The camera is single-eyed and therefore true vision of depth is impossible, but the image projected on the flat screen gives us a feeling of depth by variations in size and intensity, by perspective and parallax: a man walking away from the camera becomes smaller, less well-defined, and moves across the background. Occasionally I have noticed that viewing the screen with two eyes gives a smaller feeling of depth than does monocular vision—perhaps because both retinal images are the same. In the absence of stereoscopy perspectival excisions are sometimes rather obvious—the corner of a newspaper in front of a man's face may cut a piece out. There is no doubt that stereoscopy is the most important factor in perception of depth (Washburn and Wright, 1938) and that if it were added to cinematography a great step towards the complete illusion of reality would have been achieved. There is no short cut to stereoscopic vision: each eye must be given a slightly different view. A few stereoscopic moving pictures have been made and shown publicly. A number of methods are possible (Norling, 1941; Langlands, 1943), some of which do not even require the spectators to wear special apparatus over the eyes—surely an amazing example of human ingenuity.

Although the eye and the camera are constructed on similar principles, and although the images on the retina and on the film are, so far as we know, very much the same, yet we do not see exactly what is projected on the retina. If I stretch out my hand it does not seem to grow bigger, in spite of the increase in the size of your retinal image. This peculiarity of vision which gives us constancy of size and form has been called by Thouless (1931a, 1931b, 1932) phenomenal regression to the real object. A square card lying on a table in front of us is always seen as a compromise (the phenomenal shape) between the shape calculated from the laws of perspective (the stimulus shape) and the actual square (the real shape). The camera images and the projected images are faithful renderings of the stimulus shape, and may thus give rise to distortion. In cartoons it may be important to draw the shapes not according to formal perspective but so that the resulting sensation is the same as that evoked by the actual objects. Regression depends on clues of depth; if, therefore, the illusion of depth is complete, as in stereoscopic cinematography, the image thrown on the screen should obey the laws of perspective. Since at present the illusion is not complete a compromise between the phenomenal and stimulus shapes would probably give the best results.

The eye readily rejects images that are obviously inappropriate—e.g., the image of a squinting eye. The eye, like the camera, can be focused accurately for only a small range (depth of focus) at any one time. Out-of-focus images are not normally seen; continuous adjustment of accommodation ensures that each plane is examined while in focus, so that the subjective impression is that the whole depth of the scene is in accurate focus. The disadvantage of camera vision has been overcome by multiplane photography in which successive planes are focused in turn and recorded without blurring of detail.

It is curious how soon after entering a cinema we forget the severe restriction of the visual field—at two screen-widths distant it is 28 degrees, at six widths only about 9 degrees. Attempts have been made to increase the size of the film and of the screen, but these have not been successful. The small field of vision makes it difficult to replace clues normally provided by the proprioceptive nerve endings. In a street scene we may be shown barrows being pushed uphill with obvious effort to give us a second-hand notion of the appropriate muscular sensation denied to us lounging in our seats. Sometimes the camera is made to look round (pan) so that we may be given a wider view; when the picture is projected we get the impression that the scenery is floating past. If the eye is fixed, movement of an external object from right to left causes movement of the retinal image from left to right, and we are aware that the object has moved. When the eye glances from left to right the retinal image again moves from left to right, but the external object does not appear to move and may not even be seen. The failure of reciprocity can be clearly seen if a neon lamp on a.c. mains is used as the test object (Bell, 1943, unpublished). It seems reasonable to deduce that proprioceptive impulses arising in the external eye muscles are responsible for the reduction of visual sensation during eye movements. Normally we take in a scene in a series of glances, but if the camera made glancing movements the projected picture would be very unsatisfactory, since our proprioceptors would be unaffected. In the present state of physiology it is hardly possible to imagine how artificial but

appropriate proprioceptive stimulation could be supplied to an audience.

We are thus a considerable distance on the road to the complete illusion of reality, but there are many problems yet to be solved. It seems to me that a great bar to improvement of film presentation lies in the multiplicity and complexity of the techniques employed in one moving picture. It may even be that if the technique for the perfect illusion were available it would be an impossible medium. The main difficulty would be to find a superhuman creative worker who would be first an artist and then a technical expert in matters tactile, olfactory, proprioceptive, and auditory, as well as in three-dimensional colour.

