An automated method according to claim 7, claim 8 or claim 10, wherein the specimen acquisition head is adapted to mix the specimen in each container presented to it, the method including actuating the specimen acquisition head to mix the specimen immediately prior to the aspirating operation.

12. An automated method according to claim 11, wherein the specimen acquisition head mixes the specimen more slowly than the mixing head.

13. An automated method according to claim 12, further comprising pressing seriatim each filter through which aspirated liquid has passed against a respective slide positioned in proximity to the processing path to transfer the particulate matter sample to the slide.

14. An automated method according to claim 7, claim 8 or claim 10, wherein each container has a removable cover and is loaded into the processing path with the cover in place, and said plurality of operating heads further comprises an uncapping head along the processing path upstream of the mixing head and adapted to grip and remove the cover from a container presented thereto.

15. An automated method according to claim 14, wherein said plurality of operating heads further comprises a container recapping head along the processing path downstream of the specimen acquisition head and adapted to apply a sealing cap to an uncapped container presented thereto.

16. An automated method according to claim 15, further comprising unloading processed and recapped containers from the processing path, and loading unprocessed specimen containers into the processing path in positions vacated by processed and recapped containers.

17. An automated method according to claim 16, wherein container unloading and loading is carried out while movement of all containers along the processing path is arrested.

18. An automated apparatus for individually processing multiple specimens of particulate matter-containing liquid in respective containers, the apparatus comprising:

a conveyor having a plurality of spaced container supports for supporting and advancing containers seriatim along a processing path;

a mixing head along the processing path adapted to mix the specimen in any container presented thereto by the conveyor;

a specimen acquisition head along the processing path downstream of the mixing head adapted to aspirate previously mixed particulate matter-containing liquid from any container presented thereto by the conveyor and pass the liquid through a respective filter; and

a controller governing operation of the mixing head, operation of the specimen acquisition head and movement of the conveyor, the controller responding to presentation of a container to the mixing head to cause the mixing head independently to mix the specimen in the container presented thereto, and the controller responding to presentation of a container to the specimen acquisition head to cause the specimen acquisition head independently to aspirate previously mixed particulate matter-containing liquid from the container presented thereto.

19. An automated apparatus according to claim 18, wherein the controller causes the mixing head to operate in accordance with a mixing protocol specific to the specimen presented thereto, and causes the specimen acquisition head to operate in accordance with an aspiration protocol specific to the specimen presented thereto.

20. An automated apparatus according to claim 18 or claim 19, further comprising a slide presentation station in proximity to the specimen acquisition head, wherein the specimen acquisition head is movable relative to the processing path and is adapted to acquire and remove the filter from the separation chamber after aspiration of the liquid specimen and press the filter against a slide to transfer the particulate matter sample to the slide, and the controller allows the conveyor to advance after the filter is removed by the specimen acquisition head.

21. An automated apparatus according to claim 18 or claim 19, wherein the specimen acquisition head is adapted to mix the specimen in each container presented to it, the controller actuating the specimen acquisition head to mix the specimen immediately prior to the aspirating operation.

22. An automated apparatus according to claim 21, wherein the specimen acquisition head mixes the specimen more slowly than the mixing head.

23. An automated apparatus for individually processing multiple specimens of particulate matter-containing liquid in respective containers, each container having therein a stirrer with an upper particulate matter separation chamber adapted to receive a filter and a depending aspiration tube communicating with the separation chamber, the apparatus comprising:

a conveyor having a plurality of spaced container supports for supporting and advancing containers seriatim along a processing path;

a plurality of operating heads arranged serially along the processing path and spaced such that when one container support is positioned at one of the operating heads other container supports are positioned respectively at the other operating heads so that the operating heads can operate simultaneously on different specimens, the plurality of operating heads comprising:

a stirring head having a rotatable gripper adapted to engage and spin the stirrer in any container presented to the stirring head,

a filter loading head downstream of the stirring head having a filter magazine and adapted to dispense a filter into any particulate matter separation chamber presented to the filter loading head, and

a specimen acquisition head downstream of the filter loading head adapted to seal against the particulate matter separation chamber presented and apply suction thereto to aspirate previously stirred particulate matter-containing liquid from the container and pass the same through the filter in the separation chamber so as to collect a particulate matter sample on a surface of the filter; and

a controller governing operation of the operating heads and movement of the conveyor, the controller responding to presentation of a container to each operating head to cause such operating head to operate independently on the specimen in the container presented thereto.

24. An automated apparatus according to claim 23, wherein the controller causes the stirring head to operate in accordance with a stirring protocol specific to the specimen presented thereto, and causes the specimen acquisition head to operate in accordance with an aspiration protocol specific to the specimen presented thereto.

25. An automated apparatus according to claim 24, wherein the filter magazine of the filter loading head is adapted to store at least two types of filters, and the controller causes one of said filter types to dispense in accordance with information specific to the specimen presented.

26. An automated apparatus according to claim 23, claim 24 or claim 25, wherein the specimen acquisition head is adapted to stir the specimen in any container presented to it, the controller actuating the specimen acquisition head to stir the specimen immediately prior to the aspirating operation.

27. An automated apparatus according to claim 26, wherein the specimen acquisition head stirs the specimen more slowly than the stirring head.

28. An automated apparatus according to claim 23, further comprising a slide presentation station in proximity to the specimen acquisition head, wherein the specimen acquisition head is movable relative to the processing path and is adapted to acquire and remove the filter from the separation chamber after aspiration of the liquid specimen and press the filter against a slide to transfer the particulate matter sample to the slide, and the controller allows the conveyor to advance after the filter is removed by the specimen acquisition head.

29. An automated apparatus according to claim 23, claim 24 or claim 25, wherein each container has a removable cover and is loaded onto the conveyor with the cover in place, and said plurality of operating heads further comprises an uncapping head along the processing path upstream of the stirring head having a gripper adapted to grip and remove the cover from a container presented thereto.

30. An automated apparatus according to claim 29, wherein said plurality of operating heads further comprises a container recapping head along the processing path downstream of the specimen acquisition head and adapted to apply a sealing cap to an uncapped container presented thereto.

31. An automated apparatus according to claim 30, further comprising a specimen container loading and unloading station having a pick-and-place arm adapted to grasp a processed and recapped container and remove it from its support on the conveyor, and grasp an unprocessed specimen container and place it on a vacant support on the conveyor.

32. An automated apparatus according to claim 31, wherein the controller causes the pick-and-place arm to remove a recapped container from a support on the conveyor and load an unprocessed specimen container onto the same support on the conveyor while the conveyor is immobilized.

33. An automated method for individually processing multiple specimens of particulate matter-containing liquid in respective containers, each container having a removable cover, the method comprising:

transporting the containers seriatim along a processing path to present them to a plurality of operating stations spaced so that the operating stations can operate simultaneously on different specimens, the plurality of operating stations comprising, in sequence:

an uncapping station at which the cover of a container presented thereto is removed,

a mixing station at which the specimen in a container presented thereto is mixed,

a filter loading station at which a filter is placed into the particulate matter separation chamber adjacent the top of a container presented thereto, and

a specimen acquisition station at which the previously stirred particulate matter-containing liquid is aspirated from the container and passes through the filter so as to deposit a particulate matter sample on a surface of the filter; and

actuating each of the operating stations in response to presentation of a container thereto so as to carry out the respective operation of each operating station independently.

34. An automated method according to claim 33, further comprising a container recapping station, downstream of the specimen acquisition station, at which a container presented thereto is recapped.

35. An automated method according to claim 33, wherein the specimen acquisition station re-mixes the particulate matter-containing liquid before aspirating it from the container.

36. An automated method according to claim 33 or claim 35, wherein a slide presentation station is located in proximity to the processing path and the specimen acquisition station, the method further comprising pressing seriatim each filter through which aspirated liquid has passed against a respective slide to transfer the particulate matter sample to the slide.

37. An automated method according to claim 36, further comprising a container recapping station, downstream of the specimen acquisition station, at which a container presented thereto is recapped.

38. An automated apparatus for individually processing multiple specimens of particulate matter-containing liquid in respective containers, each container having a removable cover, the apparatus comprising:

a conveyor that supports and advances containers seriatim along a processing path;

a plurality of operating stations along the processing path, the operating stations comprising, in sequence:

an uncapping station having a gripper adapted to grip and remove the cover of any container presented thereto;

a stirring station having a rotatable gripper adapted to engage and spin a stirrer in any container presented thereto;

a filter loading station having a filter magazine and a pusher adapted to dispense a filter from the magazine into a particulate matter separation chamber adjacent the top of any container presented thereto;

a specimen acquisition station having a suction head adapted to seal against the particulate matter separation chamber presented thereto and aspirate the previously stirred particulate matter-containing liquid from the container and pass

the same through the filter in the separation chamber so as to collect a particulate matter sample on a surface of the filter; and

a container recapping station having a movable head that applies a sealing cap to any container presented thereto; and

a controller governing operation of the operating stations and movement of the conveyor, the controller responding to presentation of a container to each operating head to cause such operating head to operate independently on the specimen in the container presented thereto.

39. An automated apparatus according to claim 38, wherein the suction head is rotatable to enable re-stirring of the particulate matter-containing liquid before aspirating it from the container.

40. An automated apparatus according to claim 38 or claim 39, further comprising a slide presentation station in proximity to the processing path and the specimen acquisition station, wherein the suction head is movable relative to the processing path and is adapted to acquire and remove the filter from the separation chamber after aspiration of the liquid specimen and press the filter against a slide to transfer the particulate matter sample to the slide.

41. An automated apparatus according to claim 40, wherein the controller allows the conveyor to advance after the filter is removed by the suction head.

42. An automated method for individually processing multiple fluid specimens of biological material in respective containers, the method comprising:

transporting the containers seriatim along a processing path to present them to a preprocessing apparatus and subsequently to a specimen acquisition apparatus, the preprocessing apparatus adapted to preprocess the specimen fluid in any container presented to it, and the specimen acquisition apparatus adapted to remove preprocessed specimen fluid from any container presented to it for subsequent analytical testing or evaluation;

actuating the preprocessing apparatus in response to presentation of a container thereto so as to carry out the preprocessing operation independently; and

actuating the specimen acquisition apparatus in response to presentation of a container thereto so as to carry out the fluid removal operation independently.

43. An automated method according to claim 42, wherein the preprocessing apparatus disperses particulate components of the specimen fluid.

44. An automated method according to claim 43, wherein the specimen acquisition apparatus collects a cytology sample.

45. An automated method according to claim 43, wherein the specimen acquisition apparatus filters the removed specimen fluid.

46. An automated method according to claim 45, wherein the specimen acquisition apparatus collects a cytology sample.

47. An automated method according to claim 46, wherein the specimen acquisition apparatus places the cytology sample on a slide.

