Summary and Conclusions

The results of 200 anastomotic operations in patients with morbus caeruleus are described, nearly all of them having been followed for more than a year and several for four years. Most had Fallot's tetralogy, and here the results were excellent. Many were seriously ill, but only 8% died and 75% benefited greatly, so that they can walk a mile or more and lead lives that are almost normal without too much physical activity. In the smaller number of more complex lesions, such as tricuspid atresia, dextrocardia, and pulmonary atresia, the results were much less good. The total mortality was nearly 30%, and only 35% obtained the good results. More experience is needed to decide which of these patients can hope to benefit from operation, but some tentative suggestions are made.

Most patients have an increased capacity and lose much of their cyanosis, clubbing, and polycythaemia. Some cyanosis, at least on exercise, and some clubbing generally remain unless they were very slight. The haemoglobin usually falls from between 120 and 160% to between 90 and 120%. In nearly all the successful cases a continuous murmur can be heard at the site of the anastomosis, and the presence of this soon after the operation is often one of the best indications of success. The pulse pressure may be a little wider as the result of the anastomosis, but not often much wider.

Generally the improvement gained in the first few months after operation is a good guide to the future and is maintained. The annual mortality rate is not much above 1%, and this includes the risks to which these patients are inevitably exposed whether they have an operation or not.

Special attention has been paid to the increase in the size of the heart because this has been thought to be the great drawback to the operation. Generally the increase is not great, and is not progressive after the first few months. The cardiothoracic ratio may increase quickly from 48 to 52% and then remain constant during the period of observation. A few patients in whom the increase is great or even progressive make us anxious lest they may develop congestive heart failure, but except for three with complex lesions in whom this happened within the first six to nine months no others have yet done so.

It is a pleasure to express our thanks to the surgeons who have made this work possible: Mr. R. C. Brock, who has operated on the largest number, Mr. T. Holmes Sellors, and Mr. Ian Hill. Mr. Holmes Sellors has added to our indebtedness by the great trouble he and his surgical staff have taken in keeping us so fully informed about patients operated on in another hospital. We should also like to thank the staff of the cardiac department, who during the last four years have helped with the follow-up at different stages, the doctors who have sent us reports on their patients, and Miss M. Waldron, of the department of illustration, Guy's Hospital, for the charts.

REFERENCES

- Allanby, K. D., and Campbell, M. (1949). *Guy's Hosp. Rep.*, 98, 18.
 — Brinton, W. D., Campbell, M., and Gardner, F. (1950). *Ibid.*, 99, 110.
 Baker, C. G., Brock, R. C., Campbell, M., and Suzman, S. (1949). *Brit. Heart J.*, 11, 170.
 Blalock, A., and Taussig, H. B. (1945). *J. Amer. med. Ass.*, 128, 189.
 Brinton, W. D. (1951). *Guy's Hosp. Rep.*, 100, 148, 185, 283.
 Campbell, M. (1948). *Ibid.*, 97, 1.
 — (1951). *Lancet*, 2, 647.
 — and Gardner, F. (1950). *Brit. Heart J.*, 12, 183.
 — and Reynolds, G. L. L. (1952). *Ibid.*, 14, 317.
 — and Hills, T. H. (1950). *Ibid.*, 12, 65.
 — Reynolds, G. L. L., and Troughton, J. R. (1953). *Guy's Hosp. Rep.* In press.
 Deuchar, D. C., and Knebel, R. (1952). *Brit. Heart J.*, 14, 225.
 Fleisch, A. (1927). *Handbuch der normalen und pathologischen Physiologie*, 7, Part 2, p. 1273, edited by Bethe and Emsden. Springer, Berlin.
 Lovell, R. R. H. (1950). *Clin. Sci.*, 9, 299.
 Taussig, H. B. (1948). *Brit. Heart J.*, 10, 65.
 — King, J. T., Bauersfeld, R., and Padavathi-Iyer, S. (1951). *Trans. Ass. Amer. Phys.*, 64, 67.
 Wilson, G. M. (1952). *Quart. J. Med.*, 21, 201.

RADIOACTIVE PHOSPHORUS (P³²) IN TREATMENT OF MENORRHAGIA*

BY

H. C. McLAREN, F.R.C.O.G.

J. C. HEATH, B.Sc.

AND

A. QUINTON, M.Sc.

(From the Department of Obstetrics and Gynaecology, Queen Elizabeth Hospital, Birmingham)

If menorrhagia persists after curettage in the over-40 age group a decision on radical treatment either by induction of the menopause or by surgery may be necessary to avoid anaemia and increasing general debility. Both methods have disadvantages, however; radium or deep x rays practically castrate the patient, so that flushings and premature age-effects such as senile "spotting" of the vagina or introital fissuring may develop (McLaren, 1950). Surgery with ovarian conservation may avoid these sequelae, but it carries a small but definite mortality and morbidity.