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ENCEPHALOMYELITIS FOLLOWING VACCINATION IN FIFE

BY

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The three outbreaks of smallpox which occurred in Scotland during 1942—in Glasgow in May (32 cases), Methilhill, Fife, in August (29 cases), and in Edinburgh in October (36 cases)—were each followed in Fife by a public demand for vaccination. The vaccinal state of the public was low. It was estimated that in Methilhill only 20 to 30% of the population had been previously vaccinated; while at Cowdenbeath, a town in which one case of smallpox occurred at a late stage in the outbreak, between 40 and 50% had been vaccinated. The percentage of vaccinated infants in the county as a whole is normally 30.7. The number of people at all ages who received primary vaccination following upon the outbreaks was therefore in excess.

During the Glasgow outbreak free vaccination was offered in Fife through general medical practitioners, and no specific instructions were issued as to any method of insertion; but when cases at Methilhill were found to be suffering from an infection of high potency, and when one of them who had been vaccinated by the single-stroke method sickened with smallpox ten days later, instructions were given that three insertions be made 3/8 in. long and 1/8 in. apart. For the most part this method was followed, but it is known that some practitioners continued to employ the single-stroke method or undertook multiple scarification. It was not possible to collect accurate information regarding the sequelae of the methods used, but it was ascertained that severe local reactions and prostration more often followed the three-stroke method. This method was largely employed in the affected area, and absenteeism at the local coal-mines, which continued for an average of two days, rose from a normal level of 5% to 15%, and at a local emporium employing about 200 people from 0.5% to 6%.

In all, 54,698 doses of lymph were issued by the county public health department to private practitioners and to public clinics. Of these, 7,151 were obtained from a private firm immediately the presence of smallpox became known. The remainder came from the Government lymph establishment. Orders for lymph were placed daily, so that fresh material was always in use. Stocks were kept in refrigerators overnight.

On the whole, post-vaccinal disorders were of comparatively brief duration, and, although no reliable evidence was forthcoming that vaccination had in general a deleterious effect on health, the occurrence of 9 cases of encephalomyelitis following on vaccination gave rise to disquietude. Two had been vaccinated with lymph from the private firm and seven with Government lymph. The following table shows the relation of the cases to the number of vaccinations performed:

	Glasgow Outbreak	Methilhill Outbreak	Edinburgh Outbreak (Cowdenbeath)	Total
Public vaccination centres ..	—	21,232	10,961	32,193
Docks, factories, collieries, hospitals, L.A. staffs, etc. .	—	3,466	431	3,897
Medical practitioners, non-panel patients ..	1,360	19,081	5,657	26,098
Ditto, Panel patients (estimated) ..	997	8,993	3,148	13,138
Total ..	2,357	52,772	20,197	75,326
Cases of encephalomyelitis ..	—	8	1	9

All of the 9 patients were children of ages varying from 3 years to 17 years, and in each the vaccination had been a primary one. All were reported to have been in good health before vaccination, except one child who was suffering from whooping-cough, on account of which fact encephalitis following on whooping-cough could not be entirely discounted. The vaccination lesion was a single vesicle in each case, and was pursuing an apparently normal course. No information was obtained regarding the method of vaccination employed. Nervous symptoms occurred ten to twelve days after vaccination, at a time when the usual constitutional upset of vaccinia begins to subside.

In six cases the clinical findings pointed to a diagnosis of encephalitis, with headache, vomiting, and drowsiness or coma as the predominant features; four of these patients died. In two cases the symptoms and signs, localized to the spine, indicated a diagnosis of myelitis; both recovered rapidly. In one case the nervous complication took the form of an acute lymphocytic meningitis; recovery was rapid and complete.

The main features of the cases are summarized in the table opposite, but a clearer clinical picture will be conveyed by a brief summary of the case histories of the patients under our care.