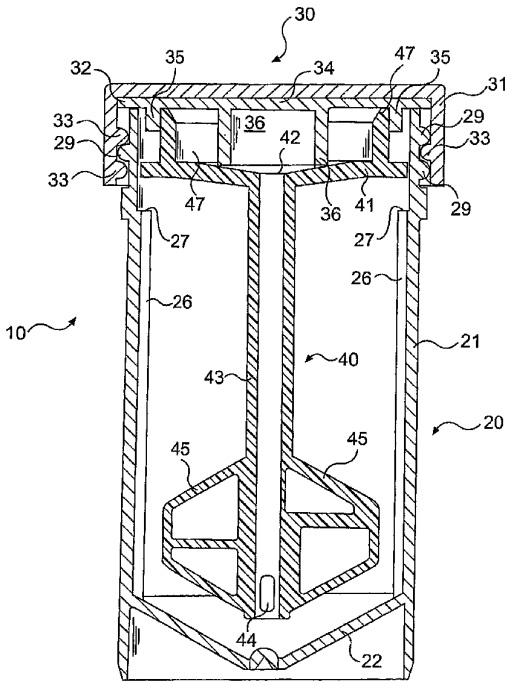
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FIG. 1

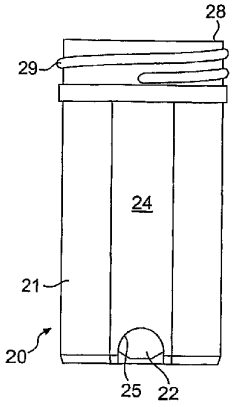


FIG. 2a

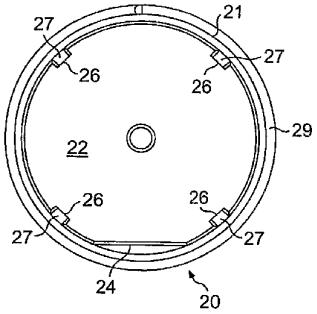


FIG. 2b

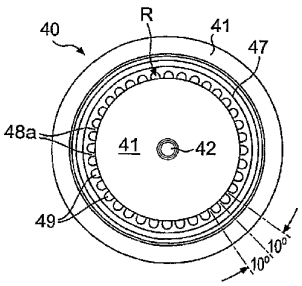


FIG. 3

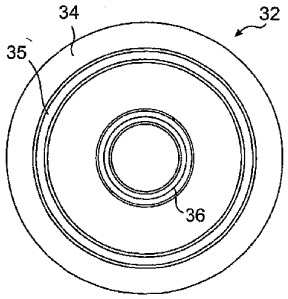


FIG. 4

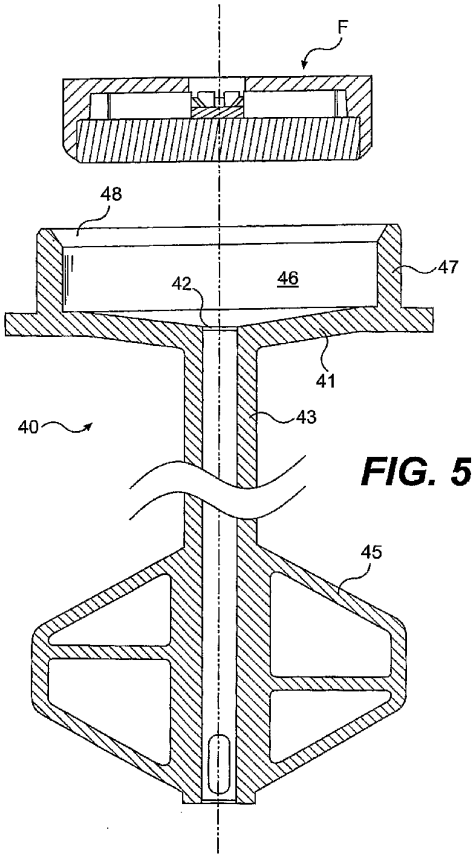
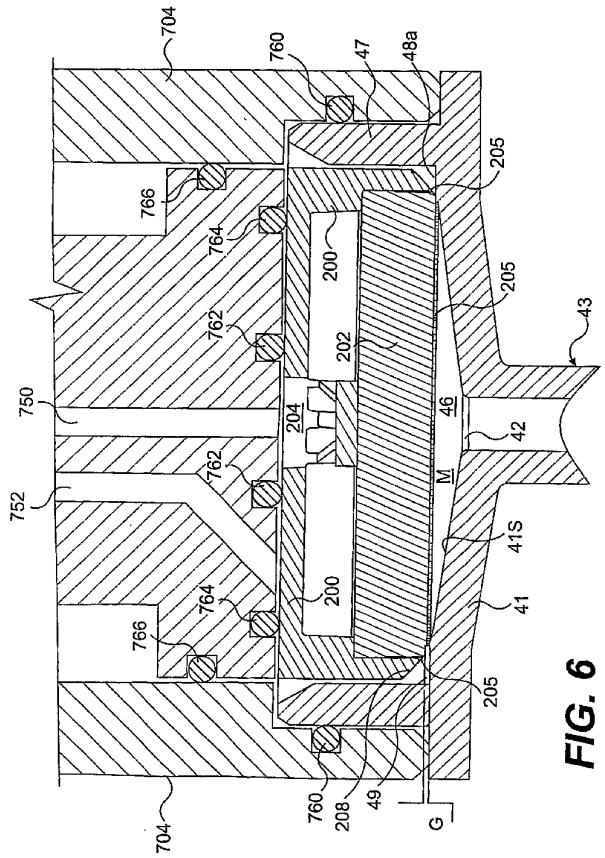


FIG. 5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48a
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766
764
200
205
762
202
43
750
204
46
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762
M
752
41S
764
200
41
766
205
760
208
49
G
704

FIG. 6

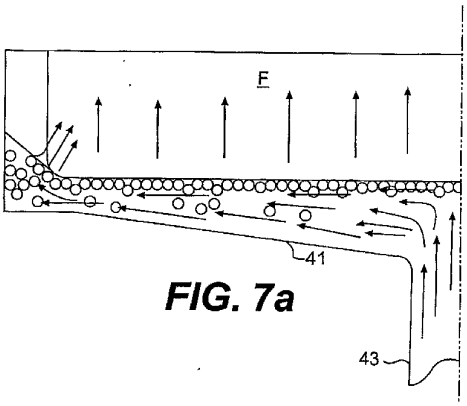

FIG. 7a

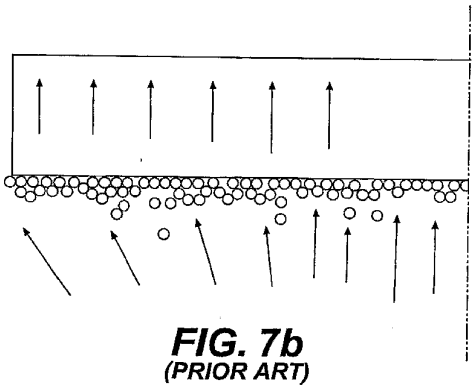

FIG. 7b
(PRIOR ART)

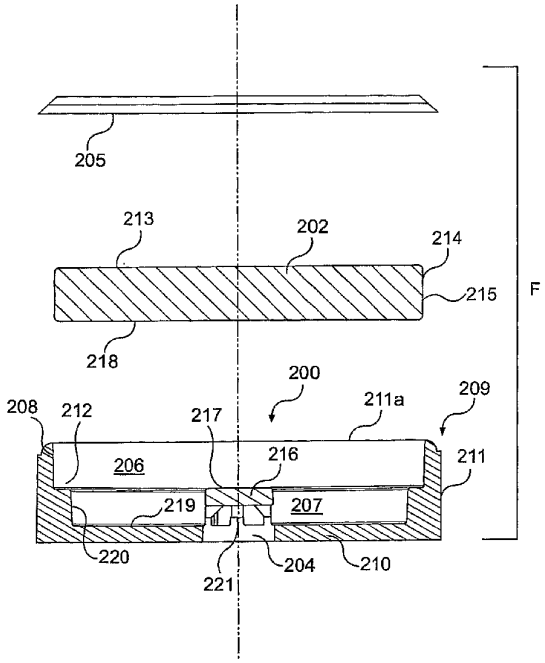
205
213
202
214
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FIG. 8

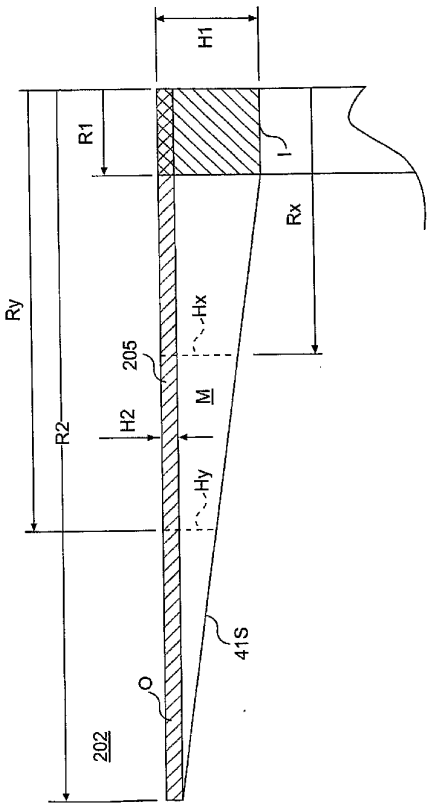

FIG. 9

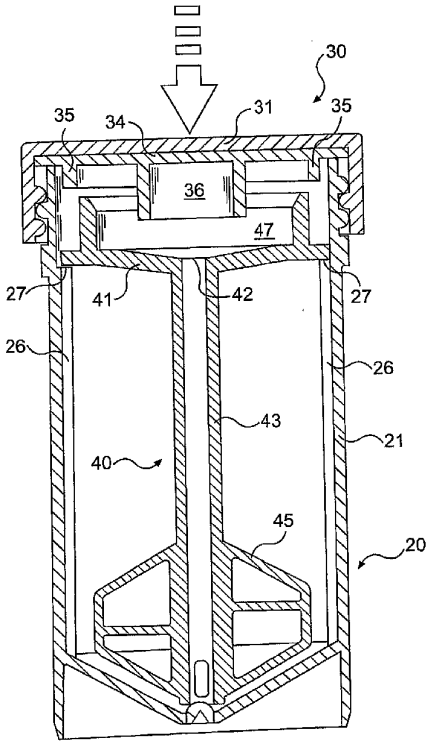

FIG. 10

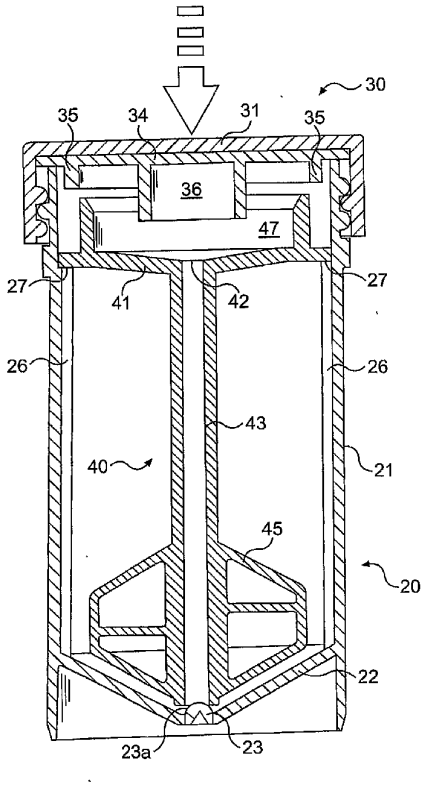

FIG. 10a

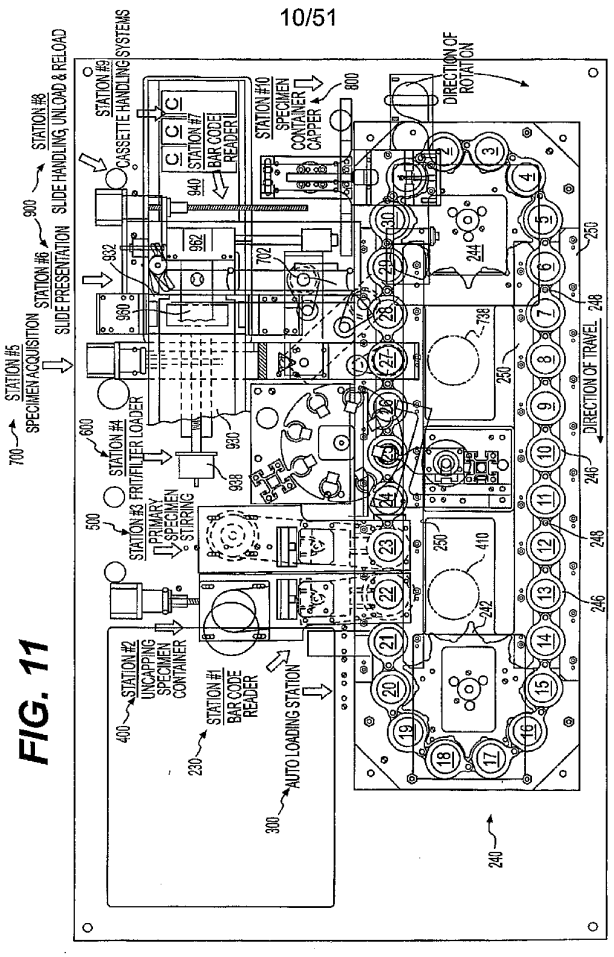
STATION #9
CASSETTE HANDLING SYSTEMS
STATION #8
SLIDE HANDLING, UNLOAD & RELOAD
STATION #6
SLIDE PRESENTATION
STATION #5
SPECIMEN ACQUISITION
STATION #10
SPECIMEN CONTAINER CAPPER
STATION #7
BAR CODE READER II
DIRECTION OF ROTATION
DIRECTION OF TRAVEL
STATION #4
FRIT/FILTER LOADER
STATION #3
PRIMARY SPECIMEN STIRRING
STATION #2
UNCAPPING SPECIMEN CONTAINER
STATION #1
BAR CODE READER
AUTO LOADING STATION
700
900
832
890
600
938
950
500
400
230
300
800
940
992
702
738
410
242
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FIG. 11