The idea of avoiding radical treatment by destroying the endometrium is not new; ten Berge (1936) in Holland, for instance, has described a method of uterine thermocautery which had some success. Our present experiments of irradiating the uterus with beta particles were conducted on the suggestion of Dr. A. G. Glucksmann. As beta particles from a source such as radioactive phosphorus are stopped by the surface layers of tissue it seemed that surface endometrial cautery and uterine haemostasis might be achieved without destroying ovarian function.

The difficulty in constructing an applicator which would pass the human cervix yet allow irradiation of the whole of the cavity of the uterus led us to use a balloon on the lines described by Simon (1949) and by Douglas and his colleagues (1950, 1951). The human uterus, however, is not distended without a high pressure of air or fluid, and this led to difficulty in containing the balloon *in utero*. In the end a simple rod-shaped applicator designed by one of us (J. C. H.) was used, and proved to be easy and safe to handle. Despite the shape of the normal uterine cavity a wide area of endometrium was burned by P³².

The Applicator

In the preliminary experiments three layers of filter paper were wound tightly around an acrylic resin rod 4 cm. long and 1 cm. diameter (Fig. 1). An aqueous solution of sodium phosphate containing the radioactive phosphorus isotope P³² was distributed evenly over the filter paper and evaporated. The completely dry filter paper was coated with a solution of acrylic resin.

In later experiments moist filter paper was moulded over the whole surface of a cylindrical "perspex" former with a hemispherical upper end. An aqueous solution of sodium hydrogen phosphate in which the phosphorus is radioactive was allowed to evaporate to produce a dry surface evenly covered with P³². A thin sheath of perspex (0.25 mm. thick) was slipped over the filter paper and a seal made with perspex solution in chloroform at the lower end. This applicator has two advantages: (1) it is easier to assemble, more robust, and less likely to contaminate the patient; and (2)

*Read before the Birmingham and Midland Obstetrical and Gynaecological Society on March 26, 1952.

thinner filter paper may be used, and there is therefore less error due to self-absorption; the absorption in the perspex cover can be allowed for in the calculation. A "winged" applicator was also used which, when in position, formed a letter Y (Cases 10 and 14). The amount of P^{32} used per unit area was the same as for the rod applicator. The two upper short rods were 2.5 cm. long and the single rod 3.5 cm. long; the diameter of all three was 0.8 cm.

Care was taken not to damage the plastic shell containing the P^{32} at insertion into the uterus. For sterilization, 1 in 20 "dettol" was used.

FIG. 1.—The applicator consists of a rod with a covering of P^{32} -impregnated blotting-paper ensheathed in perspex.

Animal Experiments

To test the efficacy of the applicator and to prove its ability to contain the P^{32} , tests were made on the vagina of the rabbit. With the animals anaesthetized, P^{32} applicators were inserted into the lower vagina and held in position by vulval sutures of thread. Dummy applicators were used in control animals. With the loaded applicator in position the animals remained healthy, although the vulva became oedematous. Micturition, however, was undisturbed. After the removal of the applicators the vulval oedema rapidly disappeared, although even 14 days later there was a definite cuff of perivaginal thickening at the site of the P^{32} burn (Table I).

Histological Changes after P^{32} Irradiation

The beta-radiation from P^{32} caused a complete necrosis and loss of surface epithelium. Deep to this, the damage to stromal cells was difficult to interpret—that is, it was difficult to say if some of the stromal cells with granular cytoplasm and indistinct nuclei might recover. There was pronounced inflammatory reaction of the deeper tissue due to the surface burn and to those beta particles which penetrated beyond the necrotic surface layers. Leucocytes crowded the stroma, which was oedematous and showed many free erythrocytes. In this partly inflamed, partly damaged area at the periphery of the damaged vagina it was difficult to define exactly the limit of cauterization by P^{32} . Admitting these difficulties, however, it is safe to say that a cuff of vagina was destroyed to a depth of 2 mm. Deeper to that, of course, the tissues were inflamed and oedematous, but not necrotic.

Clinical Experiments

First of all a dummy applicator was inserted into the uterus of a patient due to have a hysterectomy for menorrhagia. Transcervical sutures of thread were found to hold the applicator safely in the uterus. With this normal (parous) uterus most of the endometrium was found at hysterectomy to be in contact with the applicator. The tissue subjected to histological study served as a control for the irradiated cases.