Case I

A boy aged 3½. Primary vaccination on 11/10/42, before which he had had a slight cough. He sickened on 21/10/42, and on 22/10/42 he became drowsy. On admission (23/10/42): Temperature 98.4° F.; pulse 142; respirations 30. A poorly nourished, ill-looking child, listless, limp, and drowsy. When roused he was irritable, but was apparently clear mentally. There was flaccid paralysis of lower limbs with strongly extensor plantar reflexes; trismus present; pupils equal and reacted to light; squint present; follicular tonsillitis present and also cough of whooping-cough type. The child's condition gradually deteriorated, with rising temperature and pulse rate, drowsiness deepening to coma, and onset of spasticity of limbs, particularly noticeable in the flexor muscles of the arms. He died 48 hours after admission. Permission for necropsy was refused. Although the diagnosis of whooping-cough was reasonably certain on clinical grounds, *H. pertussis* was not grown on cough plate cultures exposed on the day before death.

Treatment.—From the time of admission he had 0.5 g. of sulphapyridine four-hourly. Twenty-four hours after admission he was given 20 c.cm. of antivaccinal horse serum (Lister Institute) intramuscularly.

Case II

A boy aged 10. Was vaccinated on 11/10/42 and became ill on 22/10/42 with headache and sleepiness. On 23/10/42 he was feverish, with headache, vomiting, and drowsiness. On 24/10/42 he became delirious and was admitted to hospital. On admission: T. 102.4° F., P. 124, R. 22. A sparely built boy, unconscious, restless, and emitting short high-pitched cries at intervals, especially when disturbed; incontinence of urine. Examination was difficult on account of restlessness; eyes normal; no spinal rigidity; plantar reflex flexor on right and doubtful on left; abdominal reflexes absent; tache cérébrale present; throat acutely inflamed. 25/10/42: Still drowsy, but much less irritable; trismus present; could be made to drink with difficulty; temperature normal. 26/10/42: Simple questions answered for first time since admission; left plantar reflex flexor; pulse rate 56. 29/10/42: Plantar reflexes flexor. 4/11/42: Both legs stiff. 2/11/42: Well in all respects.

Treatment.—A few hours after admission he was given 30 c.cm. of antivaccinal horse serum (Lister Institute)—23 c.cm. intravenously and 7 c.cm. intramuscularly. His mother, who had been vaccinated in infancy, revaccinated in 1927, and again on 11/10/42, gave a quantity of her blood on 25/10/42. The boy received 140 c.cm. of his mother's serum intramuscularly—60 c.cm. on 25/10/42 and 80 c.cm. on 26/10/42. The only drug used was a soneryl suppository as a sedative during the first night.

Case III

Boy aged 8. Was vaccinated on 12/10/42 and had fairly severe vaccinia from 19/10/42 to 21/10/42. From then he was in normal health until the evening of 24/10/42, when he became listless and drowsy. On 25/10/42 he was acutely ill with severe headache and drowsiness, temperature 104° F. On 26/10/42 he became delirious and had difficulty in speaking and drinking owing to trismus.

On admission (26/10/42): T. 100° F., P. 96, R. 20. A strong, well-nourished boy, listless and drowsy; mentally clear when roused; eyes normal; tendon reflexes normal; no rigidity of spine; abdominal reflexes diminished on left side; plantar reflexes flexor on right, extensor on left; throat mildly inflamed. 27/10/42: Coma had developed during the night; by midday he could be roused only with great difficulty; trismus present; abdominal reflexes absent on left side, diminished on right side; plantar reflexes extensor on left, doubtful extensor response on right. 29/10/42: Brighter mentally; severe spasticity of legs and left arm; tendon reflexes exaggerated; spastic tremor of left leg; extensor plantar reflexes both sides. 30/10/42: Less spasticity of legs; plantar reflexes flexor. 31/10/42: Temporary return of severe spasticity of legs. 1/11/42: Mentally alert; well, apart from stiffness of left leg.

Treatment.—On 27/10/42 blood was taken from his mother, who had been revaccinated on 12/10/42. The boy was given 180 c.cm. of his mother's serum—20 c.cm. intravenously and 80 c.cm. intramuscularly on 27/10/42, and 80 c.cm. intramuscularly on 28/10/42.

