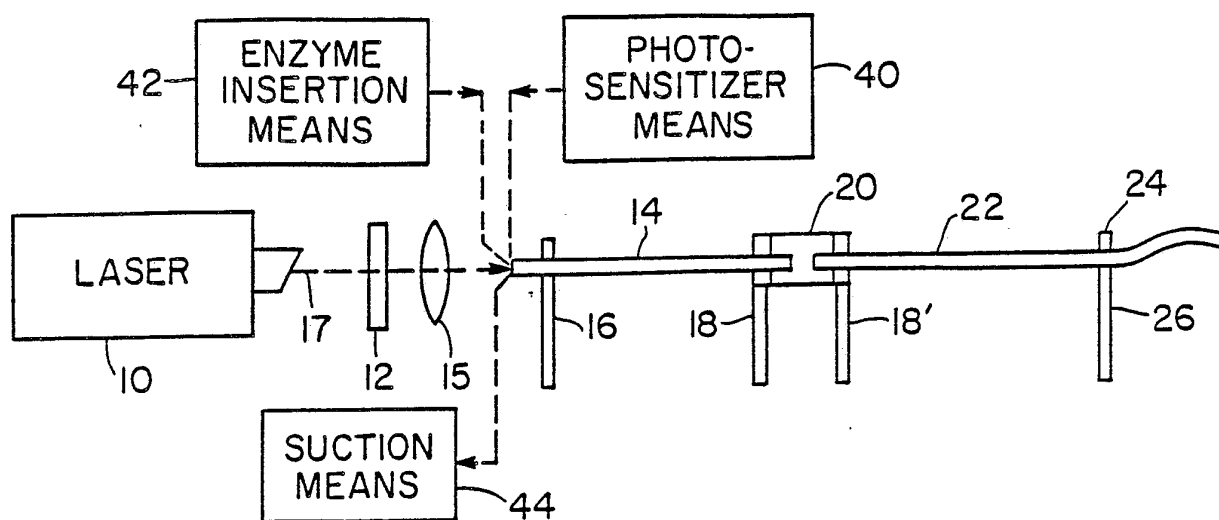


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(54) Title: METHOD AND APPARATUS FOR LASER ANGIOSURGERY



(57) Abstract

A method and apparatus for treating thrombus or plaque occluded arteries in which energy is applied to sensitized occlusions until the occlusion is gelatinized and the gelatinized occlusion is removed by suction.

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-1-

METHOD AND APPARATUS FOR LASER ANGIOSURGERYDescriptionBackground Art

5 The concept of using laser energy to recanalize
thrombus of plaque-occluded arteries has received
considerable attention since its initial description
in 1980. (Choy D.S.J., "Fiber Optic Laser Tunneling
Device: The Laser Catheter", in Beijing Shanghai
10 Proceedings of the International Conference on
Lasers, Wiler-Interscience Publications, N.Y., 1980,
pp. 685-690.) But the search for a safe method to
carry laser irradiation to thrombus in occluded
arteries is still a great challenge to medical
researchers today.

15 Several investigators have demonstrated that an
intravascular laser beam can create a new lumen in
an atherosclerotic artery. (Marcruz R. Martins
J.R.M., Tupinamba A. Lopes E.A., Vargas H. Penaaf
D.E. Carvalaho V.B., Armelin E. De'Court L.V.,
20 "Therapeutic Possibilities of Laser Beams in
Atheromas", Arg Bras Cardiol 34:9-12, 1980; Jean
Marco, Paul J. Silvernail, Gerard Fournial, Daniel
S.J. Choy, Jean Fajadet, Robert B. Case, "Complete
Patency in Thrombus-Occluded Arteries Two Weeks
25 After Laser Recanalization", Lasers in Surgery and
Medicine, 5:291-296, 1985; Radi Macruz, Ma'rcio P.
Riberio, Jose'Mauro G. Brum, Carlos Augusto
Pasqualucci, Jaime Mnitentag, Dimitrios G. Bozinis,
Euclides Marques, Adib Domingos Jatene, Luiz V.

-2-

De'court, Egas Armelin, "Laser Surgery in Enclosed Spaces: A Review", Lasers in Surgery and Medicine, 5:199-218, 1985.) This technique opens the way for revascularization of atherosclerotic arteries by a laser catheter, provided that certain potential obstacles can be overcome. Chief among these obstacles are the tendency of the vessel wall to be perforated by the laser energy perforation, the occurrence of embolization, or blood clotting, at the distal end, and the occurrence of rethrombosis at the treated site.

Abela et al. (G. Abela, D. Cohen, R.L. Feldman, S. Norman, R.C. Conti, C.J. Pping, "Use of Laser Radiation to Recanalize Stenosed Arteries in Living Rabbits", Clin. Res. 31:2, Abstract 458A, 1983) reported perforation in three of eight rabbit arteries treated with argon or Nd:YAG laser radiation and Sanborn et al. (T.A. Sanborn, D.P. Faxon, C.C. Haudenschild, S.B. Gottsman, T.J. Ryan, "Angiographic and Histopathologic Consequences of in Vivo Laser Radiation of Atherosclerotic Lesions", Am. Heart Assoc. 56th Scientific Sessions, Abstract 577, 1983) experienced perforation in three of twelve rabbit iliac arteries treated with the argon laser.

In 1985, Choy et al. (Daniel S.J. Choy, Cimon Stertz, Jean-Michel Loubeau, Howard Kessler, Phillippe Quilici, Heidrun Rotterdam, Lon Meltzer, "Embolization and Vessel Wall Perforation in Argon Laser Recanalization", Lasers in Surgery Medicine,

-3-

5:297-308, 1985) reported that many of these vessel perforations occurred with the Nd:YAG laser, which is known for its high penetration of biological tissue. The YAG laser penetrates blood, whereas
5 argon laser energy is totally absorbed by a thin layer of blood. But vessel wall perforation is less likely to occur with increasing operator experience. They also reported that a complete recanalization of a 12 cm femoral artery was accomplished with the
10 laser catheter at an argon laser power output of 3.8w in 173 seconds, and a 6 cm long tunnel of approximately normal diameter (2.0mm) was created with 3.8w in 52 seconds.

In 1985, Radi Marcus, et al. (Radi Macruz,
15 Ma'rcio P. Riberio, Jose'Mauro G. Brum, Carlos Augusto Pasqualucci, Jaime Mnitentag, Dimitrios G. Bozinis, Euclydes Marques, Adib Domingos Jatene, Luiz V. De'court, Egas Armelin, "Laser Surgery in Enclosed Spaces: A Review", Lasers in Surgery and
20 Medicine, 5:199-218, 1985.) reported the following experiment: Stenosis of common carotid artery was produced in fourteen dogs. Arteriograms were performed. The dogs were kept alive, and at the end of a period of seven days, they were submitted to a
25 new arteriographic study. The catheter was introduced, and the argon laser was applied, using a mean power of 3.8w and 1100J of total energy. In six dogs (43%), the stenosis diminished, or was eliminated, without wall lesion. In two (15%), the
30 degree of stenosis diminished, but the wall was

-4-

perforated. In six (43%), the stenosis could not be avoided in approximately 50% of the arteries, when the laser catheter was used. They also reported that it was possible to make a laser catheter, which
5 could be used without arresting the circulation; and that the laser beam was able to remove atheromas, human blood clots, and platelet thrombus.