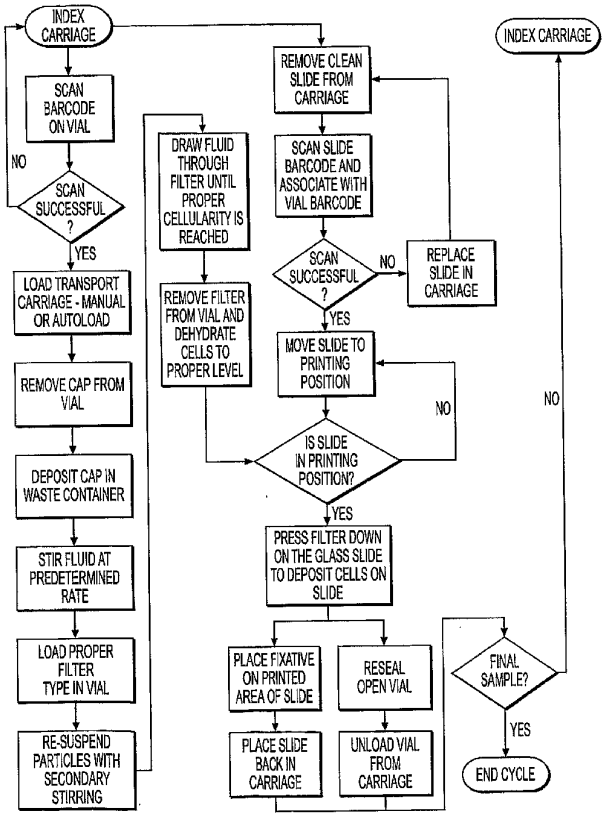
INDEX CARRIAGE
SCAN BARCODE ON VIAL
NO
SCAN SUCCESSFUL ?
YES
LOAD TRANSPORT CARRIAGE - MANUAL OR AUTOLOAD
REMOVE CAP FROM VIAL
DEPOSIT CAP IN WASTE CONTAINER
STIR FLUID AT PREDETERMINED RATE
LOAD PROPER FILTER TYPE IN VIAL
RE-SUSPEND PARTICLES WITH SECONDARY STIRRING
DRAW FLUID THROUGH FILTER UNTIL PROPER CELLULARITY IS REACHED
REMOVE FILTER FROM VIAL AND DEHYDRATE CELLS TO PROPER LEVEL
REMOVE CLEAN SLIDE FROM CARRIAGE
SCAN SLIDE BARCODE AND ASSOCIATE WITH VIAL BARCODE
SCAN SUCCESSFUL ?
NO
REPLACE SLIDE IN CARRIAGE
YES
MOVE SLIDE TO PRINTING POSITION
NO
IS SLIDE IN PRINTING POSITION?
YES
PRESS FILTER DOWN ON THE GLASS SLIDE TO DEPOSIT CELLS ON SLIDE
PLACE FIXATIVE ON PRINTED AREA OF SLIDE
RESEAL OPEN VIAL
PLACE SLIDE BACK IN CARRIAGE
UNLOAD VIAL FROM CARRIAGE
FINAL SAMPLE?
NO
YES
END CYCLE
INDEX CARRIAGE

FIG. 11a

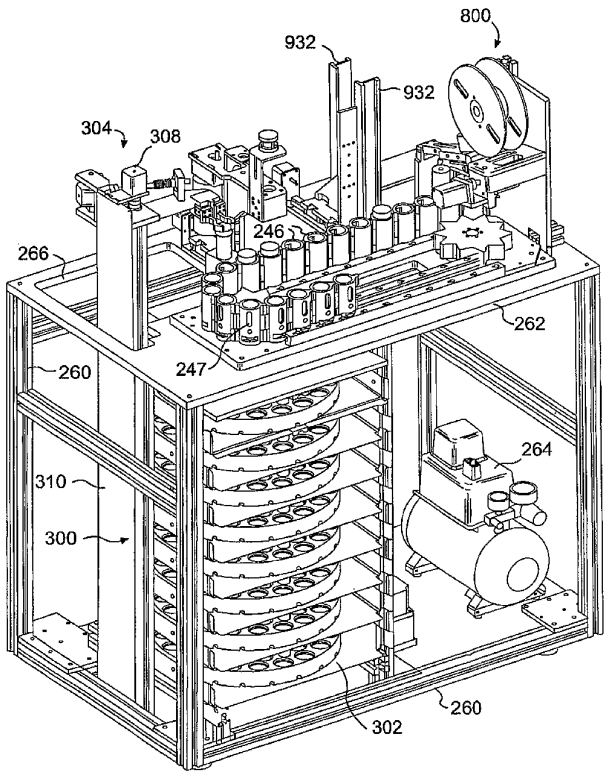

FIG. 12

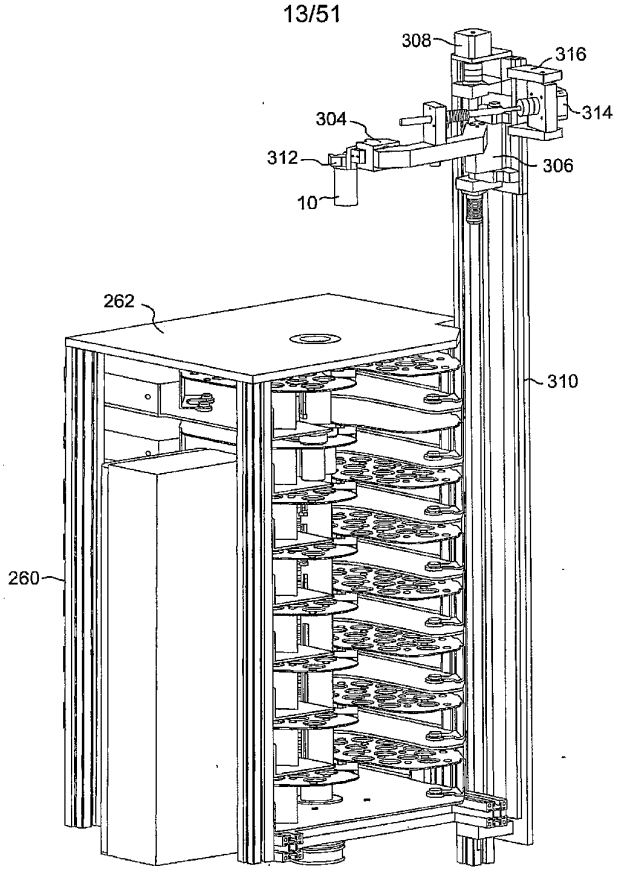

FIG. 13

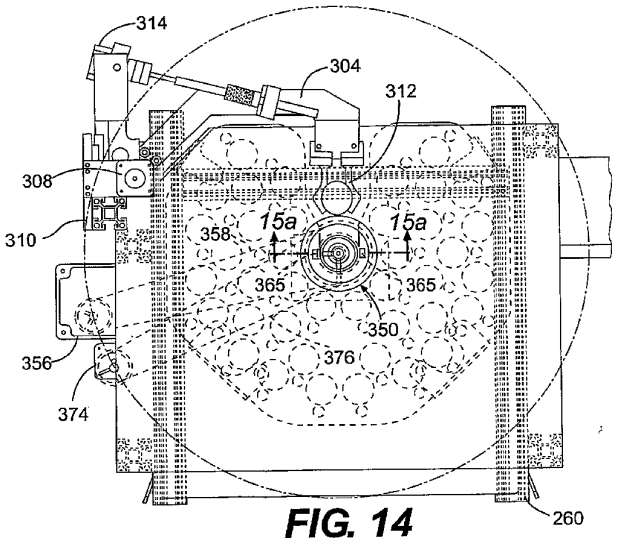

FIG. 14

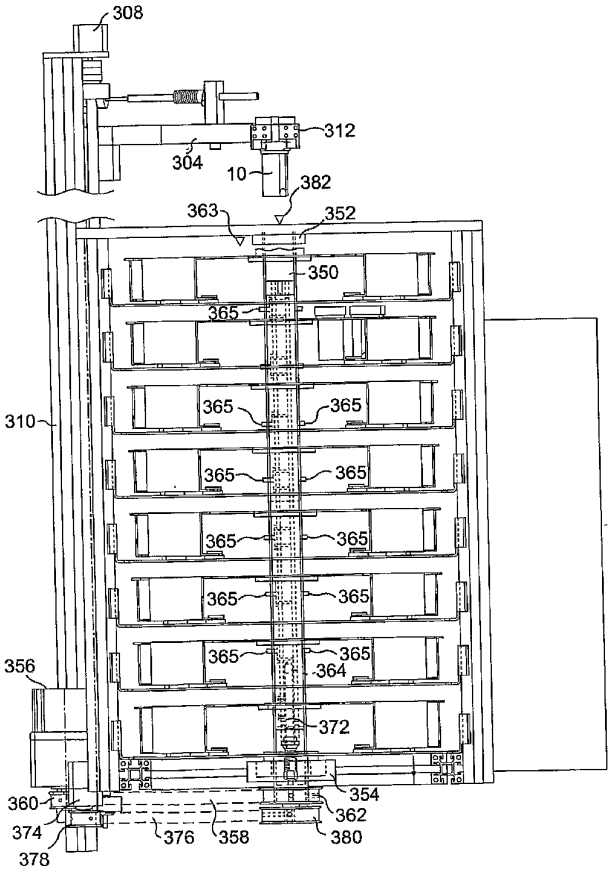
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FIG. 15

