The recognition of such a lesion is not a simple matter, and before surgical treatment is advised a most thorough investigation of the urinary tract must be undertaken, and in cases of doubt repeated in three months. Since treatment was urgent in this case, it was fortunate that repetition of the investigation was not required. The tests described here are, with the exception of the administration of the spinal anaesthetic, those employed in the routine examination of hypertensive patients. Experience has shown that the most informative combination of investigations for this purpose is the Volhard-Fishberg concentration and excretion test, with intravenous pyelography and the differential test of renal function. The basis and the value of the first two are too well known to require any explanation here; the value of testing differential renal function by collection and analysis is not generally appreciated.

The method favoured consists in the catheterization of both ureters at cystoscopy, preferably without an anaesthetic, and the collection of specimens from each kidney for bacteriological examination and analysis. The bladder urine obtained at the cystoscopy is also examined bacteriologically and analysed, as the results provide a useful comparison with those obtained from the examination of the renal urines. The specimens are collected in tubes graduated in ml. for a period which varies from case to case. Wastage to the bladder is minimal. In this instance the collection was made over twenty minutes. The quantity is measured, the pH estimated in a B.D.H. capillometer, and the urea content obtained by analysis in a Doremus ureometer, using a 1-ml. tuberculin syringe graduated in hundredths and a specially curved needle to deliver the urine to the ureometer. This permits the use of small quantities when only these are available. Blood is withdrawn for the estimation of non-protein nitrogen.

Consideration of the results of this analysis in conjunction with the intravenous pyelogram gives a reasonably accurate indication of glomerular activity and tubular function, and a reliable picture of the relative function of each kidney is therefore obtained. It cannot be emphasized too strongly, however, that both the intravenous pyelogram and the differential function test must show similar trends before surgical abnormality is accepted and the renal region is explored with a view to nephrectomy. In the present case the results of these investigations were thought to indicate gross diminution of glomerular activity with excessive tubular absorption.

The high spinal anaesthetic was administered here in an endeavour to discover if any change in the excretion of "pyelosil" would be effected by its influence. If this had occurred the surgical attack would have been directed at the thoracic ganglia and splanchnic nerves on the left side. The muscle biopsy was done at this time for convenience and to exclude polyarteritis as a cause of the rather unusual grouping of symptoms presented by this case.

The cause of the lesions in the kidney is obscure. The possibility of pregnancy was not admitted, and it is therefore likely that there has been a haematogenous pyelonephritis with much subsequent scarring of the cortex. The gross tubular dilatation may also have been due to this cause, or possibly it was the result of some congenital defect in the tubular architecture. Whatever the primary cause, the lesion has had a profoundly constrictive effect on the cortical blood flow. This was suggested clinically by the appearance of the intravenous pyelograms and the differential renal function test. These findings and the subsequent clinical course of the case, considered with the histology of the kidney, form strong evidence in favour of renin elaborated in this cortex as the cause of the hypertension. More detailed histological examination is being made of

this kidney, and the result will be published by Dr. W. A. Taylor in due course.

The prognosis must for the moment be guarded, but if the present position is maintained for a year it will be good. This prophecy is based on the early return of renal function to a high normal level, the continuance of a normal blood pressure despite a return to full activity, and the absence of necrosis or fibrosis in the media of the peripheral arteriole examined under the microscope.

Summary

A case of severe hypertension with advanced retinitis and papilloedema in a young woman of 20 is described.

The presenting symptom of headache, with vomiting and diplopia, suggested an intracranial lesion, but investigation revealed the left kidney as the likely cause. The removal of that organ with the adrenal produced a return of the blood pressure to normal in half an hour and a complete recovery from the retinal changes in a few weeks. This has been maintained to date.

In the discussion reference is made to the significance of this result in relation to the experimental work of Goldblatt. It is also suggested that, if these cases can be recognized before the vascular changes elsewhere are permanent, nephrectomy offers the hope of a cure; reasons are given in support of this view.

The rarity of successful treatment in this type of case is mentioned, and stress is laid on the necessity for a most thorough investigation of the renal tract before surgical measures are advised.

The value of differential renal analysis in the general investigation of hypertensive patients and in the recognition of this type is noted. The method favoured is described.

My thanks are due to Professor D. F. Cappel for valuable criticism during the preparation of this article; to Dr. W. A. Taylor for the great interest and care he has taken with the histology and for the photomicrograph; and to Mr. W. W. Galbraith, in whose wards the patient was treated. I am also indebted for Chart 2 to Professor C. F. W. Illingworth's staff in the department of surgery. The radiographs are reproduced by courtesy of Dr. S. D. Scott Park, director of the x-ray department, Western Infirmary.

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BLOOD CHANGES IN LUMINIZERS USING RADIOACTIVE MATERIAL

BY

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[WITH PHOTOGRAPHURE PLATE]

"Luminizing" is defined in the Factories (Luminizing) Special Regulations of 1947 as "the application of luminous compound to any surface, or the introduction of luminous compound into glass tubing," while "luminous compound" means "luminous material containing a radioactive substance." In its dry form luminous compound is a powder consisting of zinc sulphide with a small admixture of radium or mesothorium, the usual proportion for non-civilian purposes being 70 micrograms of radioactive substance per gramme of compound. Only a small amount is used dry, the greater part being converted into a paint by the addition of various mucilages and solvents. In the wartime industry of luminizing, this paint was applied by hand, by operatives called "luminizers," to aeroplane or watch dials, compasses, gun-sights, and various electrical instruments.