Gessman et al. (L.J. Gessman, C.W. Reno, K.S. Chang, "Feasibility of Laser Catheter Valvulotomy
10 for Aortic and Mitral Stenosis", Am. J. Cardiol. 54, 1375-7, 1984) found an absence of filterable debris after laser treatment of a single cadaver coronary artery. Case et al. (R.B. Case, D.S.J. Choy, E.M. Dwyer, P.J. Silvernail, "Absence of Distal
15 Embolization During In Vivo Laser Recanalization", Lasers Surg. Med., 5:281-189, 1985) have confirmed these findings by finding an absence of distal embolization in laser-recanalized, living canine thrombus-occluded femoral arteries, and human
20 cadaver carotid arteries. Choy et al. (D.S.J. Choy, S.H. Stertz, R.K. Myler, J. Marco, G. Fournial, "Human Coronary Laser Recanalization", Clin. Cardiol. 7:377-381, 1984 and D.S.J. Choy, S.H. Stertz, R.B. Case, J. Marco, G. Fournial, P.J.
25 Silvernail, R.K. Myler, "Update on Laser Recanalization", Lasers Surg. Med. 3(4):357, 1984) have reported that six of seven human coronary arteries, recanalized with an argon laser during coronary artery bypass surgery, reoccluded within 25
30 days of the procedure, which could be due to

-5-

competition between the newly laser-recanalized coronary artery and vein bypass graft. The success or failure of preventing rethrombosis in laser-recanalized vessels depends on many factors:

5 Laser operator experience and ability to minimize wall damage, competitive flow within a bypass graft, low flow owing to inadequate revascularization, arterial spasm during or after the procedure leading to low flow in the newly recanalized vessel, and

10 possibly, the post-recanalization pharmacologic regimen.

Ginsburg et al., Radiology 1985; 156:619-624
September 1985, page 623 report that:

15 "Argon laser radiation ablates occlusions by a thermal process which, if delivered in high enough energies for significant debulking, causes injury to normal surrounding tissue."

20 As an alternative, they suggest use of a selective target enhancer to permit less total delivery (citing the tetracycline treatment of plaque by Murphy-Chutorian D., et al. American Journal of Cardiology 1985; 55:1293-1297) or use of shorter

25 wavelengths in the UV range and/or pulsed laser energy with a high power peak and low total energy. In 1983, Spears et al. reported the selective fluorescence of atheromatous plaques of the aorta of animals within 48 hours after injection with

30 hematoporphyrin derivative (HPD).

The fluorescence of parenterally injected hematoporphyrin and its derivatives (HPD) within

-6-

tissues exposed to UV light has been used to localize malignant tumors, and the cytotoxic effect of light-activated HPD has been used in cancer therapy. Although HPD may be photoactivated at a variety of wavelengths in the visible portion of electromagnetic spectrum, light at $\lambda = 635$ nm has recently been used because of its greater penetration at this wavelength. Upon HPD photoactivation, release of singlet oxygen with subsequent damage to the cell membrane may be the primary mechanism for the cytotoxicity.

Spears et al., at page 397, speculated that:

"If selective plaque fluorescence is found in man, plaque destruction following HPD photoactivation, such as might be accomplished with an intraluminal laser-transmitting optical fiber, may be limited to the cellular fibrous capsule that commonly surrounds an acellular lipid-rich material within a fibrous plaque, the latter being the most common lesion associated with clinical events ---. Further problems might include control of the inflammatory reaction, usually noted before tissue necrosis, and the potentiation thrombogenicity of the plaque's acellular core upon exposure to the arterial lumen.

Irrespective of the uncertainty of the potential clinical utility of HPD localization in atheromatous plaques, the observations of this study are likely to provide impetus to further experimental investigations regarding the affinity of HPD for atheromatous lesions. In addition, intraluminal identification of HPD fluorescence with angioscopy, if.

-7-

feasible, might permit investigators to study the localization of atheromatous plaques and the temporal course of plaque progression/ regression in vivo in a manner that has hitherto not been possible."

Despite extensive efforts by numerous workers in the art, such as briefly described above, a need exists for method and apparatus for treating plaque and thrombus for the removal thereof from arterial or vascular tissue without substantial penetration or damage to human or animal tissue.

Disclosure of the Invention

A method and apparatus is described for the liquification of plaque and/or thrombus in the blood carrying body vessels of humans and/or animals. The thrombus is located by well known means, such as, X-ray or magnetic resonance imaging. A light absorbing, or photosensitizing dye, such as HPD, is injected into arteries containing the thrombus/plaque. A catheter is provided having optical fiber(s) contained therein with the fiber(s) coupled at the proximal end to a source of relatively low power pulsed (repetition rate 5 KHz) laser energy having a wavelength centered at secondary or tertiary absorption peak of both the plaque/thrombus and the photosensitizer. In the case of HPD, the tertiary peak occurs at about 578 nanometers. The catheter is inserted into the vessel until the distal end(s) of the fiber(s) are closely adjacent to the cite of the thrombus/plaque.

-8-

The thrombus is irradiated with the laser energy of about 1-6 Joules/mm² depending upon the length of the thrombus, i.e., 10-30mm in length.

At an average power level of 1 watt applied for
5 3 seconds and with a beam diameter of two millimeters, the thrombus gels in about 1 to 2 minutes with observable small bubbles appearing in the clot. Next, a thrombolytic enzyme, such as, urokinase, or equivalent, is infused into the vessel
10 to dissolve the gelatinized thrombus and the liquified material is removed by suction.

In an alternative embodiment, specifically directed at plaque, HPD treated plaque is dissolved by irradiating it with laser energy from a catheter
15 while simultaneously flowing a non-toxic detergent at the plaque. The wavelength of the laser energy may be at 510 nm or 578 nm, but preferably, both wavelengths are used concurrently to achieve rapid dissolution of the plaque at low power levels. The
20 average power level of the laser radiation applied to the plaque using both 510 nm and 578 nm, simultaneously, is 1.5 w. At the exit of the catheter, the power density is about 2 to 10 Joules/mm². The radiation is applied for a duration
25 of about 1 to 5 minutes, depending upon the size of the plaque. At these power levels, very little thermal heating of the plaque or surrounding tissue occurs, thereby minimizing the danger of perforation of vessels. The tissue temperature is preferably
30 not elevated more than 1 or 2°C and should not be

-9-

allowed to rise more than 7°C. Concurrent with application of the laser radiation, a solution of a non-ionic detergent, such as, Triton X-100 of 2% concentration is injected, or circulated, through the catheter into the artery or vessel to the site of the plaque. Triton X-100 is a non-toxic detergent, which serves to dissolve the fat particles in the clot. In general, the injection of suitable non-toxic detergent helps to dissolve protein and lipid aggregates in the clot during the irradiation. Also, the solution of 2% detergent in water may be cooled or kept at ambient to assist in maintaining body tissue around the site of the plaque at a relatively low temperature during irradiation; thus, further minimizing the potential for thermal damage or injury to healthy tissue..