Four patients—three of whom had uterine fibroids—were then treated with the rod-shaped applicator carrying P^{32} . Total hysterectomy and bilateral salpingo-oophorectomy was carried out within 21 days. After histological studies a further 11 patients were treated with P^{32} , and to judge its curative effect on menorrhagia three months were allowed to pass before hysterectomy.

Prior to insertion of the applicator a bimanual examination of the uterus and appendages was made; curettage of the uterus was also carried out in most cases. On three occasions, however, despite careful bimanual examination and uterine exploration by curette, we failed to diagnose fibroids which were obvious in the uterine muscle on section after hysterectomy. Our failure to make the diagnosis is perhaps excusable because of the intramural position of the fibroids.

After hysterectomy the uterus was opened, photographed, and sectioned to show the depth of burn produced by P^{32} , the degree of endometrial regeneration, and the state of the tubes and ovaries.

Clinical Observation with P^{32} in Utero

As we gained confidence in the technique the patients were allowed up in the ward with the applicator *in utero*. They felt no discomfort or "radium-sickness," although mild flushes of the face affected two patients (out of 15). One patient (Case 6) complained of a pink discharge during the three months between treatment and hysterectomy. She proved to have a mild endometritis with mild endosalpingitis. At operation she had the first "menstrual" loss for three months, and the resulting congestion of the abdominal wall and pelvis made haemostasis difficult. Although the degree of endometrial inflammation was slight, no doubt it added to the physiological congestion of ovarian-pituitary origin. This "menstrual" congestion caused difficulty with haemostasis in another patient (Case 16), although there was no warning uterine bleeding. These two cases are of special interest, since the menstrual congestion of ovarian origin no doubt affected all other patients, whether they menstruated or not.

The need to remove the lower uterus and cervix in another patient led to an unusually difficult dissection of old-standing tough scar between rectum and posterior cervix. A small puncture of rectum followed, but it was easily sutured and caused no trouble during convalescence.

Lastly, our 15-year-old patient, who was bedridden with gross rheumatic heart disease, caused anxiety at hysterectomy.

TABLE I.—Effect of P^{32} on the Vagina of a Rabbit: Severe Tissue Damage was Caused to a Depth of About 2 mm.

No.	Details of Applicator				Surface Dose r.e.p.	Depth Dose in Röntgens Equivalent Physical					When Killed	Gross Effects	Histology
	Quantity	Time Hours	Length cm.	Diam. cm.		1 mm.	2 mm.	3 mm.	4 mm.	5 mm.			
1	4.75	120	4	1	190,000	59,000	21,000 10,000 r.e.p. at 2.8 mm.	7,000	2,500	900	Immediately	Vulvar oedema; perivaginal oedema with slough of mucosa	Severe burn, but not complete destruction of tissues down 2 mm.; marked vascularity
2	4.75	120	4	1	190,000	59,000	21,000 10,000 r.e.p. at 2.8 mm.	7,000	2,500	900	After 8 days	Vulvar oedema and marked perivaginal thickening	Slough of lining mucosa and submucosa to a depth of 2 to 3 mm. Deeper to the burn, marked oedema and capillary dilatation
3	4.75	120	4	1	190,000	59,000	21,000 10,000 r.e.p. at 2.8 mm.	7,000	2,500	900	After 14 days	Thickening of perivaginal tissue	Slough separating; lumen packed with inflammatory cells and necrotic tissue; marked submucosal fibrosis and capillary thrombosis, especially in cavernous tissue of clitoris

This girl had been almost exsanguinated with menorrhagia on several occasions; she had repeated transfusions and repeated curettage, and had resisted all efforts to cure her with hormones. After 12 months of bleeding it was thought that hysterectomy might extend the short life

prognosticated by her physician. P^{32} produced only temporary benefit, and hysterectomy with ovarian conservation was undertaken. She collapsed at operation, but a blood transfusion brought a remarkable improvement, and the operation was concluded without difficulty. Convalescence was satisfactory.