The salient features of Cases VII, VIII, and IX are given in the accompanying table. These three fatal cases were not observed by us, but from the histories obtained there is little doubt regarding the diagnosis.

In all of the six cases described the picture is one of encephalitis, with headache, vomiting, and drowsiness or coma, producing paralyses, at first flaccid and later spastic. In most of the cases the upper motor neurones affected were notably those related to the limbs, especially the lower limbs. Thus in five cases positive Babinski signs were recorded at some time during the illness—in the sixth no mention is made of the test being carried out. In the three cases seen by us trismus was a feature of the early stages of the disease, causing difficulty in drinking and speaking. In the two cases which recovered there was no evidence of residual weakness at the time of discharge from hospital, and five months later there was no suggestion of mental or nervous disturbance.

We regard Cases IV and V as examples of post-vaccinal nervous complication in which the inflammation of the central nervous system is localized to the spinal cord. Encephalomyelitis is often referred to in the literature, but we can find only three references to post-vaccinal myelitis as a clinical entity (Zappert, quoted by Rolleston in *Acute Infectious Diseases*, 1940, p. 420; and McKenzie, *Proc. roy. Soc. State Med.*, 1943, 36, 235. Inconclusive reference is made to a case in the Report of the Committee on Vaccination, 1930).

Case IV

A healthy boy aged 10. Was vaccinated on 14/10/42 and became acutely ill on 26/10/42, with severe backache in the lower thoracic region and pain radiating round his side to the right subcostal region. He had slight headache and sickness on 28/10/42, and was admitted to hospital. On admission: T. 98° F., P. 112, R. 20. A strong, well-nourished boy, alert and bright mentally; marked spinal rigidity with obvious "tripod" sign present; Kernig's sign positive; no nuchal rigidity, but any attempt to flex the spine, even the cervical spine, produced acute pain in the lower thoracic region and sharp pain in the right subcostal area; abdominal reflexes absent; plantar reflexes flexor on right side and extensor on left side; tendon reflexes normal. The spinal rigidity gradually passed off during the next three days, and he was discharged well on 4/11/42. He had had no drugs or immune serum.

Case V

A girl aged 6. Was vaccinated on 13/10/42, and became ill on the evening of 24/10/42 with nausea, listlessness, and later drowsiness. On admission (27/10/42): T. 97° F., P. 100, R. 20. A well-nourished, bright, and alert child; extreme stiffness and pain on

movement of lower half of spine; no nuchal rigidity or stiffness of legs; plantar reflexes flexor on left and extensor on right. 28/10/42: Lumbar puncture; cerebrospinal fluid clear; 35 mononuclear cells per c.mm.; spine still stiff and painful in the lumbar region. 30/10/42: No stiffness of spine; left plantar reflex extensor. 3/11/42: Well in all respects; no weakness of legs. She was given no drugs or immune serum.

Acute myelitis of this type is unlikely to endanger life, and has therefore neither the gravity nor the importance of encephalitis. Severe backache is a common feature of severe vaccinia, and it seems probable that post-vaccinal myelitis occurs more frequently than is generally realized. Thus Dr. J. Veitch, Cowdenbeath, in a private communication informs us that in his practice during the vaccination campaign "several cases (males) previously unvaccinated complained of pain and

leg. 6/11/42: Child improving, but still severe stiffness of neck and spine; still very irritable; there was difficulty in inducing her to drink. 7/11/42: Much brighter and less stiffness of spine; stiffness of the left leg. 9/11/42: Well in all respects excepting marked stiffness of both legs; reflexes normal. 14/11/42: Discharged well.

Treatment.—On 4/11/42 blood was taken from the child's father, who had been revaccinated on 22/10/42. 140 c.cm. of the father's serum was given intramuscularly—40 c.cm. on 4/11/42, 80 c.cm. on 5/11/42, and 20 c.cm. early on 6/11/42. Starting at noon 5/11/42 with 1 g. and continuing with 0.5 g. four-hourly, 15 g. of sulphapyridine was given.