Brief Description of the Drawings

Fig. 1 is a block diagram of the optics system of the invention.

Fig. 2 is a cross-sectional schematic view of various catheter embodiments useful for the process of the invention.

Fig. 3 is a plot of theoretical photoreaction yield (λ) versus depth of penetration "d" in mm for different wavelengths.

Fig. 4 is a plot of absorption versus wavelength for human blood.

Fig. 5 is a plot of absorption versus wavelength for HPD in saline.

-10-

Fig. 6 is a plot of absorption versus wavelength for an experimental thrombus column.

Best Mode of Carrying Out the Invention

In accordance with the invention, in situ and
5 in vivo tests on thrombi prepared, as described
below, were performed. In these tests, the thrombi
was subjected to a controlled thermal injury using
laser irradiation from a 578 nm line of copper vapor
laser source. The radius of the direct beam
10 measured at the surface of the thrombus was 1.55 mm.
The power distribution across the beam follows that
of a normal Gaussian curve. A power level of 1 W
was used to determine the duration (in seconds)
required to completely penetrate the thrombus. The
15 power output from the laser source was monitored by
an external power meter.

The apparatus of the invention comprises a
laser source coupled to a suitable catheter and an
attenuator, each of which is described below in
20 connection with Figs. 1 and 2.

I. LASER

A model 151 Copper Vapor Laser (CVL) from
Copper LaserSonics, Inc. was used as the laser
energy source 10. A single 578 nm Yellow/Green line
25 output, without mixture of the other 510 nm line
produced by this laser, is obtained by choosing a
certain coating on the total reflection mirror of

-11-

the laser system. One third of the laser output power is in the 578 nm line. Table 1 gives the specification of the Model 151 CVL.

Table 1: Specification of Model 151 CVL

5	Wavelength (nm).....	510, 578
	Ave. Power (W).....	10
	Peak Power (kW).....	70
	Beam Rep. Freq. (kHz).....	5
	Pulse Energy (mJ).....	2
10	Pulse Width (ns).....	30
	Beam Dia. (cm).....	2.5
	Divergence (mrad).....	5
	Cooling Required	
	(L/Min.Water).....	4
15	Power Required (kW).....	5
	Size (cm, L/H/W)	
	Head.....	190/25/24
	Electronics.....	69/115/59
	Gas Handling System...	59/49/36

20 II. ATTENUATOR

A tab actuated iris diaphragm 12, made by Melles Griot, with variable aperture between $D = 30.0$ mm and $D = 1.2$ mm, is interposed between laser 10 and single fiber 14. Fiber 14 is mounted on supports 16 and 18. The laser beam 17 is focused onto the end surface of an optical fiber 14 by a lens 15. The laser light is almost a parallel beam, therefore, covering of any fraction of the laser beam does not displace the focal point at the end of the optical fiber. Consequently, the output light at the output end of the optical fiber just changes linearly with the area of the aperture.

-12-

Table 2 reproduces data concerning the output intensity of 578 nm line as a function of the aperture of the iris.

5 Table 2: The Intensity of 578 nm Line Output
 Varying with the Aperture of the Iris

	Dia. (mm)	Intensity (W)	Relative Int.
	2.5	0.139	0.015
	5	0.478	0.054
	10	1.633	0.185
10	15	3.612	0.500
	20	5.963	0.676
	25	7.773	0.882
	30	8.817	1.000

15 III. THE OPTICAL FIBER CATHETER AND
 COUPLING TO THE LASER

 An optical fiber catheter 22 is used to transport the laser light from fiber 14 to a thrombus (not shown) in a blood vessel. Catheter 22 serves as a chemical transporter for the enzyme solution, which is injected through the catheter into the vessel. The catheter also transports the unwanted products of the liquified thrombus from the vessel, which is sucked out by a suction tube coupled to the catheter. The simplest catheter may consist of an outer sheath 34 within which is disposed one single optical fiber 30 of 0.6 mm and one suction tube 32 of 0.4 mm, which also functions as an injection tube (See Fig. 2a). In order to increase the speed of suction, one would like to use a considerably larger diameter suction tube (1 mm

-13-

diameter). Figs. 3b-f show different optical structures of the catheter used in the experimental procedure. Note that A denotes an optical fiber, C a suction tube and D a fiber bundle.

5 A two-stage coupling is used to couple the laser energy to a single fiber 14 and then to a fiber bundle within catheter 22. The second coupling 20 connects the single fiber 14 with the adjacent fiber bundle in catheter 22. The advantage
10 of this construction is that the divergent light from the first fiber 14 falls gently on the second fiber bundle, rather than focusing on a point. This avoids burning of the surface of the second fiber bundle.

15 IV. SAMPLES

In Vitro Samples

Blood withdrawn from normal human volunteers was immediately placed into a glass tube and allowed to mix with thrombin (15 NIH units/ml of blood) and
20 with HPD (0.008 cc HPD/cc blood). Then, the blood was injected into vessel-like experimental tubes and refrigerated overnight for 15 to 20 hours. Forty samples of thrombi were measured, each with lengths varying from 10 mm to 30 mm.

25 In Vivo Samples

For in vivo studies, 10% calcium chloride (CaCl_2) solution was injected directly into dog's

-14-

arteries to form thrombus. 2.5 mg/kg of PHD was injected, intravenously, two hours after the thrombus formation. The artificially occluded arteries with thrombi were then removed from the
5 dog's bodies two hours after the HPD injection, because there was a rapid uptake of HPD, by living cells, over the first two hours of the injection.

V. EXPERIMENTAL PROCEDURE

In general, a sequence of irradiation for t_1
10 seconds, followed by enzyme circulation for t_2 seconds, and a subsequent suction for t_3 seconds, is recommended. After obtaining products of the liquified thrombus out, the catheter should be moved further into the vessel and the same steps repeated,
15 until the blood vessel is completely recanalized. Typical time periods for t_1 , t_2 and t_3 are 3 seconds, 30 seconds, and 2 seconds, at a power density of about 1 Joule per mm^2 , repeated after removal of about 5 mm length of thrombus.

20 The experimental procedure for recanalization of a 3 cm thrombus in occluded arteries is summarized in the following steps:

- 1) Insert catheter into an HPD artificial treated blood vessel 2 mm away from the surface of the
25 thrombus.
- 2) Irradiate with 1 W Yellow-Green light from CVL (578 nm) for 3 seconds at power density of about 2 Joules per mm^2 .

-15-

3) Circulate a Urokinase solution (10,000 u/c.c.) inside the vessel for 30 seconds.