TABLE II.—Control of Menorrhagia by P^{32}

Case	Age	Curettage	1st Menses	2nd Menses	3rd Menses
5	49	Metropathia	Normal	Normal	Normal
6	49	No curettings obtained	Nil	Nil	Began at operation
7	44	"Normal" proliferative phase	Trace	Normal	Normal
8	15	Metropathia (undiagnosed fibroid)	Loss slightly less flooding	Loss slightly less flooding	Relapse: flooding
9	48	Metropathia (undiagnosed fibroid)	Flooding	Flooding	Emergency hysterectomy
10	43	No curettage	Trace	Nil	Nil
11	36	Patchy metropathia	Nil	"	Normal loss
12	45	Premenstrual (undiagnosed small fibroid)	Heavy	Trace	Normal (4th period flooding)
13	45	Proliferative	Flood	"	Normal
14	45	Metropathia	Nil	Nil	Nil
16	47	No curettage	"	Trace	"

Of 11 patients, 7 were successfully treated; 1 relapsed after 3 months; another was improved for only 2 months; while 2 (with unsuspected fibroids) were failures.

Control of Menorrhagia by P^{32}

Of 16 patients treated with P^{32} , 11 were given a three-months trial before hysterectomy. The period of three months was laid down by the Medical Research Council, who advised us in these experiments. It is, of course, not sufficient time to assess the value of P^{32} as a haemostatic agent. Nevertheless, improvement as judged by the onset of amenorrhoea or normal menstruation was achieved in eight of eleven patients; one patient was improved for two periods and then relapsed, while the following two patients with unsuspected fibroids of the myometrium were failures.

Case 9.—A 6-para aged 38. At curettage the uterus measured 3 in. (7.6 cm.) by sound; it was uniformly bulky, but it was not thought to contain a fibroid. Curetting showed metropathia. After P^{32} she had 45 days of amenorrhoea followed by a severe uterine loss over 10 days. She was admitted to a neighbouring hospital as an emergency and after three pints (1.7 litres) of blood

TABLE III.— P^{32} Histology.

Case	Age	Curettings	Hysterectomy	Details of P^{32} Applicator					Surface Dose r.e.p.	Estimated Depth of Burning mm.	Clinical Results	Pathology
				Type	Quantity mc.	Time Hours	Length cm.	Diam. cm.				
701	53	No curettings obtained	17th day	Rod	3.82	71	4.0	1.1	150,000	2.5	Insufficient time	Fibroids, 5 in. (12.7 cm.) sound, surface burn, deeper endometrium intact; pre-cancer of cervix (see text)
702	36	No curettage	18th "	"	3.14	68	4.0	1.1	118,500	2.3	" "	Sound 3½ in. (8.9 cm.). Myometrium 1½ in. (3.8 cm.) thick. Surface burn with deeper gland regeneration and marked capillary dilatation (Fig. 3)
703	42	Normal proliferative	15th "	"	2.72	101	4.0	1.1	147,000	2.5	" "	Fibroids: sound 4 in. (10 cm.). Surface burn. Glands persist; epithelial radiation-distortion
15	45	Metropathia	7th "	"	3.40	123	3.5	0.8	187,000	2.75	" "	Fibroids: sound 5 in. (12.7 cm.) Polyp of endometrium showing surface slough; premenstrual endometrium: corpus luteum (Fig. 2)
5	49	"	3 months	"	4.75	120	4.0	1.0	250,000	3.0	Normal menses	Sound 3 in. (7.6 cm.). No evidence of burn, normal endometrium
6	49	No curettings obtained	3 "	"	4.75	120	4.0	1.0	250,000	3.0	Amenorrhoea	Sound 3 in. (7.6 cm.). Absence of glands; endometritis with mild tubal inflammation. Burn membrane
7	44	" "	3 "	"	3.50	152	4.0	1.0	240,000	2.9	3 improved periods then relapse	Sound 3½ in. (9.5 cm.). Patchy regeneration of endometrium (menses, day 1). No evidence of burn
8	15	Normal proliferative	3 "	"	4.75	128	4.0	1.0	265,000	3.1	Amenorrhoea, 6 weeks, 1 normal period then relapse	Sound 3 in. (7.6 cm.). Stroma free from glands except at fundus. Burn membrane
9	48	Metropathia	2 "	"	4.6	57	4.5	1.0	110,000	2.25	Flooding	Sound 3 in. (7.6 cm.). Undiagnosed fibroid and adenomyosis. Burn membrane
10	43	No curettage	3 "	3-piece	7.25	100	3.5 (2.5)	0.8	194,000	2.65	Amenorrhoea	Sound 3 in. (7.6 cm.). Metropathia, post-irradiation epithelial distortion (Fig. 4)
11	36	Metropathia	3 "	Rod	4.75	100	4.5	1.0	200,000	2.8	Amenorrhoea 8 weeks, then normal period	Sound 3 in. (7.6 cm.). Surface hyaline burn membrane, replaces most of endometrium. Metropathia at fundus (Fig. 5)
12	45	Normal premenstrual	3 "	"	4.35	84	4.0	1.0	176,000	2.65	Normal menses	Sound 3½ in. (8.9 cm.). Endometrial polyp and 2 small intramural fibroids. Premenstrual endometrium. Corpus luteum
13	45	Proliferative normal	3 "	"	4.75	123	4.0	1.0	252,000	3.0	" "	Sound 3 in. (7.6 cm.). Proliferative normal endometrium. No evidence of burn
14	45	Metropathia	3 "	3-piece	7.6	123	3.5 (2.5)	0.8	190,000	2.8	Amenorrhoea	Sound 3 in. (7.6 cm.). Small intramural fibroid. Metropathia. No burn effects
16	47	No curettings obtained	3 "	Rod	4.75	124	4.0	1.0	255,000	3.05	"	Sound 2½ in. (7 cm.). Area of endometrium in contact with P^{32} replaced by burn membrane; much untreated unaffected metropathia in upper uterus; epithelial cell distortion (cervical)