Case VI appears to be an example of post-vaccinal meningitis or meningo-encephalitis. An alternative diagnosis is benign lymphocytic choriomeningitis, a virus infection giving a

Table showing Principal Features of the Cases

Case	Age (yrs.) and Sex	Date of Vaccination (Primary)	Onset of Illness	Admission to Hospital	Leading Symptoms and Signs	Cerebrospinal Fluid	Final Diagnosis	Evidence of Concurrent Infection	Treatment	Result
I Methilhill	3½ M	11/10/42	21/10/42	23/10/42	Drowsiness; vomiting; paralysis of legs	Clear; pressure increased; Pandey's test pos.; 8 mononuclear cells per c.mm.	Encephalitis	Whooping-cough and follicular tonsillitis	Sulphapyridine 0.5 g. 4-hourly; 20 c.cm. antivaccinal horse serum on 24/10/42	Died 25/10/42
II Methilhill	10 M	11/10/42	22/10/42	24/10/42	Headache; drowsiness; delirium	Clear; pressure slightly increased; Pandey's test pos.; 60 mononuclears per c.mm.	"	Follicular tonsillitis	30 c.cm. antivaccinal horse serum; 140 c.cm. maternal serum	Recovered. Discharged 5/11/42
III Coal town of Balgonie	8 M	12/10/42	24/10/42	26/10/42	Headache; drowsiness; trismus	Clear; pressure slightly increased; Pandey's test neg.; 50 mononuclears per c.mm.	"	Mild tonsillitis and pharyngitis	180 c.cm. maternal serum	Recovered. Discharged 5/11/42
IV Markinch	10 M	14/10/42	26/10/42	28/10/42	Backache; neuritis; stiffness of spine	Clear; pressure slightly increased; Pandey's test neg.; 15 mononuclears per c.mm. Wassermann neg.	Myelitis	Nil	Lumbar puncture only	Recovered. Discharged 4/11/42
V Methilhill	6 F	13/10/42	24/10/42	27/10/42	Backache; stiffness of spine	Clear; pressure normal; Pandey's test neg.; 35 mononuclears per c.mm.	"	"	" " "	Recovered. Discharged 3/11/42
VI Coal town of Wemyss	5 F	22/10/42	3/11/42	4/11/42	Drowsiness; headache; spinal rigidity	Clear; pressure increased; 300 mononuclears per c.mm.	Lymphocytic meningitis	Tonsillitis and pharyngitis	140 c.cm. paternal serum; 15 g. sulphapyridine	Recovered. Discharged 14/11/42
VII Buckhaven	4½ F	11/10/42	22/10/42	—	Drowsiness; coma; flaccid paralysis of legs; Babinski's	Clear; pressure increased	Encephalitis	Rales all over chest	15 c.cm. paternal serum on 25/10/42	Died 26/10/42
VIII Buckhaven	3 M	11/10/42	22/10/42	—	Vomiting; drowsiness; coma	—	"	History of laryngitis at onset	—	Died 23/10/42
IX Cowdenbeath	17 F	18/11/42	30/11/42	1/12/42	Headache; vomiting; drowsiness; coma; spinal rigidity; Babinski's; hyperpyrexia; incontinence	Clear; pressure normal; sterile	"	Nil	Lumbar puncture only	Died 3/12/42

rigidity in the cervical spine on the tenth to twelfth day after vaccination." Discussing the various types of nervous sequelae of vaccinia, Rolleston (*loc. cit.*) refers to Zappert's description of a meningeal form simulating tuberculous meningitis. Case VI in our series falls into this category.