4) Operate the suction pump to remove the resultant fluidized thrombus.

5 In experimental studies, a thermocouple was used to measure the variation of temperature within the thrombus during laser irradiation. The thrombus was pre-treated with HPD, as outlined above.

10 Table 3 shows the data at the condition of 1 mm spacing between the thermocouple tip and the surface of the thrombus and 4 mm distance between the optical fiber tip and the surface of the thrombus.

The temperature resolution is 0.1.C. A thermocouple with a 0.5 mm diameter tip was used to
15 measure the temperature within the thrombus.

Table 3. Temperature Measurement During Irradiation

	<u>Time After Irradiation</u> <u>in Sec.</u>	<u>Temperature</u> <u>in Degrees C</u>
	0	24.1
20	2	25.0
	3	26.8
	5	32.1
	7	33.1
	10	34.2

25 The preceding results are in sharp contrast with previously reported results, when an argon laser is used to evaporate a thrombus (Ivan P. Kaminow, Jay M. Wiesenfeld and Daniel S.J. Choy, "Argon Laser Disintegration of Thrombus and
30 Atherosclerotic Plaque", Applied Optics, Vol. 23, No. 9, 1984). With an argon laser, the thrombus is

-16-

readily vaporized using 5 W of output power at 488 nm. Most of the energy, in this instance, is required to produce vaporization, and as a result, it raises the local temperature of the thrombus to above 100°C.

VI. EXPERIMENTAL RESULTS AND CONCLUSIONS

As noted earlier, HPD has been reported by a number of investigators to be preferentially retained in tumors and atherosclerotic plaque (Radi Macruz, Ma'rcio P. Riberio, Jose'Mauro G. Brum, Carlos Augusto Pasqualucci, Jaime Mnitentag, Dimitrios G. Bozinis, Euclydes Marques, Adib Domingos Jatene, Luiz V. De'court, Egas Armelin, "Laser Surgery in Enclosed Spaces: A Review", Lasers in Surgery and Medicine, 5:199-218, 1985; T.J. Dougherty, D.G. Boyle, K.R. Weishaupt, B.A. Henderson, W.R. Potter, D.A. Bellnier and B.E. Wityk, "Photoradiation Therapy--Clinical and Drug", Advances in Experimental Medicine and Biology, 160:3-14, 1983, Plenum Press, New York; J. Richard Spears, Juan Serur, Deborah Shropshire and Sven Paulin, "Fluorescence of Experimental Atherosclerotic Plaques with Hematoporphyrin Derivative (HPD)", Clin. Invest. 75:395-399 (1983). The therapeutic effect is based on the fact that many porphyrins are efficient photosensitizers.

HPD exhibits the characteristic absorption of porphyrins with a major absorption band near 400 nm and four minor bands of

-17-

decreasing magnitude at 507 nm, 540 nm, 573 nm, and 624 nm (Daniel R. Doiron, Lars. O. Svaasand, and A. Edward Profio, "Light Dosimetry in Tissue: Application to the Photoradiation Therapy", Advances in Experimental Medicine and Biology, 160:63-76, 1983, Plenum Press). The greatest tissue penetration and least absorption by HPD occur at 624 nm, and the least tissue penetration and highest HPD absorption occurs at 402 nm. Although absorption in HPD is small, most photochemotherapy for tumor treatment with HPD has been performed with red light at around 630 nm, because of a greater depth of penetration in tissue, compared to that at shorter wavelengths ("Dosimetry Considerations in Phototherapy", Medical Physics, 8:191, 1981).

In our experiments, a laser line at 578 nm was chosen, because compared to that at 488 nm, it has a suitable rate of penetration and absorption in thrombus. (See Fig. 3, which is a plot of theoretical photoreaction yield (y) versus depth of penetration "d" in mm, at different wavelengths, labelled 410 nm, 510 nm, 578 nm, and 630 nm, respectively.)

The cytocidal mechanism of HPD is believed to be due to a photodynamic reaction involving oxidation of tissue via porphyrin-catalized production of singlet oxygen (H. Kato, C. Konaka, J. Ono, Y. Matsushima, K. Nishimiya, J. Lay, H. Sawa, H. Shinohara, T. Saito, K. Kinoshita, T. Tomono, M. Aida and Y. Hayata, "Effectiveness of HPD and

-18-

Radiation Therapy in Lung Cancer", Advances in Experimental Medicine and Biology, 160:23-40, 1983, Plenum Press, New York). This phenomena was also observed in our experiments. During the CVL (578 nm) irradiation of the thrombus, many singlet oxygens were produced, which function as a cytotoxic agent for the blood cells. This is probably the cause of the gelatinizing liquifaction of the blood clot.

In Fig. 4, 5 and 6, the absorption peaks of human blood, HPD in saline (0.0075 cc HPD/1 cc saline) and an experimental thrombus column (blood, 0.1 cc, 5% CaCl + 0.0075 cc HPD/1 cc blood), respectively, is plotted versus wavelength.

Sample 1.	human blood
Sample 2.	HPD
Sample 3.	experimental thrombus column

These experiments show that the 578 nm line was one of the minor absorption peaks in both human blood, HDP, and the experimental thrombus column.

According to our experiments, the energy density of the CVL 578 nm line required for the liquifaction of a 10 mm long thrombus (dyed with HPD) was $1 \pm 0.2 \text{ J/mm}^2$; and for 12 mm clots, it was $2 \pm 0.3 \text{ J/mm}^2$ and for 15-30 mm clots, $6 \pm 0.4 \text{ J/mm}^2$.

For the same length of thrombus, the radiation dose of CVL at 578 nm for liquification is much smaller than required for an argon laser at 488 nm and 514 nm lines. The 488 nm line is so heavily attenuated by the blood, that its effectiveness is

-19-

only superficial. At depths greater than 7 mm, the 578 nm light yield is much greater (See Fig. 3).

VII. SUMMARY

In accordance with the invention, the combined
5 action of HDP, the copper vapor laser at 578 nm and
the urokinase infusion, is shown to be effective in
the treatment of occluded vessels/arteries with
thrombus. Complete patency in 10 mm to 20 mm
thrombus occurred after 3 seconds of laser irradiation
10 at power density of 6 Joule/mm², followed by a
5 second urokinase (10,000 U/cc) infusion and
suction. The temperature increase inside the
vessels, 2 seconds after 1 W irradiation, is between
1°C and 2°C. There is no apparent change of the
15 vessel wall from irradiation. Compared to the
vaporization effects of the laser or the Nd:YAG
laser, the temperature increase inside the vessels
is 50 times less than all the other reports. The
major effect of the CVL irradiation is the
20 liquifaction/geletanization of the thrombus. Since
plaque is formed of material similar to thrombus,
the data supplied herein, with respect to thrombus
and the method and apparatus herein, is intended to
apply equally to either thrombus or plaque.

25 More recently, we have found that the
combination of irradiation at a wavelength of 510
nanometers and 578 nanometers in the presence of a
non-toxic ionic detergent solution is useful for
dissolving HPD treated plaque at low power levels.