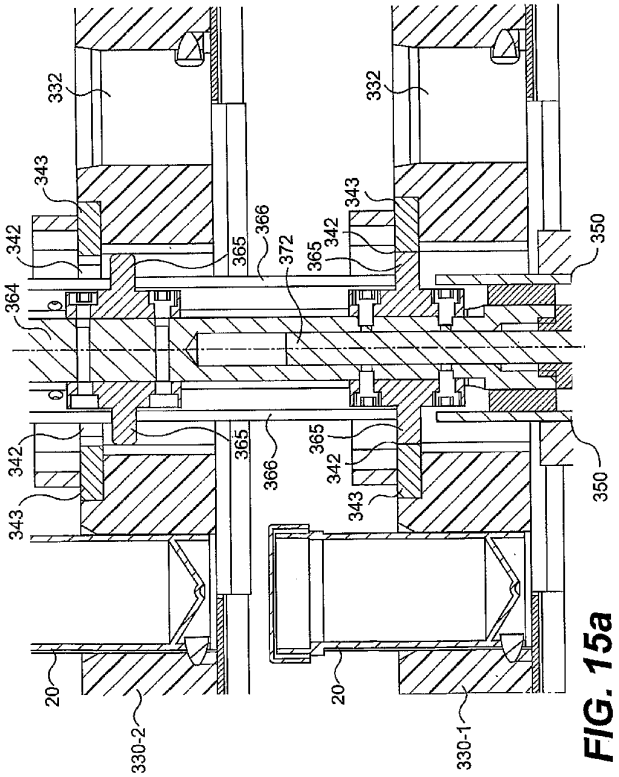


FIG. 15a

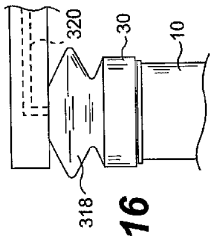


FIG. 16

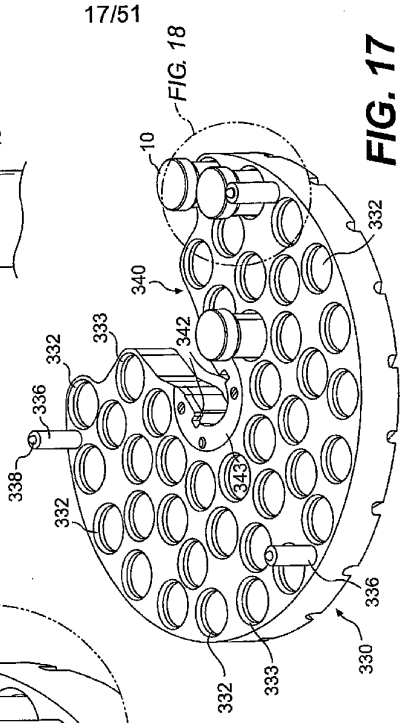


FIG. 17

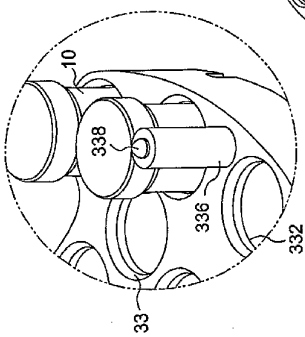
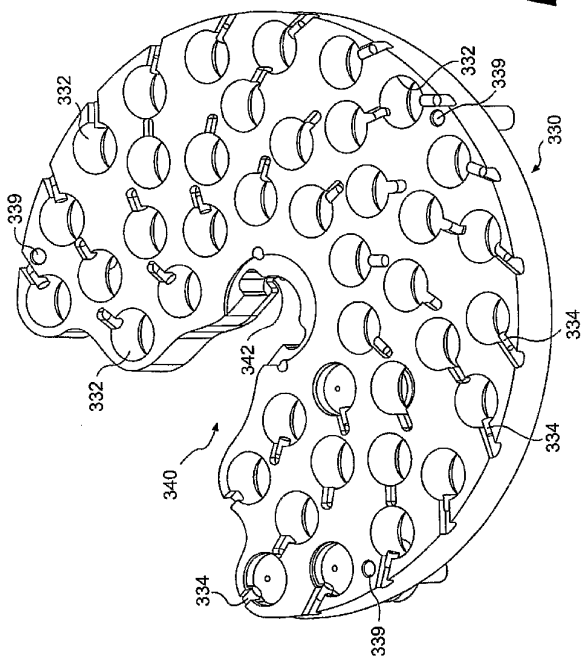


FIG. 18

FIG. 19



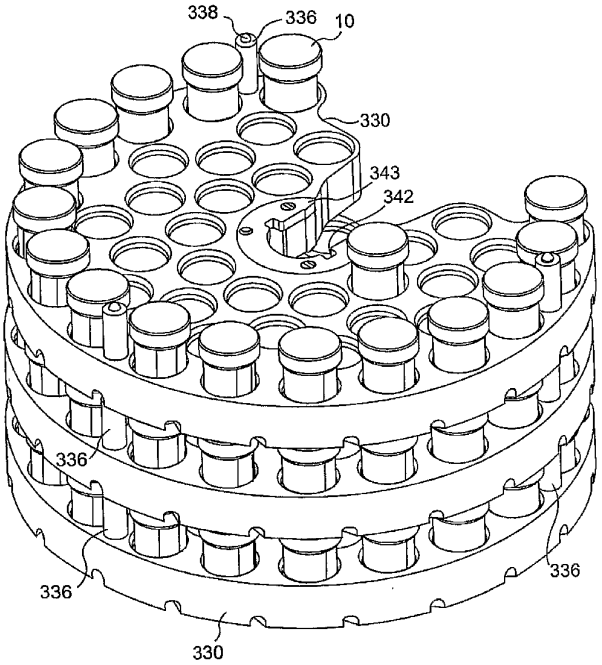


FIG. 20

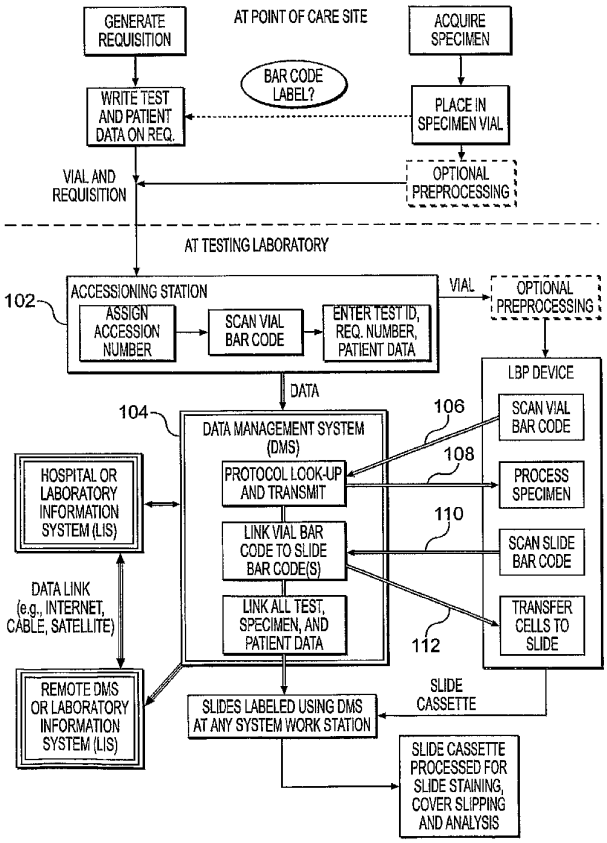

GENERATE REQUISITION
AT POINT OF CARE SITE
ACQUIRE SPECIMEN
BAR CODE LABEL?
WRITE TEST AND PATIENT DATA ON REQ.
PLACE IN SPECIMEN VIAL
VIAL AND REQUISITION
OPTIONAL PREPROCESSING
AT TESTING LABORATORY
102
ACCESSIONING STATION
ASSIGN ACCESSION NUMBER
SCAN VIAL BAR CODE
ENTER TEST ID, REQ. NUMBER, PATIENT DATA
VIAL
OPTIONAL PREPROCESSING
LBP DEVICE
DATA
104
DATA MANAGEMENT SYSTEM (DMS)
106
SCAN VIAL BAR CODE
108
PROTOCOL LOOK-UP AND TRANSMIT
PROCESS SPECIMEN
110
LINK VIAL BAR CODE TO SLIDE BAR CODE(S)
SCAN SLIDE BAR CODE
HOSPITAL OR LABORATORY INFORMATION SYSTEM (LIS)
DATA LINK (e.g., INTERNET, CABLE, SATELLITE)
LINK ALL TEST, SPECIMEN, AND PATIENT DATA
TRANSFER CELLS TO SLIDE
112
REMOTE DMS OR LABORATORY INFORMATION SYSTEM (LIS)
SLIDES LABELED USING DMS AT ANY SYSTEM WORK STATION
SLIDE CASSETTE
SLIDE CASSETTE PROCESSED FOR SLIDE STAINING, COVER SLIPPING AND ANALYSIS

FIG. 21

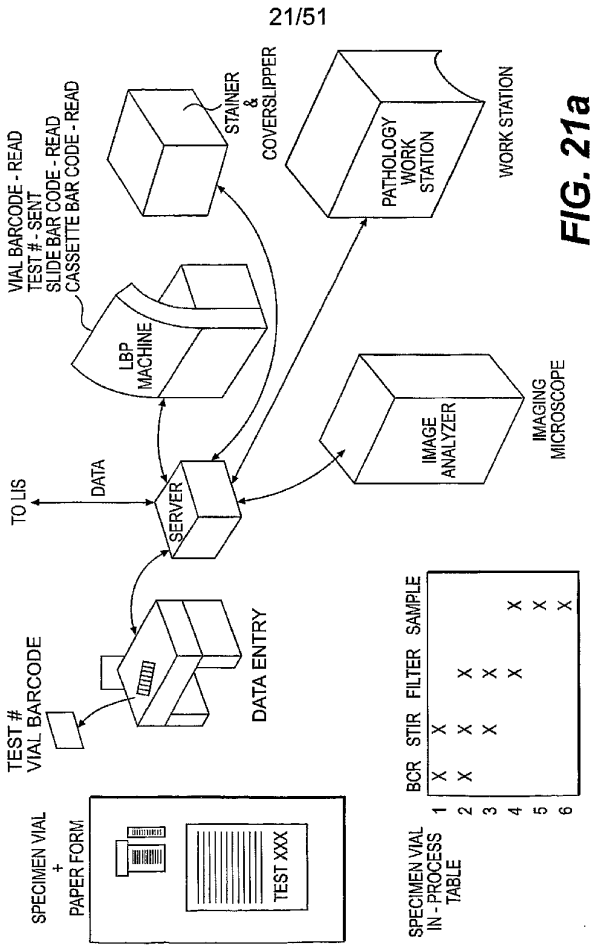

VIAL BARCODE - READ
TEST # - SENT
SLIDE BAR CODE - READ
CASSETTE BAR CODE - READ
STAINER & COVERSLIPPER
PATHOLOGY WORK STATION
WORK STATION
LBP MACHINE
IMAGE ANALYZER
IMAGING MICROSCOPE
TO LIS
DATA
SERVER
TEST # VIAL BARCODE
DATA ENTRY
SPECIMEN VIAL + PAPER FORM
TEST XXX
SPECIMEN VIAL IN - PROCESS TABLE
BCR STIR FILTER SAMPLE
1 X X
2 X X X X
3 X X X
4 X X
5 X
6 X