Case VI

A girl aged 5. Was vaccinated on 22/10/42, and was taken ill on 3/11/42 with drowsiness, headache, and backache. On admission (4/11/42): T. 98.6° F., P. 128, R. 26. A well-nourished child of spare build, rather pale and acutely ill. There was a tendency to drowsiness, but she was cross and irritable when disturbed; throat acutely inflamed; severe nuchal rigidity; Kernig's sign strongly positive. Abdominal plantar and tendon reflexes normal; eyes normal. Cerebrospinal fluid clear; pressure increased; 300 cells, mainly mononuclear, per c.mm. Bacteriologist's report: "Protein, 40 to 50 mg. per 100 c.cm.; sugar present but markedly reduced; Lange reaction, 1112110000; Wassermann reaction negative; no acid-fast bacilli or other organisms demonstrated." 5/11/42: Still acutely ill; severe spinal rigidity; tremor of left arm and

clinical picture similar to that of Case VI. This child, however, was much more seriously ill than any of the cases of benign lymphocytic choriomeningitis seen by us, and the chance of this relatively rare disease occurring within the usual period for post-vaccinal nervous complications is very remote. It is reasonable to assume that, occurring as it did twelve days after primary vaccination and being accompanied by tremor and spasticity of the limbs, the meningitis was produced by the same cause as that of post-vaccinal encephalitis. It is of interest to note that the fatal Cases I and VIII were those of second cousins.

Commentary

Immune serum was used in the treatment of the serious cases seen by us. Cases I and II had antivaccinal horse serum (Lister Institute), but there was not enough evidence to make any decision regarding its value. It produced no serum reaction in Case II, although 23 c.cm. was given intravenously. In Case I the horse serum was probably used too late to be

effective, and in any case the fatal issue was undoubtedly hastened, and possibly caused in part, by the whooping-cough.

It was fortunate that the parents had been revaccinated about the same time as their children, since a source of human immune serum was then readily available. Parental immune serum proved to be of great value when given in large doses—e.g., 140 c.cm. The procedure can be followed without serious risk of serum reaction. It appears to us that in Case VII the dosage of parental immune serum was inadequate and, as in Case I, given too late to be effective. The rapidity of the illness seems to indicate that immune serum must be given early and in large quantity to be successful. Thus, when Case III was admitted, the patient did not appear to be ill enough to justify serum treatment, and in several hours he became comatose. We were convinced at the time that his life had been endangered by the delay of 24 hours in starting serum therapy.

The success of immune serum in the treatment of post-vaccinal encephalitis suggests that it is the virus of the vaccinia which is the causal agent. There is no method of ascertaining the virus content of lymph, and vaccinia may produce all degrees of severity of constitutional upset, and, as shown in our cases, the nervous complications may vary widely. Why should occasional cases develop serious involvement of the nervous system? Are they infections arising from the unsterile nature of calf lymph? Another possible explanation is that the susceptibility of the nervous system to the vaccinal virus may be increased by the presence of concurrent infection. In support of this theory it appears to us to be significant that most of our cases showed evidence of acute upper respiratory infection. Thus Case I had clinical whooping-cough and follicular tonsillitis; Cases II, III, and VI had acute pharyngitis; Case VII had "rales in chest"; and Case VIII had a history of laryngitis. The findings at least suggest that the hazard of encephalitis during vaccinia is much greater when there is concomitant infection in the upper respiratory tract.

Post-vaccinal encephalitis is extremely rare in infancy. Therefore, so long as the danger of smallpox exists, vaccination should be urged in infancy. With modern speed and facility in travel there is nothing to indicate that this danger is likely to disappear.

When primary vaccination of children becomes unavoidable—e.g., during an epidemic of smallpox—it would be a wise precaution to insist on vaccinating or revaccinating the parents at the same time. By so doing a source of safe immune serum would be made readily available if required, and this could be given in large doses—e.g., as a transfusion of plasma on the first indication of cerebral involvement.

Summary

In the Fife outbreak of smallpox in 1942, 8 cases of vaccinal encephalomyelitis occurred among a group of 52,772 recently vaccinated persons and 1 case among a group of 20,197 persons. The incidence in both groups is high, particularly in the first—1 in 6,600.

The case mortality was 44%.

In six of the cases symptoms were entirely of cerebral origin and in two they were of spinal origin—apparently an uncommon manifestation. In one the symptoms were predominantly meningeal.

Much benefit was obtained through the prompt use of parental immune serum in large doses.

It is suggested that there may be a liability to onset of encephalomyelitis in unvaccinated persons suffering from acute infections of the upper respiratory tract.