Although a superficial endometrial burn was caused by P^{32} , recovery with endometrial regeneration followed. Nevertheless, haemostasis was obtained in 9 out of 12 cases.

hysterectomy was necessary. The anterior wall of the uterus was found to contain a fibromyoma the size of a hen's egg (see also Tables II and III).

Case 12.—A 3-para aged 45. At preliminary curettage the uterus was carefully palpated and fibroids were sought in the uterine cavity with the curette. The uterus was bulky, the cavity 3½ in. (8.9 cm.). A small cervical polyp was removed. The curettings accorded with her menstrual cycle (secretory phase). After P^{32} , menstruation followed at about monthly intervals—namely, heavy loss for seven days, then two normal periods, then a relapse with severe bleeding. At operation a cluster of fibroids some 2 cm. in diameter occupied the upper myometrium.

Two further cases were only partially relieved by treatment with P^{32} .

Case 7.—This patient, aged 44, had three normal periods—that is, an improvement for 103 days—then a recurrence of heavy bleeding. The uterus was bulky, with a myometrium 3½ in. (8.3 cm.) thick but without fibroids. No histological evidence of P^{32} burning persisted.

Case 8.—A girl aged 15 had severe cardiac disease; she had been treated by repeated curettage and blood transfusions. P^{32} led to some improvement for eight weeks, but her third period was heavy. Hysterectomy with ovarian conservation was performed, but there was no uterine abnormality, apart from a hyaline "burn" necrosis of the endometrial stroma.

Effects of P^{32} on the Uterus

Gross Pathology.—Apart from the presence of fibroids or thick myometrium (see Table III), there was little of note to record in the specimens removed at hysterectomy. The ovaries, of course (which would have been severely damaged

by radium), showed obvious signs of activity such as follicles or corpora lutea. In the endometrium the site of burning by P^{32} was obvious—for example, in Case 15, subjected to hysterectomy seven days after P^{32} , the endometrium was burned and congested at the site of irradiation, while as long as three months after irradiation the site of burning was still definable in some specimens.

Histology (Table III).—No specimen was obtained earlier than seven days after irradiation, so that, although the surface dose of beta-irradiation amounted to about 200,000 r.e.p. in both animal and human experiments, we have no human tissue obtained on the conclusion of irradiation. From Cases 15 (seven days after P^{32}) and 702 (18 days after P^{32}) it appeared, however, that the depth of endometrial burn was no more than 1.5 to 2 mm. in the human uterus (Figs. 2 and 3). As in the rabbit's vagina, the surface epithelium and endometrium was necrotic, while the deeper layers were severely damaged and inflamed, with capillary dilatation and clotting, oedema of the stroma, leucocytic infiltration, and so on. As in the rabbit histology, it was difficult to draw an exact outer limit to the depth of cautery achieved by P^{32} . With previous curettage of the uterus, of course, a surface burn and inflammatory reaction affect the deeper part of the endometrium. Nevertheless, the deeper glands and stroma nearest to the myometrium or embedded in the surface muscle appeared to escape irradiation injury, and as recovery proceeded regeneration of endometrium followed. After three months the surface epithelium occasionally showed marked irradiation distortion

FIG. 2.—Case 15. P^{32} caused a surface slough (S), seen separating from tissue which is infiltrated with inflammatory cells.

FIG. 3.—Case 702. Irradiation necrosis of the surface endometrium has not penetrated far enough to destroy deeper glands and stroma.

FIG. 4.—Case 10. After three months. Although some specimens showed apparent recovery from P^{32} , others showed areas of surface epithelium with the irradiation distortion depicted here.