FIG. 21a

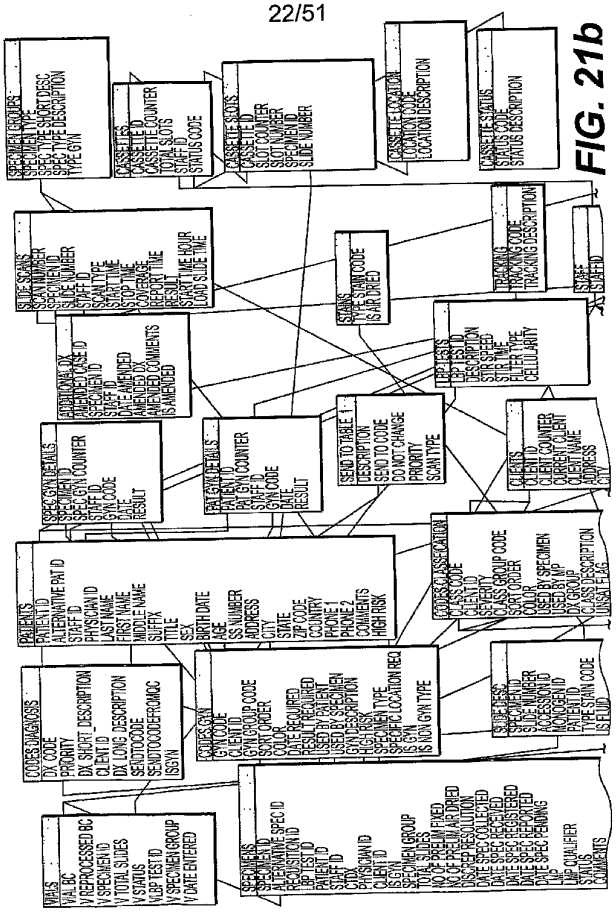

SPECIMEN GROUPS
SPECIMEN TYPE
SPEC. TYPE SHORT DESC.
SPEC. TYPE DESCRIPTION
TYPE GYN
CASSETTES
CASSETTE ID
CASSETTE COUNTER
CASSETTE SLOTS
TOTAL SLOTS
STAFF ID
STATUS CODE
CASSETTE SLOTS
CASSETTE ID
SLOT COUNTER
SLOT NUMBER
SPECIMEN ID
SLIDE NUMBER
CASSETTE LOCATION
LOCATION CODE
LOCATION DESCRIPTION
CASSETTE STATUS
STATUS CODE
STATUS DESCRIPTION
SLIDE SCANS
SCAN NUMBER
SPECIMEN ID
SLIDE NUMBER
STAFF ID
SCAN TYPE
START TIME
STOP TIME
COVERAGE
REPORT TIME
RESULT
START TIME HOUR
LOAD SLIDE TIME
SCANS
TYPE SCAN CODE
IS AIR DRIED
TRACKING
TRACKING CODE
TRACKING DESCRIPTION
STAGE
STAGE ID
ADDITIONAL DX
ADDITIONAL DX ID
SPECIMEN ID
STAFF ID
STAFF AMENDED DX
AMENDED COMMENTS
IS AMENDED
LTP TESTS
LBP TEST ID
DESCRIPTION
DESCRIPTION
STAIN TYPE
FILTER TYPE
CELL QUANTITY
NONSPECGYN DETAILS
SPECIMEN ID
SPEC GYN COUNTER
STAFF ID
STATE CODE
DATE
RESULT
PAT GYN DETAILS
PATIENT ID
PAT GYN COUNTER
STAFF ID
GYN CODE
DATE
RESULT
SEND TO TABLE 1
DESCRIPTION
SEND TO CODE
DO NOT CHANGE
PRIORITY
SCAN TYPE
CLIENTS
CLIENT ID
CLIENT COUNTER
CURRENT CLIENT
CLIENT NAME
ADDRESS
CITY
PATIENTS
PATIENT ID
ALTERNATIVE PAT ID
STAFF ID
PHYSICIAN ID
LAST NAME
FIRST NAME
MIDDLE NAME
SUFFIX
TITLE
SEX
BIRTH DATE
AGE
SS NUMBER
ADDRESS
CITY
STATE
ZIP CODE
COUNTRY
PHONE 1
PHONE 2
COMMENTS
HIGH RISK
CODES CLASSIFICATION
CLASS CODE
CLIENT ID
SEVERITY
CLASS GROUP CODE
SORT ORDER
COLOR
USED BY SPECIMEN
USED BY MP
SCK GROUP
CLASS DESCRIPTION
UNSAT FLAG
CODES DIAGNOSIS
DX CODE
PRIORITY
DX SHORT DESCRIPTION
CLIENT ID
DX LONG DESCRIPTION
SENDTOCODE
SENDTOCODEFROMDC
IS GYN
CODES GYN
GYN CODE
CLIENT ID
GYN GROUP CODE
SORT ORDER
COLOR
DATE REQUIRED
RESULT REQUIRED
IS USED BY PATIENT
IS USED BY SPECIMEN
GYN DESCRIPTION
HIGH RISK
SPECIMEN TYPE
SPECIFIC LOCATION REQ
IS GYN
IS NON GYN TYPE
SLIDE ITEMS
SLIDE NUMBER
ACCESSION ID
ACCIDENT ID
PATIENT ID
TYPE STAIN CODE
IS FLUID
SPECIMENS
SPECIMEN ID
ALTERNATIVE SPEC ID
ACCESSION ID
LBP TEST ID
PATIENT ID
STAFF ID
CYTO
PHYSICIAN ID
CLIENT ID
IS GYN
SPECIMEN GROUP
TOTAL SLIDES
NO OF PRELIM FIXED
NO OF PRELIM AIR DRIED
DISCARD RESOLUTION
DATE SPEC COLLECTED
DATE SPEC RECEIVED
DATE SPEC REGISTERED
DATE SPEC REPORTED
DATE SPEC PENDING
LMP
LMP QUALIFIER
STATUS
COMMENTS
RVALS
VAL BC
V REPROCESSED BC
V SPECIMEN ID
V TOTAL SLIDES
V STATUS
V LBP TEST ID
V SPECIMEN GROUP
V DATE ENTERED

FIG. 21b

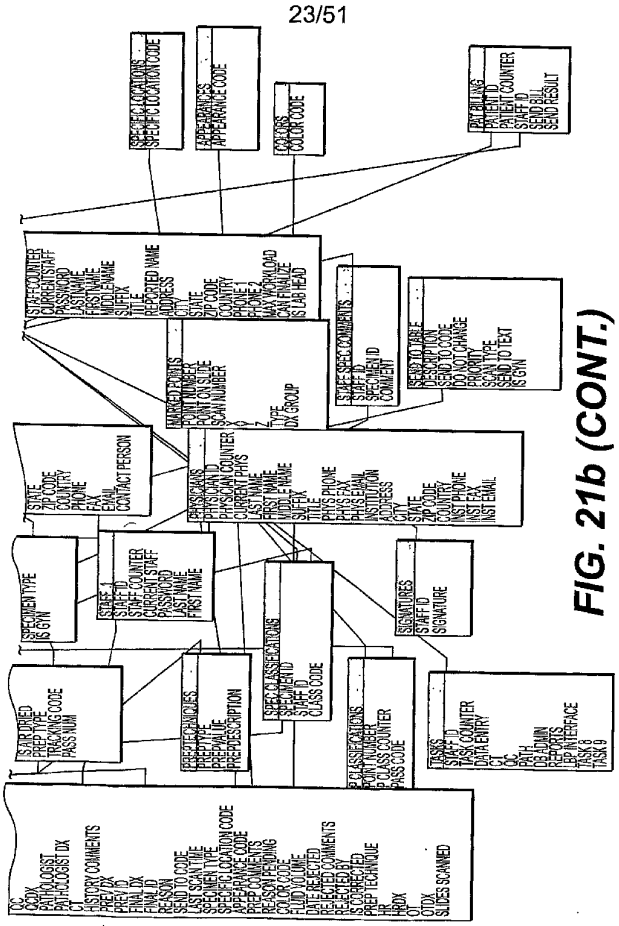

SPECIFIC LOCATIONS
SPECIFIC LOCATION CODE
APPEARANCES
APPEARANCE CODE
COLORS
COLOR CODE
BAT BILLING
PATIENT ID
PATIENT COUNTER
STAFF ID
SEND BILL
SEND RESULT
STAFF COUNTER
CURRENT STAFF
PASSWORD
LAST NAME
FIRST NAME
MIDDLE NAME
SUFFIX
TITLE
REPORTED NAME
ADDRESS
CITY
STATE
ZIP CODE
COUNTRY
PHONE 1
PHONE 2
MAX WORKLOAD
CAN FINALIZE
IS LAB HEAD
STAFF SPEC COMMENTS
STAFF ID
SPECIMEN ID
COMMENT
REPORTABLE
DESCRIPTION
SEND TO CODE
DO NOT CHANGE
PRIORITY
SCAN TYPE
SEND TO TEXT
IS GYN
MARKED POINTS
POINT NUMBER
POINT ON SLIDE
SCAN NUMBER
X
Y
Z
TYPE
IDX GROUP
STATE
ZIP CODE
COUNTRY
PHONE
FAX
EXAM
CONTACT PERSON
PHYSICIANS
PHYSICIAN ID
PHYSICIAN COUNTER
CURRENT PHYS
LAST NAME
FIRST NAME
MIDDLE NAME
SUFFIX
TITLE
PHYS PHONE
PHYS FAX
PHYS EMAIL
INSTITUTION
ADDRESS
CITY
STATE
ZIP CODE
COUNTRY
INST PHONE
INST FAX
INST EMAIL
SPECIMEN TYPE
IS GYN
STAFF 1
STAFF ID
STAFF COUNTER
CURRENT STAFF
PASSWORD
LAST NAME
FIRST NAME
SIGNATURES
STAFF ID
SIGNATURE
SLIDE CLASSIFICATIONS
SPECIMEN ID
STAFF ID
CLASS CODE
IS STAT DRIED
PREP TYPE
TRACKING CODE
PASS NUM
PREP TECHNIQUES
PREP TYPE
PREP VALUE
PREP DESCRIPTION
P CLASSIFICATIONS
PCMY NUMBER
P CLASS COUNTER
PASS CODE
TASKS
STAFF ID
TASK COUNTER
DATA ENTRY
CT
QC
PATH
DB ADMIN
REP PRTS
LIP INTERFACE
TASK 8
TASK 9
TQC
QADIV
PATHOLOGIST
PATHOLOGIST IDX
CT
HISTORY COMMENTS
PREV IDX
PREV ID
FINAL IDX
FINAL ID
REASON
SEND TO CODE
LAST SCAN TYPE
SPECIMEN TYPE
SPECIMEN DESCRIPTION CODE
APPEARANCE CODE
PREP COMMENTS
RESCAN PENDING
COLOR CODE
FLUID VOLUME
DATE REJECTED
REJECTED COMMENTS
REJECTED BY
IS CORRECTED
PREP TECHNIQUE
HR
HADIX
OT
OTDX
SLIDES SCANNED

FIG. 21b (CONT.)

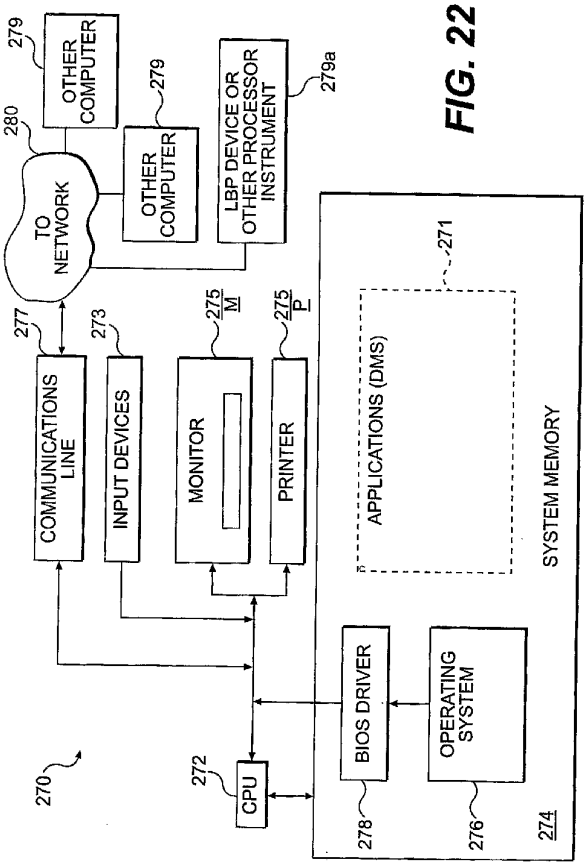

279
OTHER COMPUTER
279
OTHER COMPUTER
279a
LBP DEVICE OR OTHER PROCESSOR INSTRUMENT
280
TO NETWORK
277
COMMUNICATIONS LINE
273
INPUT DEVICES
275 M
MONITOR
275 P
PRINTER
271
APPLICATIONS (DMS)
SYSTEM MEMORY
BIOS DRIVER
OPERATING SYSTEM
270
272
CPU
278
276
274

FIG. 22

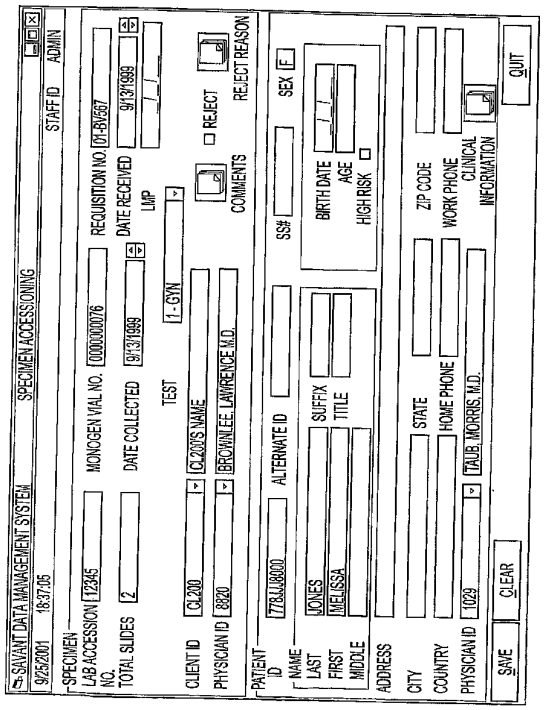

SAVANT DATA MANAGEMENT SYSTEM
SPECIMEN ACCESSIONING
9/25/2001 18:37:05
STAFF ID ADMIN
SPECIMEN
LAB ACCESSION NO. 12345
TOTAL SLIDES 2
MONOGEN VIAL NO. 0000000076
DATE COLLECTED 9/13/1999
REQUISITION NO. 01-R/667
DATE RECEIVED 9/13/1999
TEST
1 - GYN
LMP
CLIENT ID CL200
CL200'S NAME
PHYSICIAN ID 8820
BROWNLEE, LAWRENCE M.D.
REJECT
COMMENTS
REJECT REASON
PATIENT ID 7788JJ8800
ALTERNATE ID
SS#
SEX F
NAME
LAST JONES
FIRST MELISSA
MIDDLE
SUFFIX
TITLE
BIRTH DATE
AGE
HIGH RISK
ADDRESS
CITY
STATE
ZIP CODE
COUNTRY
HOME PHONE
WORK PHONE
PHYSICIAN ID 1029
TAUB, MORRIS, M.D.
CLINICAL INFORMATION
SAVE
CLEAR
QUIT