-20-

Circulating the detergent past or around the plaque site aids in maintaining the surrounding tissue at ambient temperature and helps to dissolve the plaque. While irradiation at 510 nm or 578 nm is
5 useful, we have found, experimentally, that use of the laser, described above at page 11, which emits both 578 nm and 510 nm radiation, simultaneously, when combined with a circulating detergent, gives superior results. Such results include dissolving
10 of plaque at low power levels in short time periods without damage to tissue. We have found that a suitable detergent to aid in dissolving the HPD treated, irradiated plaque is a polyethoxy-type non-ionic detergent, such as TRITON X-100
15 surfactant. TRITON is a trademark for surfactants based on alkyl-aryl polyether alcohols, sulfanates and sulfates. In other respects, the equipment and process is the same as that above-described for thrombus removal, except that an enzyme injection is
20 not required.

The enzyme injection means may therefore be used to inject and circulate the detergent solution at the same time the copper vapor laser produces energy at both 510 nm and 578 nm. This energy is
25 coupled to the plaque through catheter 14/22. Photo-sensitizer means 40 and suction means 44 are shown in Fig. 1 as also preferably coupled through the single catheter 14/22 through passages provided as in Fig. 2. Separate catheters for each treatment
30 may be supplied in the alternate.

-21-

Equivalents

This completes the description of the preferred
embodiments of the invention. Those skilled in the
art may recognize other equivalents, which
5 equivalents are intended to be encompassed by the
claims attached hereto.

-22-

CLAIMS

1. A method for irradiating and removal of thrombus and/or plaque in blood carrying body vessels, such as arteries, comprising the steps
5 of:
 - a) treating the thrombus and/or plaque with a photosensitizer which is preferentially absorbed by the thrombus and/or plaque;
 - b) irradiating the photosensitized
10 thrombus/plaque with laser energy at a wavelength corresponding substantially to a minor absorption peak of the photosensitizer and the thrombus/plaque, until the thrombus/plaque is substantially
15 gelatinized; and
 - c) removing the gelatinized thrombus/plaque.
2. The method of Claim 1 wherein the photosensitizer is HPD, the wavelength is 578 nm, and the gelatinized thrombus/plaque is removed by
20 injecting the thrombus or plaque with an enzyme to liquify the thrombus or plaque and suctioning the liquified contents.
3. Apparatus for liquifying and removal of thrombus in blood carrying body vessels, such
25 as arteries, comprising:
 - a) a catheter through which a photosensitizer which is preferentially absorbed by

-23-

- the thrombus is introduced into the vessel at the cite of the thrombus;
- b) a laser source for irradiating the photosensitized thrombus with laser energy coupled through said catheter, said energy being at a wavelength corresponding substantially to a minor absorption peak of the photosensitizer and the thrombus, until the thrombus is substantially gelatinized; and
- c) suction means for removing the gelatinized thrombus through said catheter.
4. The apparatus of Claim 3 wherein the photosensitizer is HPD, the wavelength of the laser energy from the laser source is 578 nm, and the gelatinized thrombus is removed by injecting into the gelatinized thrombus with an enzyme to liquify the thrombus prior to suctioning the gelatanized thrombus.
5. The method of Claim 2 wherein the enzyme for liquifying the thrombus or plaque is urakinase.
6. The method of Claim 1 wherein the applied laser energy power density at which the photosensitized thrombus/plaque is irradiated in the order of 1 Joule/mm², or less, to maintain the temperature increase of the tissue in the vessel below a predetermined level.

-24-

7. The apparatus of Claim 4 wherein the enzyme injected into the gelatinized thrombus is urakinase and the laser source is a copper vapor laser.
- 5 8. The apparatus of Claim 3 including enzyme means for dissolving said thrombus.
9. A method for removal of plaque in blood carrying body vessels, such as arteries, comprising the steps of:
 - 10 a) treating the plaque in the vessel with a photosensitizer which is preferentially absorbed by the plaque;
 - b) introducing a laser catheter into the vessel;
 - 15 c) irradiating the photosensitized plaque with laser energy from said catheter at a wavelength of 510 and 578 nanometers while contacting said plaque with a circulating detergent solution until the plaque is
 - 20 substantially dissolved; and
 - d) removing the dissolved gelatinized plaque from said vessel by suction means.
10. The method of Claim 9 wherein the photosensitizer is HPD.

-25-

11. The method of Claim 10 wherein the solution is comprised of a non-ionic surfactant detergent and water.
12. The method of Claim 11 wherein the detergent is Triton X-100.
- 5 13. The method of Claim 9 wherein the power applied from said laser is maintained at a level insufficient to elevate the temperature of the tissue in the area of the plaque more than 7°C.
- 10 14. Apparatus for dissolving of plaque without substantive thermal damage to surrounding tissue in blood carrying body vessels, such as arteries, comprising:
 - 15 a) a catheter through which a photosensitizer which is preferentially absorbed by the plaque is introduced into the vessel at the cite of the thrombus;
 - b) a laser source for irradiating the photosensitized plaque with laser energy coupled through said catheter, said energy
20 being a mixture of wavelengths of 510 and 578 nanometers;
 - c) detergent means introduced through said catheter in contact with said plaque and surrounding tissue to assist, in
25 combination with said laser energy, in dissolving said plaque without

-26-

substantially raising the temperature of said plaque and surrounding tissue; and

d) suction means for removing the dissolved plaque through said catheter.

- 5 15. The apparatus of Claim 12 wherein the photo-sensitizer is HPD and the detergent means is comprised of Triton X-100.