Vaccination is urged in infancy in view of the risk of involvement of the nervous system in later years.

If primary vaccination of children becomes unavoidable steps should be taken to secure a source of immune serum as a precaution.

Speaking at the twentieth meeting of the German Dermatological Society last year, Conti (*Dtsch. med. Wschr.*, 1942, 68, 1230) said that it was hoped in the future to have a uniform specialist service attached to the health offices. The obligation to obtain treatment must be enforced more strictly. Thus, in the case of syphilis, the accepted salvarsan treatment was obligatory, but a patient was not forced to accept some therapeutic measures, such as cystoscopy, catheterization, dilatation of the urethra, and lumbar puncture. The duty of secrecy still existed, and it was laid down that a patient who had not refused treatment must not be notified by name.

PHENIODOL: A NEW CONTRAST MEDIUM FOR CHOLECYSTOGRAPHY

BY

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The object of this communication is to introduce a new contrast medium for cholecystography which is claimed to be better than tetraiodophenolphthalein.

Literature of the Phthaleins

Graham and Cole, in 1924, first succeeded in visualizing the gall-bladder by means of a radiopaque substance excreted through the liver. They were influenced by the pharmacological studies of Abel and Rowntree (1909–10), who showed that the phthaleins and some of their derivatives were mainly excreted in the bile. The first experiments were made with the free acid and sodium salt of tetraiodophenolphthalein, but unfortunately the preparations proved toxic and some of their animals died. Ultimately they achieved success with the calcium salt of tetrabromophenolphthalein. The drug was injected intravenously in doses of 5 to 5.5 g. in 40 c.cm. of distilled water, and films were taken 7, 8, 24, and 32 hours afterwards. A second report (Graham, Cole, and Copher, 1924) showed that the sodium salt was better.

The possibilities of the new test aroused the keenest interest. Within a year other American workers—notably Carmen and Counsellor (1924)—had confirmed its value. It was shown that the most common and most reliable sign of disease is failure of the gall-bladder to fill with the drug. However, many patients experienced severe toxic reactions after the injection, as the dose had too small a margin of safety.

Meanwhile, Graham and his associates (1925) had continued their researches. They reported that the toxic effects of tetraiodophenolphthalein were due to impurities, and could not advocate this compound for clinical use owing to the difficulties of obtaining pure preparations. Shortly afterwards Whitaker and Milliken (1925) showed that a pure preparation of tetraiodophenolphthalein had definite advantages. Though there was little difference in the comparative toxicity of the iodine and bromine compounds, the former was clinically superior because in a dose of only about half the size of that necessary with the latter it gave a denser and more sustained shadow. These findings were confirmed as preparations of tetraiodophenolphthalein became available.

At first tetraiodophenolphthalein was given intravenously, but some of the early workers were not entirely satisfied with this procedure and persisted with other methods. Stewart and Ryan (1925) stated that a considerable number of persons showed unpleasant reactions when it was given intravenously—"so much so, that in hospitals with which we are connected it was not deemed advisable to continue intravenous injections except when all other methods of diagnosis had failed." For routine purposes they preferred oral administration, and were supported by no less authorities than Carmen and Moore (1925). This view gradually gained support as the quality of the preparations improved, and nowadays oral administration is the method of choice.

With the oral method the majority of patients experience some unpleasant reactions. Some of them complain of its disagreeable taste, many have nausea, a few are sick, and many have diarrhoea. There seem to be differences in the severity of the reactions with various preparations in different localities. Menees and Robinson (1938) tried to find a better preparation. They examined calcium, lithium, potassium, and magnesium salts of tetraiodophenolphthalein, but for various reasons all were rejected except the magnesium salt. They found that a 5-g. dose of this salt gives a shadow of the same density as 3.5 g. of the sodium salt of tetraiodophenolphthalein. It was more palatable and was less apt to produce reactions. After use of the magnesium salt, 76% were symptom-free, whereas only 12% had no symptoms after the sodium salt. Though this report was favourable the manufacture of the magnesium salt was not taken up in this country.