FIG. 23

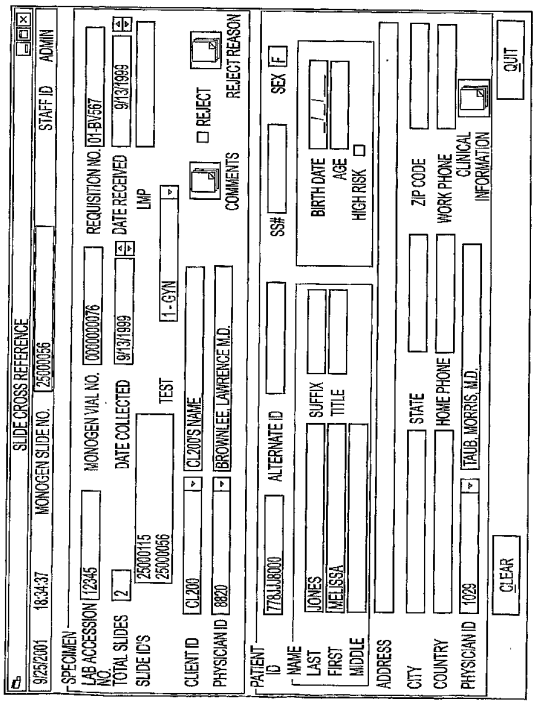

SLIDE CROSS REFERENCE
9/25/2001
16:34:37
MONOGEN SLIDE NO. 25000056
STAFF ID ADMIN
SPECIMEN
LAB ACCESSION NO. 12345
TOTAL SLIDES 2
SLIDE ID'S 25000115 25000668
MONOGEN VIAL NO. 0000000076
DATE COLLECTED 9/13/1999
TEST
REQUISITION NO. 01-BV1687
DATE RECEIVED 9/13/1999
LMP
1 - GYN
CLIENT ID CL200
CL200'S NAME
PHYSICIAN ID 3920
BROWNLEE, LAWRENCE M.D.
REJECT
COMMENTS
REJECT REASON
PATIENT ID 778ALL8000
ALTERNATE ID
SS#
SEX F
NAME
LAST JONES
FIRST MELISSA
MIDDLE
SUFFIX
TITLE
BIRTH DATE
AGE
HIGH RISK
ADDRESS
CITY
STATE
ZIP CODE
COUNTRY
HOME PHONE
WORK PHONE
PHYSICIAN ID 1029
TAUB, MORRIS, M.D.
CLINICAL INFORMATION
CLEAR
QUIT

FIG. 24

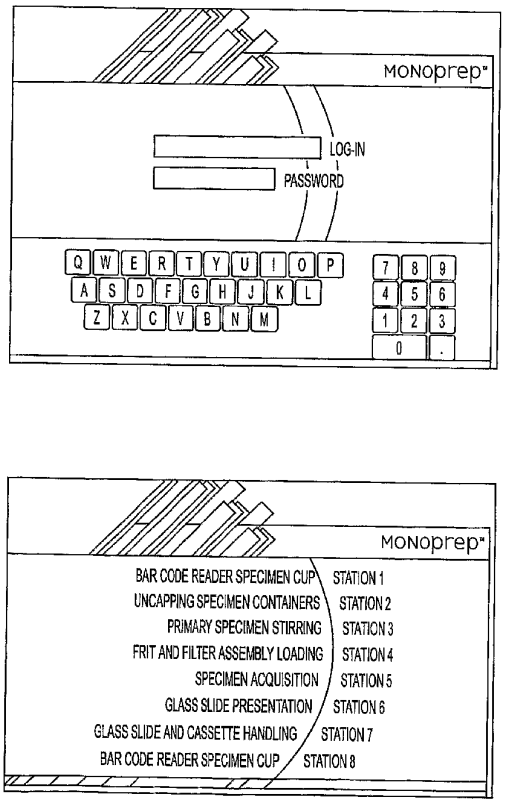

MONOprep
LOG-IN
PASSWORD
Q W E R T Y U I O P
A S D F G H J K L
Z X C V B N M
7 8 9
4 5 6
1 2 3
0 .
MONOprep
BAR CODE READER SPECIMEN CUP
UNCAPPING SPECIMEN CONTAINERS
PRIMARY SPECIMEN STIRRING
FRIT AND FILTER ASSEMBLY LOADING
SPECIMEN ACQUISITION
GLASS SLIDE PRESENTATION
GLASS SLIDE AND CASSETTE HANDLING
BAR CODE READER SPECIMEN CUP
STATION 1
STATION 2
STATION 3
STATION 4
STATION 5
STATION 6
STATION 7
STATION 8

FIG. 25

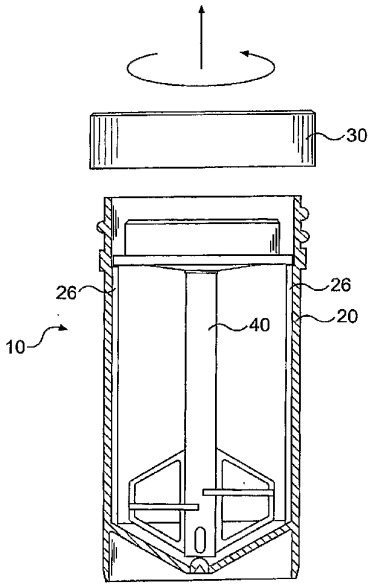


FIG. 26

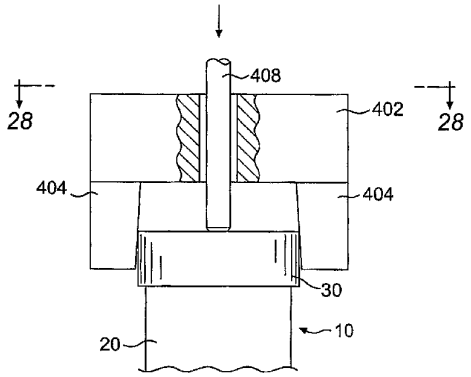

28
408
402
28
404
404
30
10
20

FIG. 27

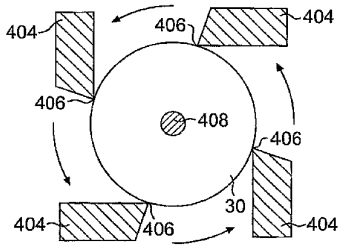

404
406
404
406
408
406
30
404
406
404

FIG. 28

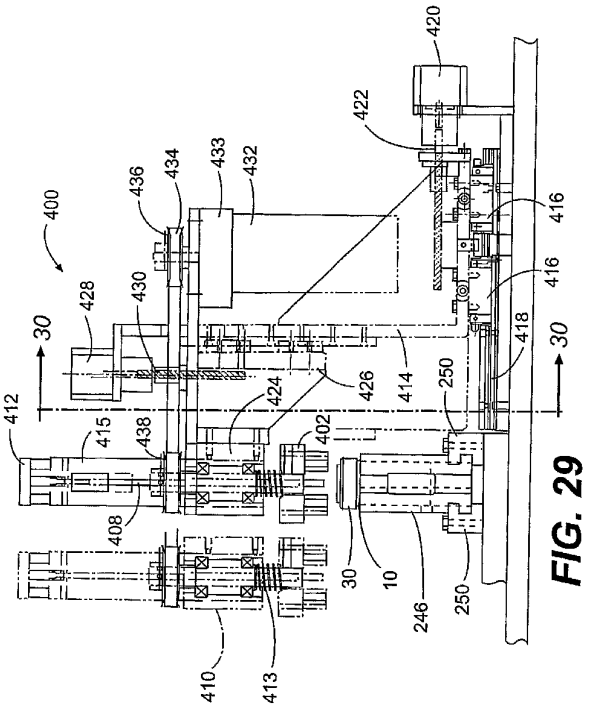

400
402
408
410
412
413
414
415
416
416
418
420
422
424
426
428
430
432
433
434
436
438
246
250
250
10
30
30
30
30