1/5

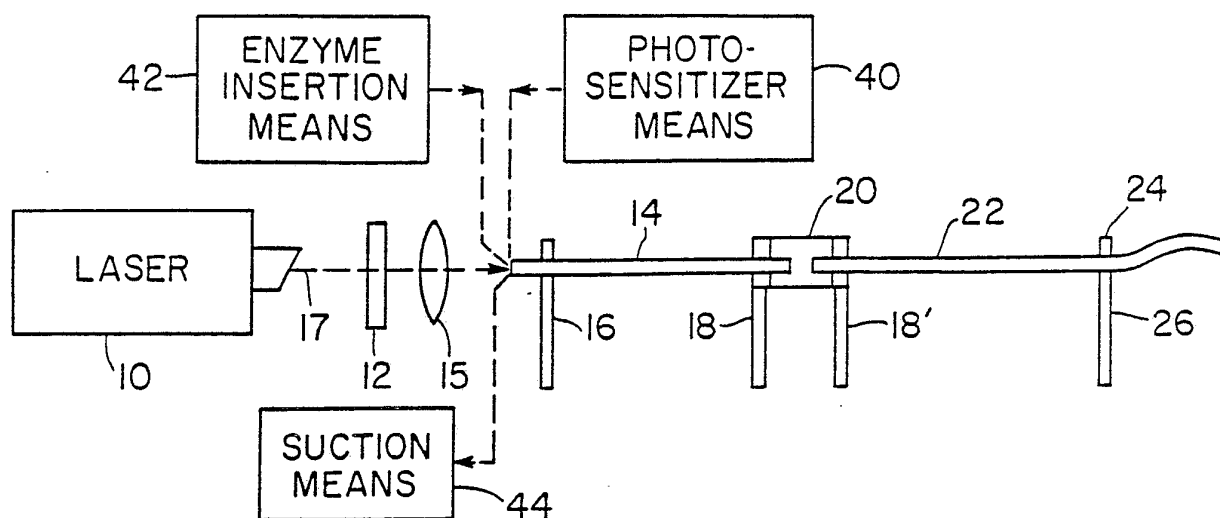


Fig. 1

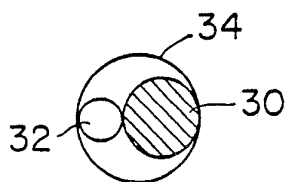


Fig. 2a

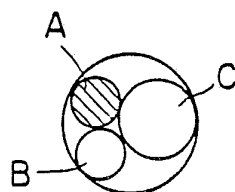


Fig. 2b

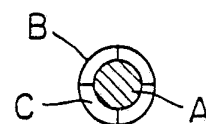


Fig. 2c

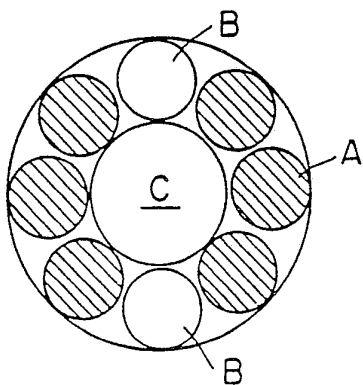