FIG. 5.—Case 11. Three months after 200,000 r.e.p. a type of hyaline or waxy necrosis of stroma developed beneath the lining epithelium (M). In this specimen the "burn membrane" extended down to the upper part of the cervical canal.

tion, while below the surface a waxy or hyaline appearance of the stroma was observed. This we have called a "burn membrane," and it was obvious in four specimens (Figs. 4 and 5). Finally, the ovaries were sectioned in all specimens for evidence of irradiation effects, but, apart from simple follicular cysts, the ovaries were normal.

Intra-epithelial Cancer.—It was an extraordinary coincidence that the first patient to be treated with P^{32} should prove to have what Dr. A. G. Glucksmann calls "near or pre-cancer" of the cervix. The patient was used as a "carrier" of P^{32} , and, of course, surgery was planned when she had recovered from her anaemia. Dr. C. W. Taylor writes: "At the squamo-columnar junction of the cervix there is considerable epidermization of the mucous glands with areas of atypical epithelial proliferation. One section shows apparent pre-cancerous changes with a suggestion of early carcinomatous infiltration, but serial sections taken from the block show, in fact, no more than an indirect cut of a 'cleft' with atypical proliferation of the basal epithelium. The lesion found, therefore, is no more than a tiny fragment of pre-cancer without true carcinomatous infiltration."

The area of cervix in question was well outside the range of beta particles emanating from the applicator, so that the pre-cancerous changes were coincidental.

Discussion

P^{32} produced a surface burn of the endometrium some 2 mm. in depth without ovarian damage. The resulting slough with inflammatory reaction and vascular thrombosis was healed in about 90 days with endometrial regeneration. A recurrence of menorrhagia, however, did not follow in all cases, and, although only 11 out of 16 cases were subjected to a three-months trial, we can report a cure in seven and an improvement in two. Menstruation usually reappeared, suggesting that no more than temporary haemostasis can be expected of the method. Nevertheless, even temporary haemostasis, if it could be guaranteed, would be valuable—for example, in younger women who declined radical treatment or who wished to have children. Not only would the patient be freed from serious haemorrhage, but menstruation when re-established might be normal. The same possibility of normal menstruation after P^{32} exists in the older age group studied in this series, although, of course, the achievement of the amenorrhoea of the menopause without ovarian destruction is the aim of treatment.

The carcinogenic action of x rays or repeated small doses of gamma rays on the skin raises the possibility of endometrial cancer as a sequela of beta-irradiation of the uterus. If, however, the endometrium heals after a surface burn, as happened in most of our cases, and, secondly, if menstruation and shedding of the endometrium follow, it seems unlikely that cancer will develop. Nevertheless, cells which have been irradiated by sublethal doses of beta rays must undergo proliferation, and it is not known if these cells have a tendency to become carcinomatous. The problem must therefore be held *sub judice*, and certainly all patients treated with P^{32} (without hysterectomy) will require a prolonged follow-up so that in time we may have the answer to the question of the risk of carcinogenesis.

The possibility of foetal abnormality is another theoretical objection to the irradiation of the uterus without castration, in that the ovum, by embedding itself in damaged tissue, might in some way grow abnormally. By the time the endometrium has been shed at menstruation, however, and by the time it has recovered sufficiently to develop premenstrual endometrium, it seems a very remote possibility that a healthy ovum would suffer any damage as it developed *in utero*. The ovaries, of course, are not subjected to beta-irradiation, and there is therefore no question of fertilization of a damaged ovum.

Finally, with the idea of achieving a deeper endometrial burn we are now experimenting with cerium¹⁴⁴. Beta particles from this have a maximum energy of 3.1 MeV., and in theory the radiation should burn endometrium to a

depth of 5 to 7 mm. If this calculated depth is in fact achieved we may obtain better clinical results. A further improvement may also follow the development of an applicator which will irradiate all of the endometrium.

APPENDIX A

Calculation of Dose in Equivalent Röntgens at Various Depths

Absorption experiments in tissue-like materials (alkathene wax) show that the beta rays from the P^{32} emerging from the applicator had a half-value layer of 0.075 cm. and an absorption coefficient of 9.23 cm.⁻¹ in tissue. The blackening of photographic film was used to confirm the even distribution of the P^{32} along the applicator and also the calculated dose rates.

Let l = length of filter paper in cm.
 $2a$ = diameter of filter paper in cm.
 t = thickness of perspex sheath in cm.
 q_0 = strength of P^{32} in mc. when applicator inserted.
 q = " " " removed.
 Decrease in "strength" = $(q_0 - q)$ mc.
 Number of beta particles emitted during treatment = $(q_0 - q) 6.57 \times 10^{13} = N$.