FIG. 29

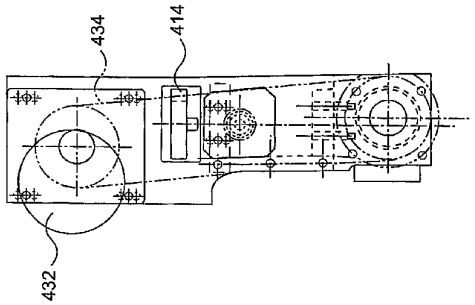


FIG. 31

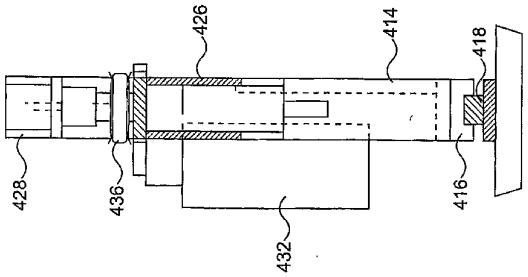


FIG. 30

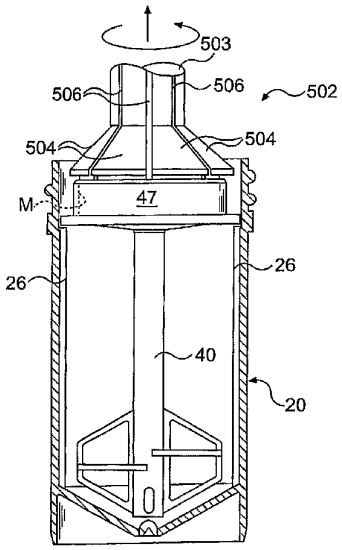


FIG. 32

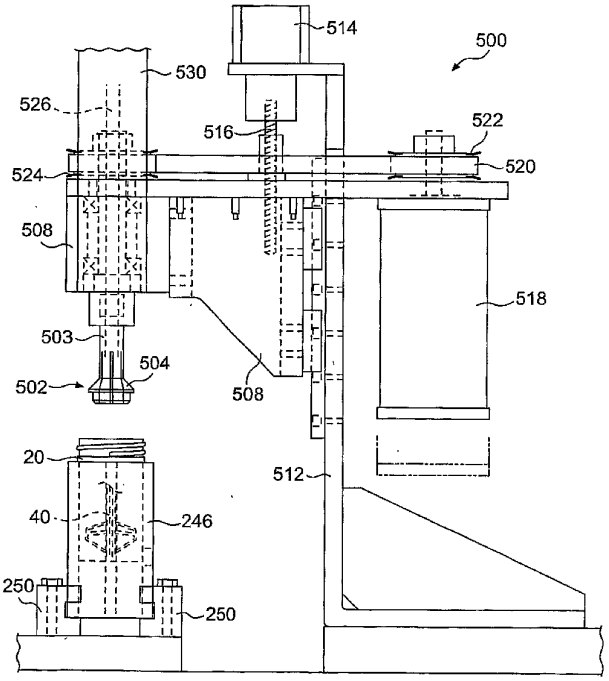

514
500
530
526
516
522
524
520
508
518
503
504
502
508
20
512
40
246
250
250

FIG. 33

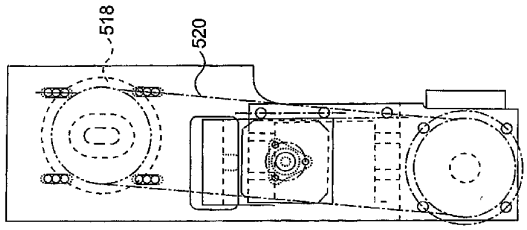


FIG. 35

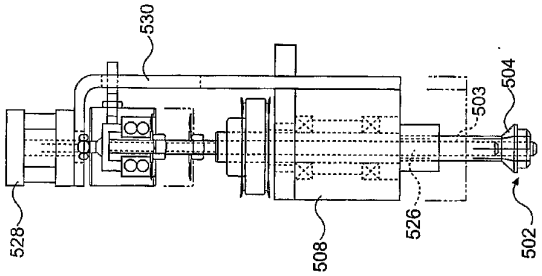


FIG. 34

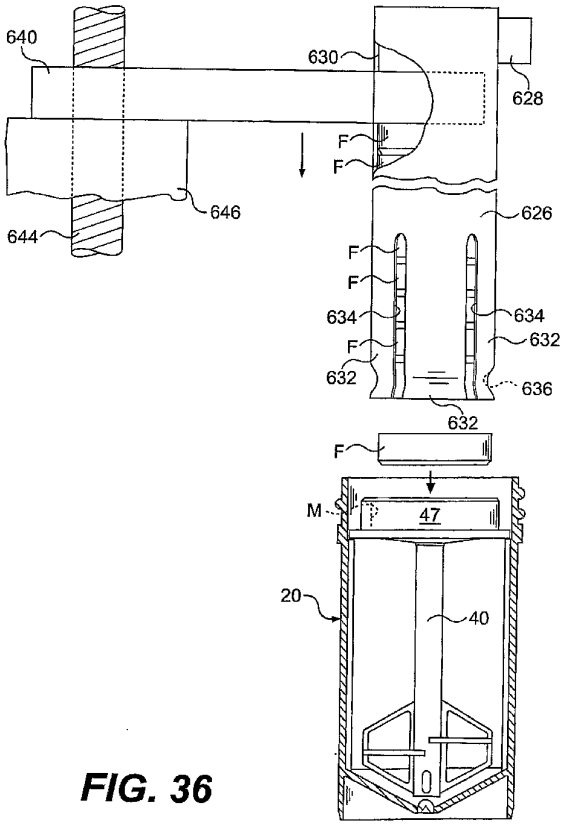


FIG. 36

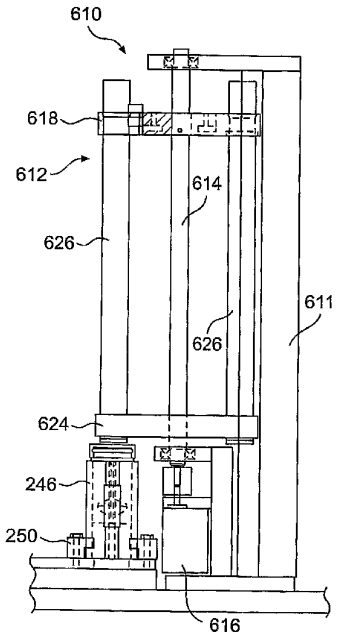


FIG. 37

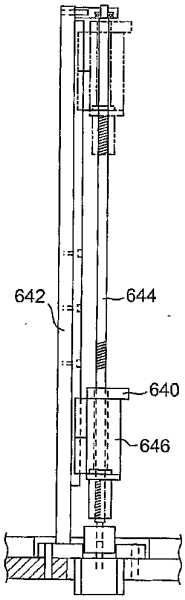


FIG. 38

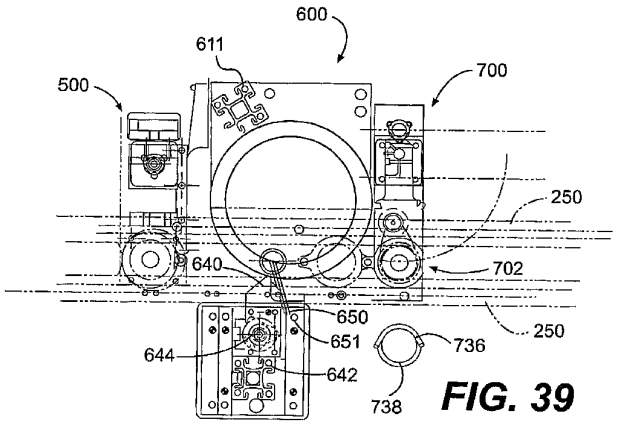

600
611
500
700
250
640
702
650
651
644
642
736
738
250

FIG. 39

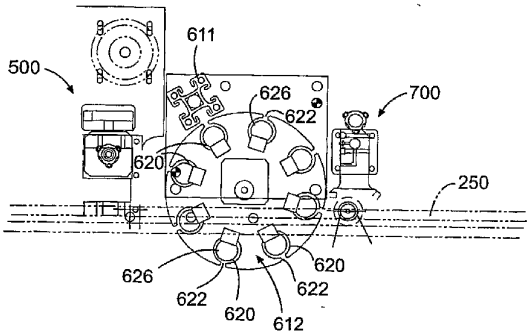

611
500
626
622
700
620
250
626
622
620
622
620
612

FIG. 40

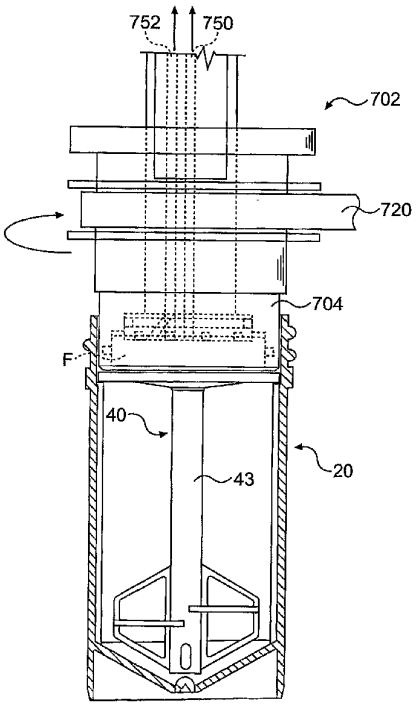


FIG. 41

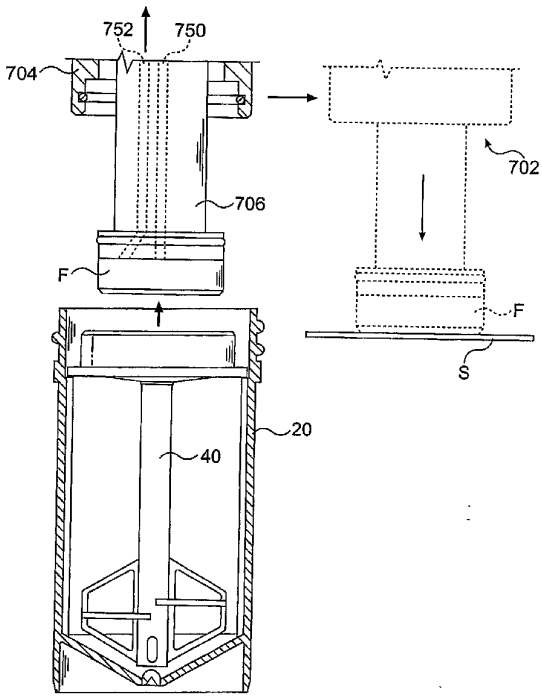


FIG. 42

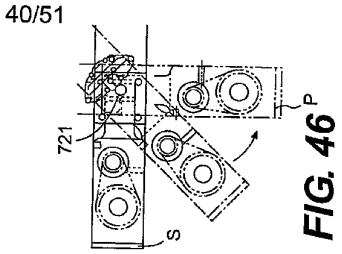


FIG. 46

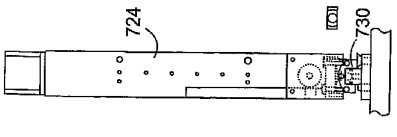


FIG. 44

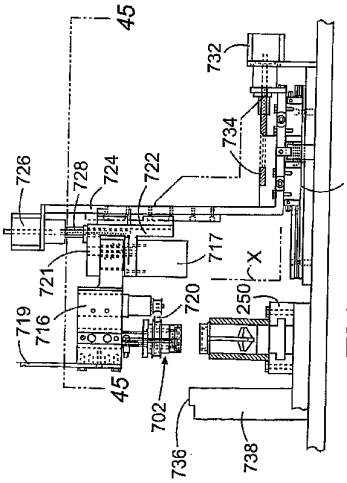


FIG. 43

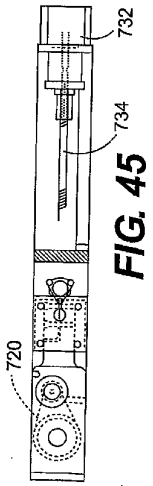


FIG. 45

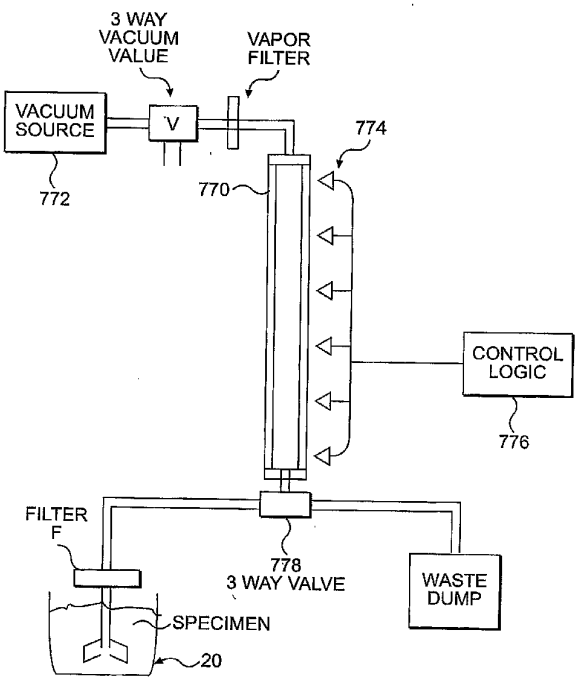

3 WAY
VACUUM
VALUE
VAPOR
FILTER
VACUUM
SOURCE
V
774
772
770
CONTROL
LOGIC
776
FILTER
F
778
3 WAY VALVE
WASTE
DUMP
SPECIMEN
20