Fig. 2d

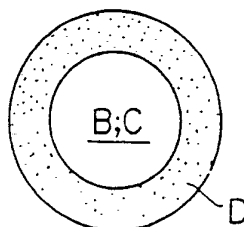


Fig. 2e

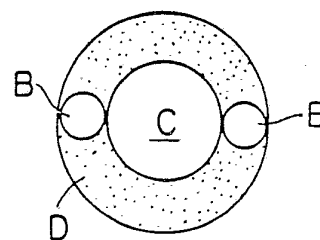
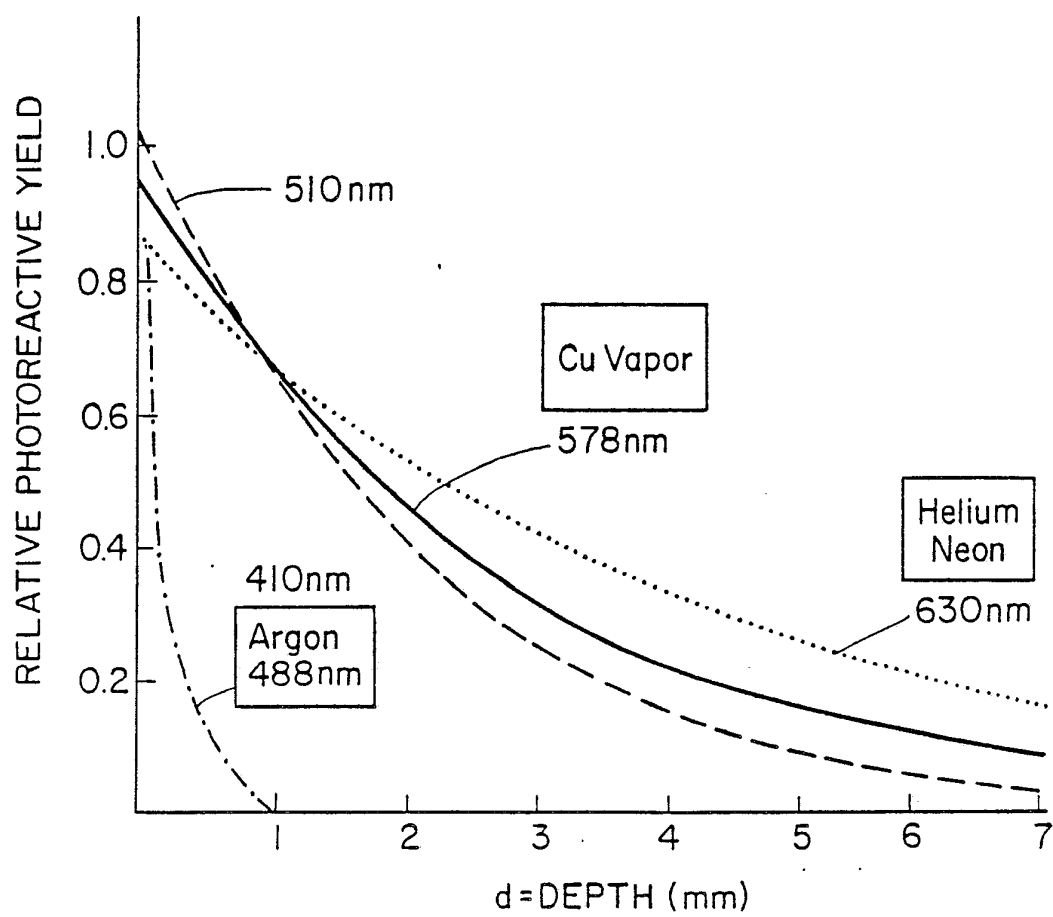
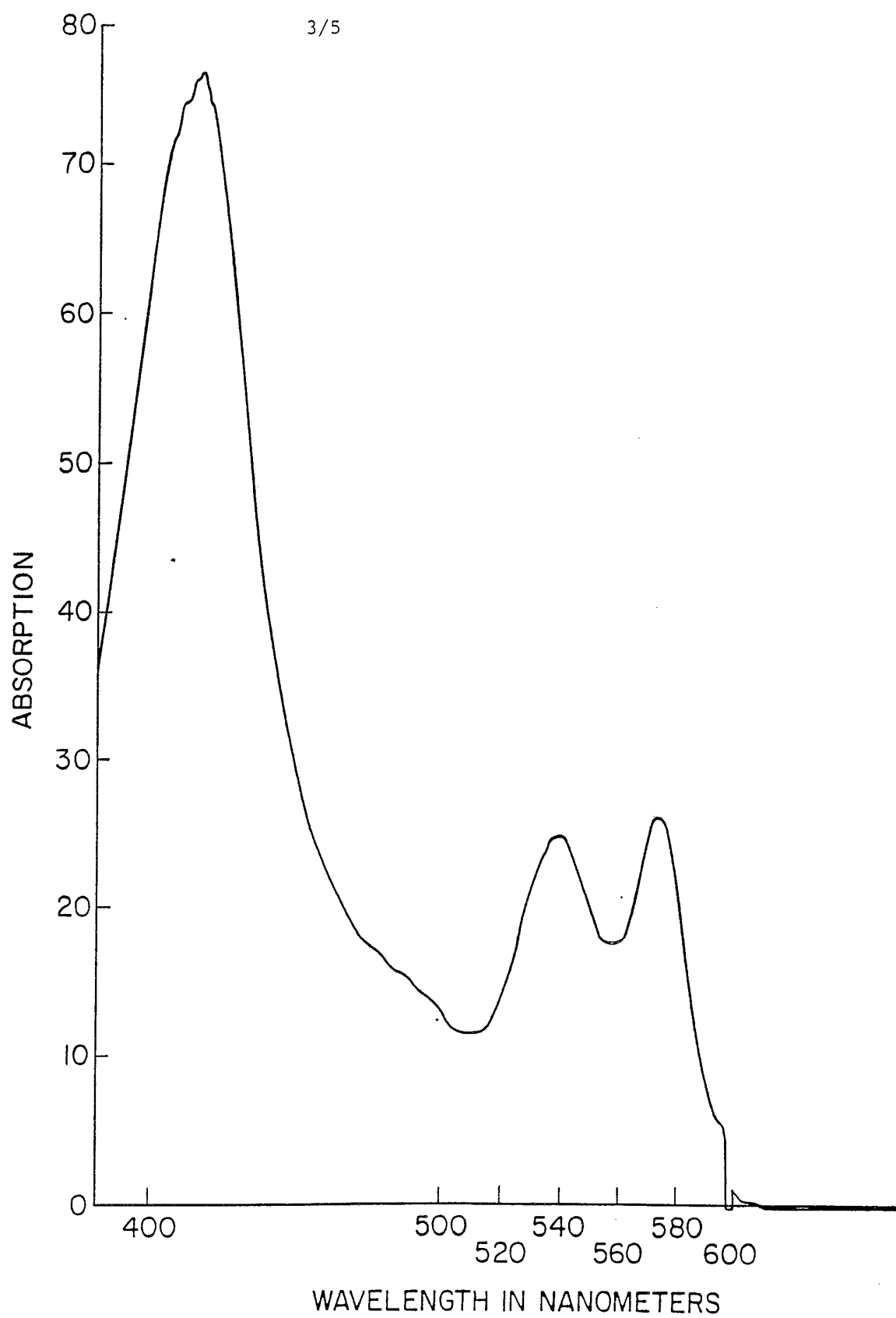
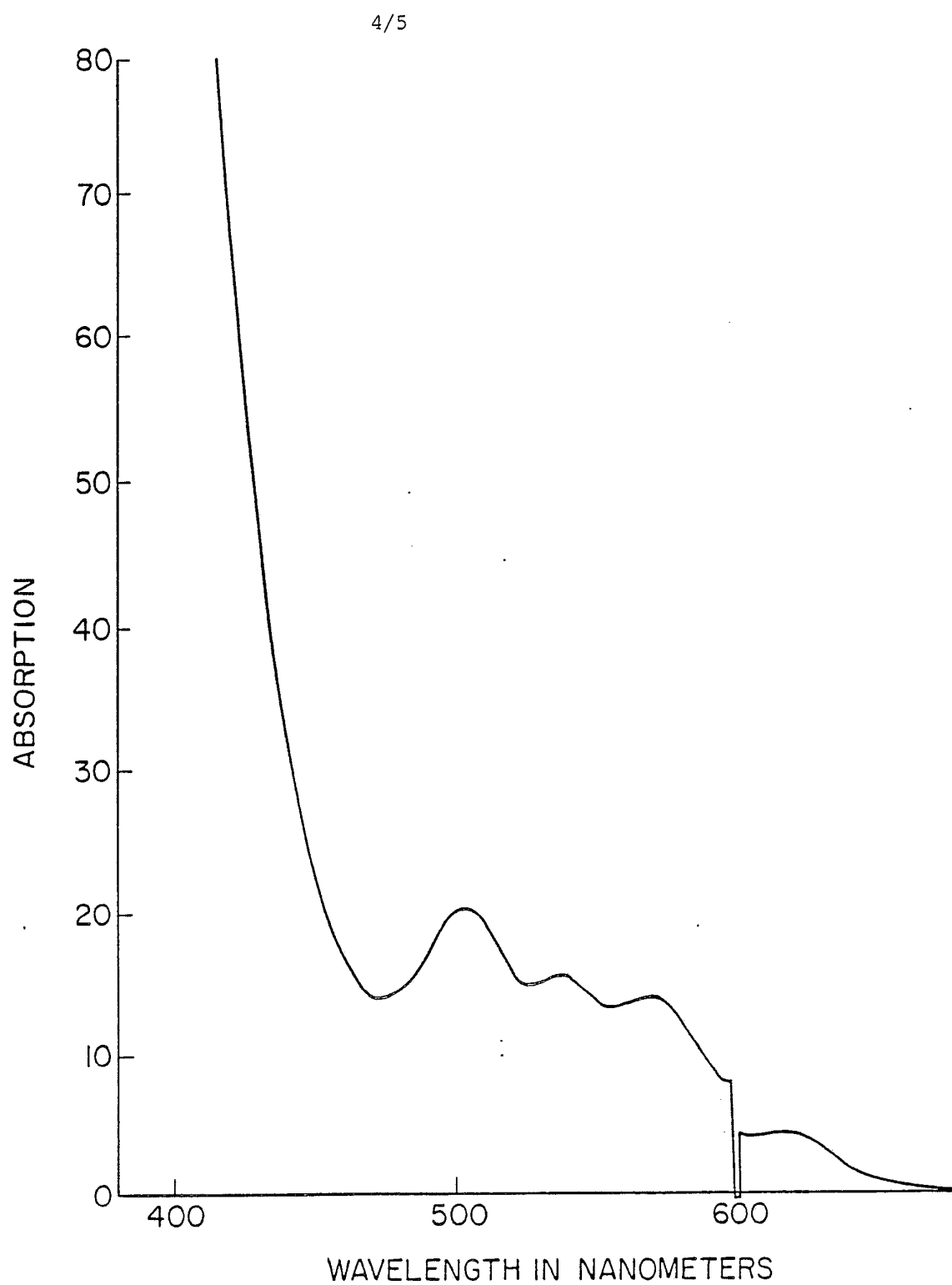