Consider the number of particles crossing the boundary of an elementary cylinder diameter 2 r.

Half the particles emitted will be ejected outwards from the filter paper, and allowing for the absorption of the rays:

$$\text{No. of particles crossing the boundary} = \frac{N e^{-9.23(r-a)}}{2}$$

$$\text{No. of particles absorbed in the elementary volume } 2 \pi r l dr = \frac{N}{2} \times 9.23 \times e^{-9.23(r-a)} \times dr.$$

$$\text{No. of particles absorbed per unit volume} = \frac{N \times 9.23 \times e^{-9.23(r-a)}}{4 \pi r l}$$

Assuming that the beta particles have an average energy 1.12×10^{-6} erg.

$$\text{Energy absorbed} = \frac{N \times 9.23 \times e^{-9.23(r-a)}}{4 \pi r l} \times 1.12 \times 10^{-6} \text{ erg/g.}$$

$$\text{Depth dose} = \frac{N \times 9.23 \times e^{-9.23(r-a)} \times 1.12 \times 10^{-6} \text{ r.e.p.}}{4 \pi r l \times 85}$$

If we put $r = a + t$,

$$\begin{aligned} \text{Surface dose } S &= \frac{N \times 9.23 \times e^{-9.23 \cdot t} \times 1.12 \times 10^{-6} \text{ r.e.p.}}{4 \pi r l \times 85} \\ &= \frac{(q_0 - q) 6.57 \times 10^{13} \times e^{-9.23 \cdot t} \times 1.12 \times 10^{-6}}{4 \pi (a+t) l \times 85} \end{aligned}$$

$$\text{Surface dose } S = \frac{(q_0 - q) e^{-9.23 \cdot t} \times 6.36 \times 10^5}{(a+t) l} \dots \dots \dots (1)$$

$$\begin{aligned} \text{Tissue dose} &= S \times \frac{(e^{-9.23(r-a)})}{(e^{-9.23 \cdot t})} \times \frac{a+t}{r} \dots \dots \dots (2) \\ &= S e^{-9.23(r-a+t)} \times \frac{a+t}{r} \text{ r.e.p.} \end{aligned}$$

For the standard applicator $l = 4$ cm., $a = 0.475$ cm., $t = 0.025$ cm. The value of $q_0 - q$ varies, but is approximately 1 mc. If we substitute these values,

$$S = \frac{e^{-9.23 \times 0.025} \times 6.36 \times 10^5 = 252,000 \text{ r.e.p.}}{2}$$

$$\text{Percentage depth dose} = 100 \times e^{-9.23(r-0.5)} \times \frac{0.5}{r} = \frac{50}{r} e^{-9.23(r-0.5)}$$

$$\text{If } d = \text{depth in cm. \% D.D.} = \frac{50}{0.5+d} e^{-9.23 \cdot d}$$

Table Showing How Dose Varies With Depth

Depth in mm.:	Surface	1	2	3	4	5
% D.D.	100	37	11.3	3.9	1.39	0.5
Tissue dose in rep	252,000	80,600	28,500	9,800	3,500	1,260

The minimal lethal dose of radiation on endometrium is not known, but if 10,000 r.e.p. is accepted as a lethal dose then the "cautery" effect of 5 mc. of P^{32} in the uterus for five days is about 3 mm.

Summary

A method is described for producing uterine haemostasis by P^{32} without damaging the ovaries.

A surface burn by P^{32} is quickly healed and regeneration of endometrium follows.

Preliminary animal experiments were followed by a clinical trial on 16 patients, 11 of whom were allowed three months between irradiation and hysterectomy. Seven cases were cured, two were somewhat improved, and two, with unsuspected fibroids, were failures.

We wish to thank Dr. A. G. Glucksmann, of the Strangeways Laboratories, Cambridge, who initiated and took part in this study, and Dr. C. W. Taylor, Director of Pathology at the Birmingham and Midland Hospital for Women, who advised us on the histology. We are also grateful to our colleagues Miss M. Neville and Mr. L. M. Park, Selly Oak Hospital, who operated on one of the patients and sent us the clinical notes and pathological material to complete this report. Finally, we wish to thank Miss M. E. Attwood and Mr. D. H. S. Boyd for technical assistance.

REFERENCES

- Douglas, D. M., Ghent, W. R., and Rowlands, S. (1950). *Lancet*, 1, 1035.
 ——— (1951). *Ibid.* 1, 492.
 McLaren, H. C. (1950). *British Medical Journal*, 2, 76.
 Simon, N. (1949). *Science*, 109, 563.
 ten Berge, B. S. (1936). *Zbl. Gynäk.*, 60, 2066.