FIG. 47

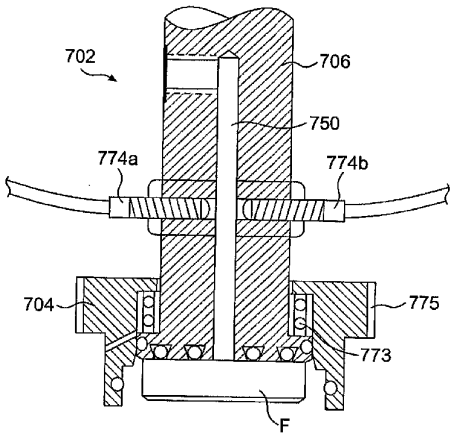


FIG. 47a

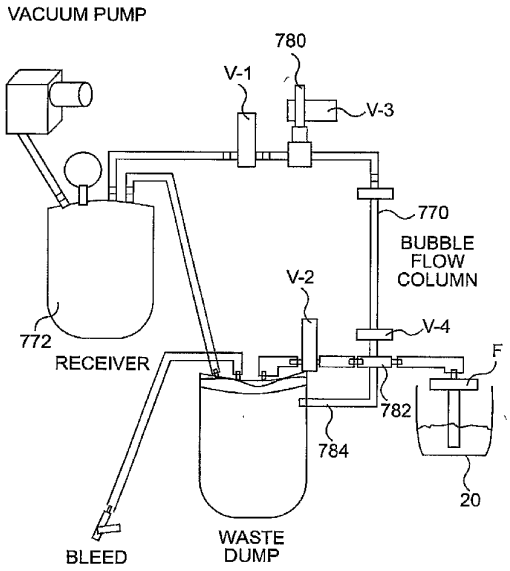

VACUUM PUMP
780
V-1
V-3
770
BUBBLE
FLOW
COLUMN
V-2
V-4
772
RECEIVER
F
782
784
20
BLEED
WASTE
DUMP

FIG. 48

FLOW SENSOR OPERATION

SEQUENCE OF OPERATIONS

	V-1	V-2	V-3	V-4
#1				
MEASURED PULL	ON	OFF	OFF	OFF
#2				
TAMP PRINT	OFF	ON	OFF	OFF
#3				
PURGE	OFF	OFF	ON	ON

FIG. 49

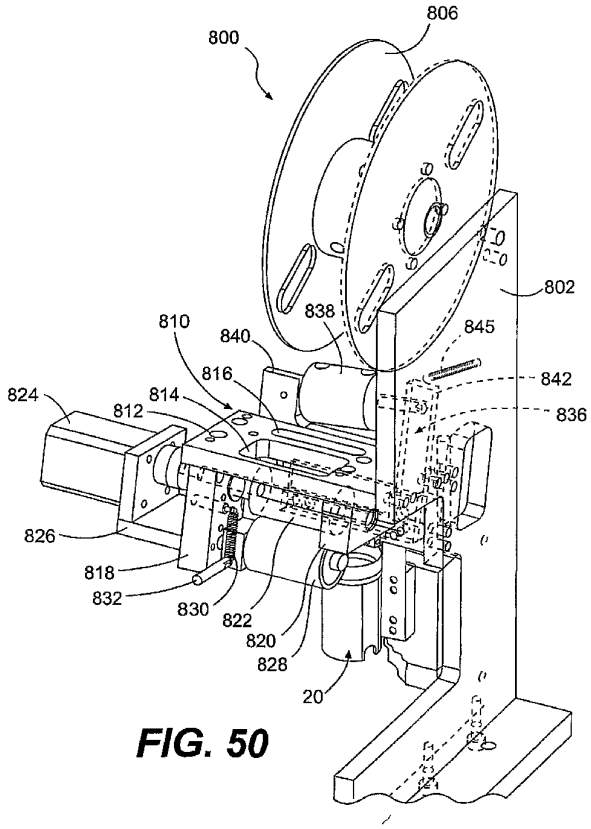
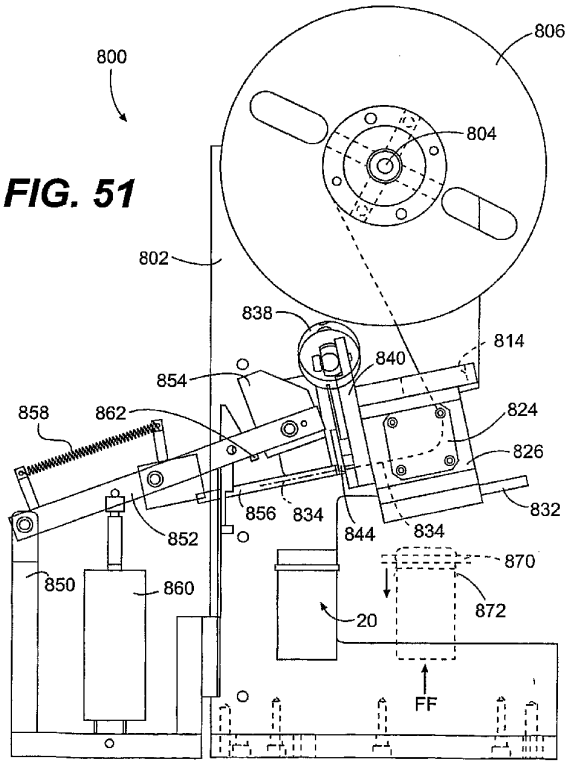

806
800
802
838
810
840
845
816
842
814
824
812
836
826
818
832
830
822
820
828
20

FIG. 50

FIG. 51


800
806
804
802
838
814
840
854
858
862
824
826
856
834
844
834
832
852
870
850
860
872
20
FF

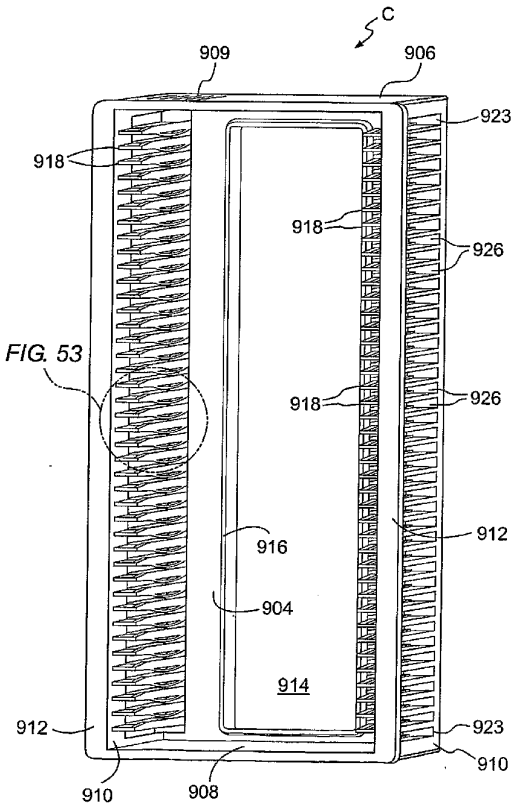

C
909
906
923
918
918
926
FIG. 53
918
926
916
912
904
914
912
923
910
910
908

FIG. 52

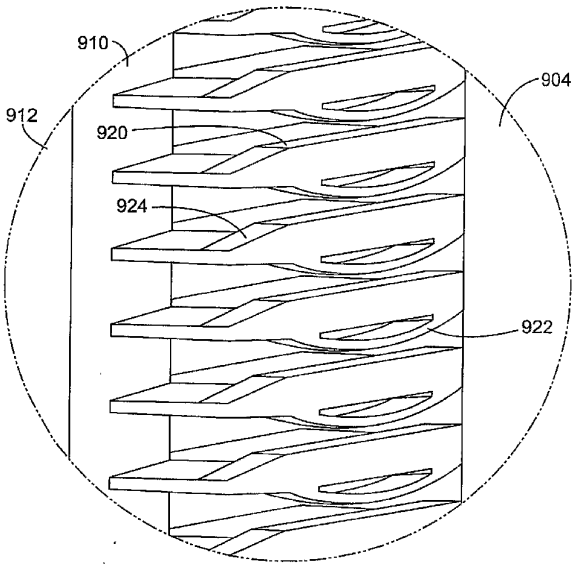


FIG. 53

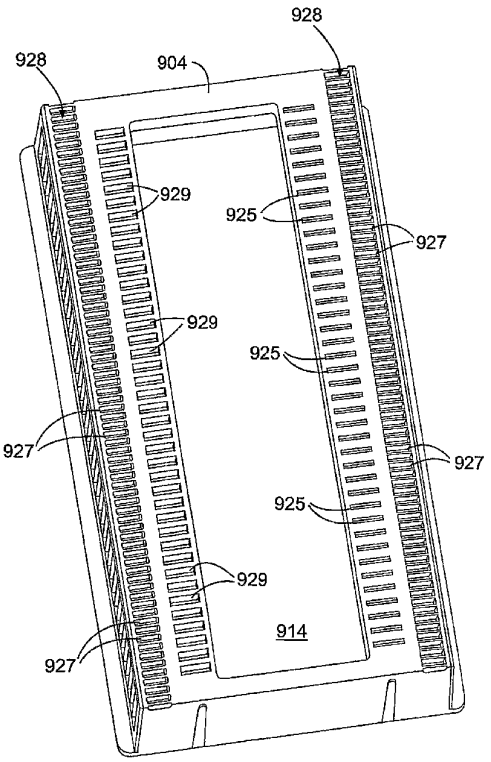


FIG. 54

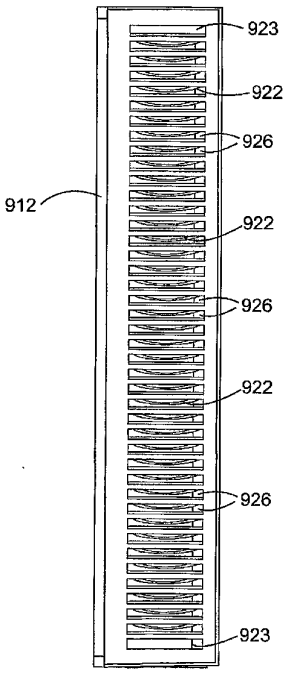


FIG. 55

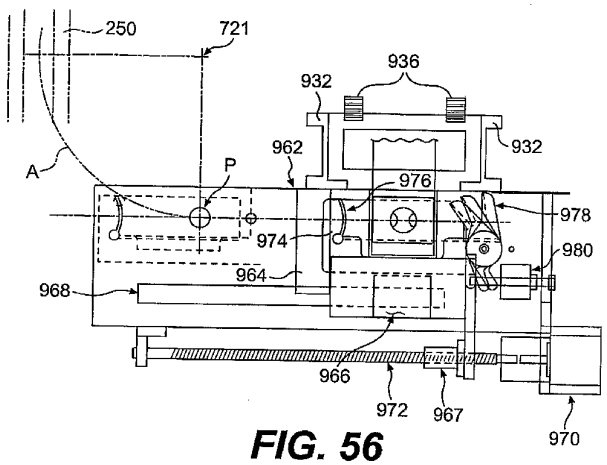

250
721
936
932
932
962
A
P
976
978
974
980
964
968
966
972
967
970

FIG. 56

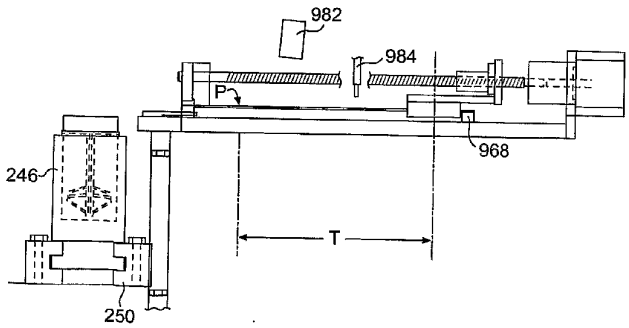

982
984
P
968
246
T
250

FIG. 57

【国際調査報告】

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/33356

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 G01N1/28 G01N35/02 G01N33/483

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 645 690 A (ROCHTE JERRY E ET AL) 29 February 1972 (1972-02-29) column 1, line 22 - line 36; figures 1,10 column 2, line 60 -column 7, line 43 column 9, line 43 -column 10, line 44 column 12, line 56 -column 13, line 28 ---	1,2,18, 19,42-46
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[X] Further documents are listed in the continuation of box C. [X] Patent family members are listed in annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 March 2003	02/04/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Strohmayer, B

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/33356

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	EP 0 465 832 A (CYTYC CORP) 15 January 1992 (1992-01-15) column 11, line 11 -column 19, line 26; figures 1-13	1-47
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Ｇ０１Ｎ 1/36	Ｇ０１Ｎ 35/00	Ｅ	
Ｇ０１Ｎ 35/00	Ｇ０１Ｎ 35/02	Ａ	
Ｇ０１Ｎ 35/02	Ｇ０１Ｎ 35/02	Ｂ	
Ｇ０１Ｎ 35/04	Ｇ０１Ｎ 35/02	Ｄ	
	Ｇ０１Ｎ 35/04	Ａ	
	Ｇ０１Ｎ 1/28	Ｆ	
	Ｇ０１Ｎ 1/28	Ｙ	

(81)指定国 AP(GH,GM,KE,LS,MW,MZ,SD,SL,SZ,TZ,UG,ZM,ZW),EA(AM,AZ,BY,KG,KZ,MD,RU,TJ,TM),EP(AT,BE,BG,CH,CY,CZ,DE,DK,EE,ES,FI,FR,GB,GR,IE,IT,LU,MC,NL,PT,SE,SK,TR),OA(BF,BJ,CF,CG,CI,CM,GA,GN,GQ,GW,ML,MR,NE,SN,TD,TG),AE,AG,AL,AM,AT,AU,AZ,BA,BB,BG,BR,BY,BZ,CA,CH,CN,CO,CR,CU,CZ,DE,DK,DM,DZ,EC,EE,ES,FI,GB,GD,GE,GH,GM,HR,HU,ID,IL,IN,IS,JP,KE,KG,KP,KR,KZ,LC,LK,LR,LS,LT,LU,LV,MA,MD,MG,MK,MN,MW,MX,MZ,NO,NZ,OM,PH,PL,PT,RO,RU,SD,SE,SG,SI,SK,SL,TJ,TM,TN,TR,TT,TZ,UA,UG,US,UZ,VC,VN,YU,ZA,ZM,ZW

（特許庁注：以下のものは登録商標）
イーサネット
パイレックス
ＵＳＢ
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アメリカ合衆国 イリノイ州 サウス バーリントン オーバーブルーク ５８

Ｆターム(参考) 2G052 AA29 AD29 AD55 CA03 CA08 CA48 DA07 DA12 EA03 EA17 FA05 FB02 FB07 GA32 HB04
2G058 AA09 CA02 CB05 CB20 CC09 CF18 CF28 FA02 GC02 GC05 GE03
4B029 AA07 AA09 AA27 BB01 BB11 CC01 CC02 CC08 FA01 HA06 HA09 HA10
4B063 QA01 QA18 QA19 QQ03 QQ05 QQ08 QR84 QS10 QS11 QS12 QS39 QX01