Fig. 2f

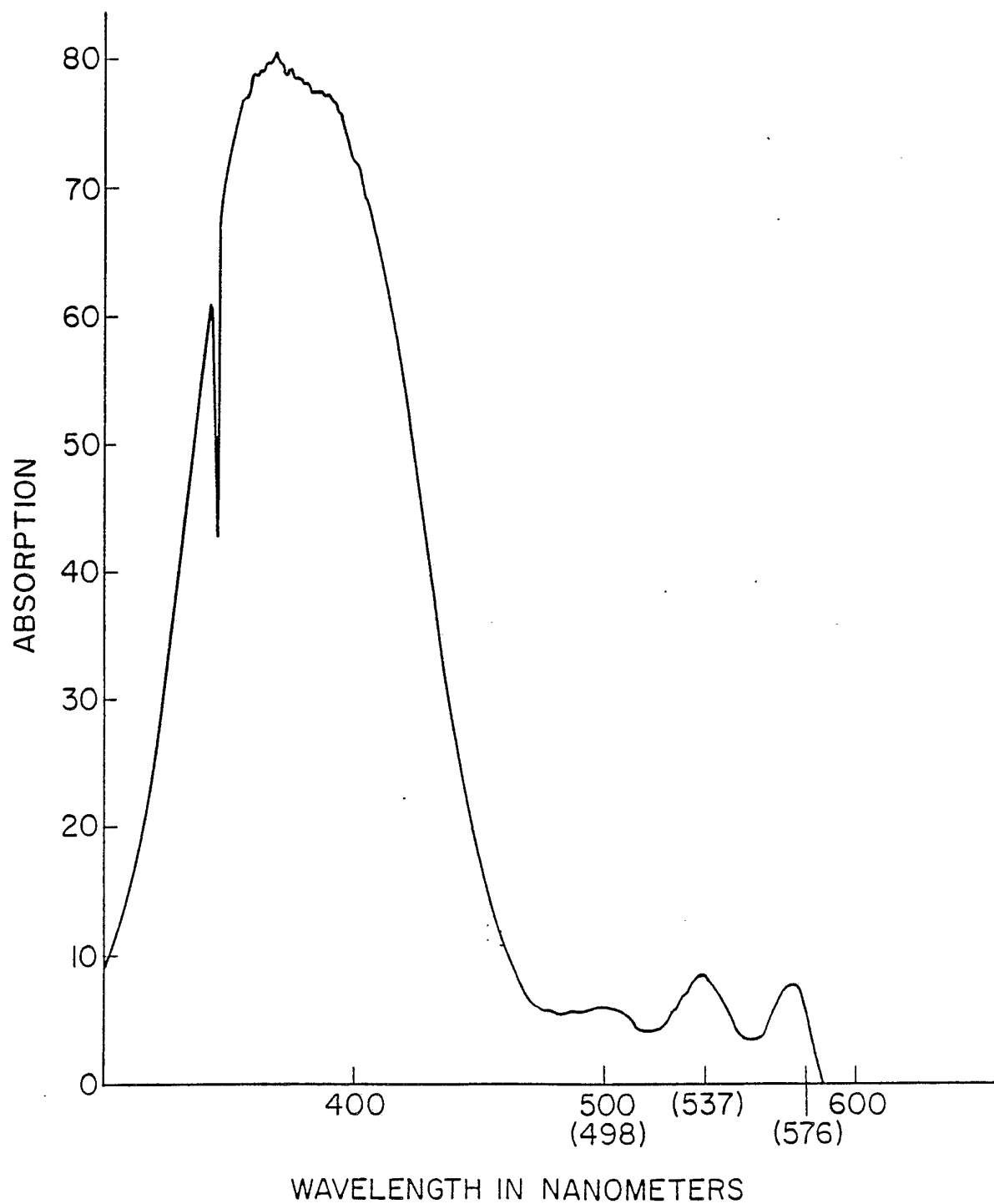
2/5

*Fig. 3*

*Fig. 4*

*Fig. 5*

5/5

*Fig. 6*

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 88/01210

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) ⁶ According to International Patent Classification (IPC) or to both National Classification and IPC IPC ⁴ : A 61 B 17/22											
II. FIELDS SEARCHED Minimum Documentation Searched ⁷ <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 25%;">Classification System</th> <th style="width: 75%;">Classification Symbols</th> </tr> <tr> <td style="height: 40px; vertical-align: top;">IPC⁴</td> <td style="vertical-align: top;">A 61 B</td> </tr> </table> Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁸			Classification System	Classification Symbols	IPC ⁴	A 61 B					
Classification System	Classification Symbols										
IPC ⁴	A 61 B										
III. DOCUMENTS CONSIDERED TO BE RELEVANT ⁹ <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <th style="width: 10%;">Category ¹⁰</th> <th style="width: 70%;">Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²</th> <th style="width: 20%;">Relevant to Claim No. ¹³</th> </tr> <tr> <td style="text-align: center; vertical-align: top;">A</td> <td style="vertical-align: top;">EP, A, 0217165 (KENNETH et al.) 8 April 1987 see figures 5,1; abstract; page 10, lines 11-22 --</td> <td style="vertical-align: top;">3,4,7,8, 14</td> </tr> <tr> <td style="text-align: center; vertical-align: top;">A</td> <td style="vertical-align: top;">EP, A, 0189329 (FISCHELL et al.) 30 July 1986 see abstract -----</td> <td style="vertical-align: top;">3,14</td> </tr> </table>			Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³	A	EP, A, 0217165 (KENNETH et al.) 8 April 1987 see figures 5,1; abstract; page 10, lines 11-22 --	3,4,7,8, 14	A	EP, A, 0189329 (FISCHELL et al.) 30 July 1986 see abstract -----	3,14
Category ¹⁰	Citation of Document, ¹¹ with indication, where appropriate, of the relevant passages ¹²	Relevant to Claim No. ¹³									
A	EP, A, 0217165 (KENNETH et al.) 8 April 1987 see figures 5,1; abstract; page 10, lines 11-22 --	3,4,7,8, 14									
A	EP, A, 0189329 (FISCHELL et al.) 30 July 1986 see abstract -----	3,14									
¹⁰ Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "G" document member of the same patent family											
IV. CERTIFICATION <table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 50%; padding: 5px;"> Date of the Actual Completion of the International Search 7th July 1988 </td> <td style="width: 50%; padding: 5px;"> Date of Mailing of this International Search Report 27. 07. 88 </td> </tr> <tr> <td style="width: 50%; padding: 5px;"> International Searching Authority EUROPEAN PATENT OFFICE </td> <td style="width: 50%; padding: 5px;"> Signature of Authorized Officer M. VAN MOL </td> </tr> </table>			Date of the Actual Completion of the International Search 7th July 1988	Date of Mailing of this International Search Report 27. 07. 88	International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer M. VAN MOL					
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International Searching Authority EUROPEAN PATENT OFFICE	Signature of Authorized Officer M. VAN MOL										

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. ☒ OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE ¹

This International search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. ☒ Claim numbers * because they relate to subject matter not required to be searched by this Authority, namely:

* Claim numbers 1,2,5,6,9 - 13

See PCT - Rule 39.I (iv) :

Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. ☐ Claim numbers because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

VI. ☐ OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING ²

This International Searching Authority found multiple inventions in this international application as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.
2. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:
3. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:
4. ☐ As all searchable claims could be searched without effort justifying an additional fee, the International Searching Authority did not invite payment of any additional fee.

Remark on Protest

- ☐ The additional search fees were accompanied by applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO.

US 8801210

SA 21950

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.
The members are as contained in the European Patent Office EDP file on 18/07/88
The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A- 0217165	08-04-87	WO-A- 8701273	12-03-87
		AU-A- 6371886	24-03-87
		JP-T- 63500987	14-04-88

EP-A- 0189329	30-07-86	None	