VARIATION IN TECHNIQUE OF INTRACUTANEOUS B.C.G. VACCINATION

BY

CARROLL E. PALMER, M.D.

*Director, Tuberculosis Research Office, World Health
Organization, Copenhagen*

AND

PHYLLIS Q. EDWARDS, M.D.

*Medical Officer, Tuberculosis Research Office, World Health
Organization, Copenhagen*

The technique for giving an intracutaneous injection is ordinarily set forth very clearly: 0.1 ml. of fluid is to be injected as superficially as possible into the skin. Yet when even such a simple procedure becomes a commonplace in the everyday work of a great number of persons, as is the case in the large public health programmes of to-day, individually insignificant errors and deviations from the prescribed technique may, when taken collectively, amount to considerable variations, and thereby create problems of unexpected magnitude. The full impact of this situation—and its possible consequences—was probably not really felt until intracutaneous injections of B.C.G. vaccine were being given to literally millions of persons in the international mass vaccination campaigns. The present paper gives the results of several studies designed to provide preliminary information on the immediate measurable results of B.C.G. vaccination in schoolchildren when the technique of intracutaneous injection of vaccine was deliberately varied within the limits likely to occur under ordinary field conditions.

There are two principal ways in which an intracutaneous injection may deviate from the recommended technique. First, more or less than the specified volume of 0.1 ml. may be given; and, secondly, the fluid may not be injected superficially into the skin. Theoretically, these two kinds of deviation ought not to be correlated: variation in volume should be independent of variation in depth.

So long as B.C.G. vaccination remained mostly in the hands of a few interested people, the technique of injection was probably more of an art than a science. Each worker undoubtedly developed his own method of gauging the volume and depth of his injections. With the start of mass vaccination, however, hundreds of new workers had to be instructed in the technique, which could no longer be left to the whim of each worker; some uniformity and standardization was essential. In mass vaccination campaigns it would be difficult, or even impossible, to enforce a standard procedure for measuring the volume from the graduated marking on the syringe, because most syringes—even new syringes—soon begin to leak badly. Experience had already shown, however, that the size of the wheal—the white, rounded elevation of the skin caused by the injection—corresponded at least roughly with the volume of fluid injected; and this method was adopted for gauging the dose. There seems, however, to be little agreement on the size of the wheal representing the standard (0.1 ml.) dose of vaccine.

The first edition of *B.C.G. Vaccination against Tuberculosis* (Holm, 1948), issued by the International Tuberculosis Campaign, contained the following instructions for making intracutaneous B.C.G. vaccination: "By the intracutaneous vaccination, 1/10 c.cm. of the vaccine is injected as superficially as possible into the skin. . . . If the injection is given correctly, a wheal will appear, in which the follicles of the hair are easily visible. The wheal must have a diameter of about 10 mm." Two years later, in the *Second Annual Report of the International Tuberculosis Campaign* (1949–50) the instructions for vaccination were revised to read: "(a) The injection should be made as superficially as possible, and very slowly. (b) The dose should be as accurate as possible—0.1 c.cm. If judged by the size of the wheal, the diameter of the wheal must be 8 mm." An account of the B.C.G. vaccination programme in Finland (Savonen, 1949) did not specify the volume of vaccine or depth of injection, but simply stated that "so much vaccine is used that the anaemic wheal appearing on the skin has a diameter of 10–12 mm."

The British Ministry of Health (1950) issued the following instructions for B.C.G. vaccination programmes: "0.1 c.cm. (ml.) of the vaccine is then injected *strictly* intradermally without loss due to leakage from the needle track. A satisfactory vaccination should produce a white wheal 5 mm. in diameter." A brochure from the Bureau of Tuberculosis Control (1952), Commonwealth of Pennsylvania and the Henry Phipps Institute in the United States, does not mention the size of the wheal but merely states: ". . . 0.1 c.cm. is injected intracutaneously as superficially as possible into the skin."

A volume of 0.1 ml. is almost always specified, yet the wheal expected to result from this volume varies in diameter from 5 to 12 mm. There must therefore be considerable variation in interpreting what is meant by a very superficial injection, for about the only way the size of the wheal could differ and still represent a constant volume of vaccine would be by variation in the depth of injection.

Thus one may be justified in thinking that intracutaneous injections of B.C.G. vaccine, and of tuberculin as well, must have varied widely in mass campaigns.

Many vaccinators began working in the campaigns after only the most cursory instruction and little