At the beginning of the 1939-45 war it became obvious that the luminizing industry would eventually involve the employment of a large number of luminizers, and in view

of the tragic results which followed, sometimes several years after cessation of work, such employment in America from 1917 to 1924 (Martland, 1931) it was decided that, in addition to the introduction of special regulations devised to protect the luminizers from excessive radiation, clinical and blood examinations should be made by a medical inspector of factories as part of the long-term research into the effects of such work on health.

At the end of the war, when the luminizing industry showed a rapid decline and consequently the number of luminizers a considerable diminution, it was recommended by the Advisory Panel on Radiology set up by the Minister of Labour that a "follow-up" of all luminizers, including a full blood examination, should be carried on for some years.

The following survey comprises the result of the blood examination of luminizers in the course of their employment from 1940 onwards, and of the "follow-ups" from 1945 to January, 1949.

No. of Luminizers Examined		No. of "Follow-ups" Examined	
1941	353	1945	68
1942	350-400	1946	167
1943	430	1947-8	131
1944	460		
1945	534		
1946	113		
1947	81		

"Control" Examinations.—The ideal method of making a controlled investigation of the blood picture of luminizers would of course have been to examine them before their exposure to radioactive substance. This was done whenever possible, but the necessity for providing the essential luminized instruments in wartime made it impossible to hold up the work in a number of cases sufficient to make the controls adequate.

Blood samples of 100 girls of comparable age group and environmental conditions (shop assistants and typists) were therefore taken. The results were compared statistically with those of the luminizers examined between 1940 and 1942.

The only significant variation in the total and differential blood counts of the luminizers at that time was found to be an increase in the number of lymphocytes. No statistical examination of the incidence of abnormal cells in the stained film was made, but no abnormal cells were observed in the films of any of the controls.

Blood Picture of Luminizers

The characteristic deviations from the normal blood picture in a fairly high proportion of all luminizers were as follows:

A Relative Lymphocytosis, with a Moderately High Total White Cell Count.—The actual incidence of relative lymphocytosis (without neutropenia) was as follows: 1941, 22% of all luminizers; 1942, 27%; 1943, 40%; 1945, 27%; 1946, 22%; 1947, 22.5%. In many of these cases the degree of lymphocytosis was high—a typical polymorph/lymphocyte ratio was 40/50—so that an absolute lymphocytosis (3,500–4,000 per c.mm.) was not uncommon.

The Presence of Some Abnormal Cells in the Stained Film.—The presence of abnormal cells, which included occasional Türk cells, occasional premyelocytes, and, most characteristic of all, large mononuclears of immature type, occurred very constantly in about 9% of all cases each year. The abnormal monocytes were of special interest. Frequently they occurred in the same film with large mononuclears of perfectly normal appearance, constituting 30–60% of all large mononuclears present. These "abnormal" mononuclears were generally of two kinds:

1. A "lymphoidocytic" type (Figs. 3 and 4) corresponding closely to those described by Hittmair (1942) as "*kleine Monocyten der Lymphknoten*," to the "young monocyte"

observed by Duvalon (1947) in the blood of the rat, and to the young monocyte which Tzanck, Dreyfus, and Bessis (1944) described as follows: "Size 15–30 μ , nucleus of 'combed' appearance, regular, with no dense masses of chromatin. The nucleus may be round, oval, or bent at several points, rectangular or trapezoid; it may be free in the cytoplasm or adherent at one point to the periphery by a wide pedicle, sometimes cutting the cytoplasm in two parts. The cytoplasm is weakly basophil, hyaline, sometimes polychromatic, the edges clear and sometimes more deeply stained than the rest, and occasionally showing azurophil granules. It is difficult to distinguish from a large lymphocyte."

2. A large "granular" type (see Fig. 5). The characteristic features of this large cell (18–25 μ in diameter), when stained by Wright's or Leishman's stain, are a ragged, spreading, dense nucleus and a heavy granulation of the cytoplasm. A few of these cells identified in smears stained by Washburn's peroxidase method could be distinguished from early cells of the myelocyte series by the small size and dark blue staining of the cytoplasmic granules, as opposed to the large greenish granules of the polymorphonuclear leucocyte.

Red Cells and Haemoglobin Levels.—Anaemia, even of slight degree, was a relatively infrequent feature in luminizers, only 8–10% showing a red cell count below 4,500,000 and a haemoglobin level below 84%. In the few cases in which the anaemia was more severe, this was accountable by pregnancy, post-operative anaemia, or other disorders of health not associated with their occupation. In about 15% of all luminizers the red cell and haemoglobin levels were rather higher than would be expected in girls of this age and social environment—red cells up to 5,000,000 per c.mm. and haemoglobin values up to 98–100%. Statistical examination showed, however, that the mean red cell count was 4,663,785 in the luminizers as compared with 4,780,000 in the controls.

Blood Picture in Ex-luminizers (Follow-ups)

So far 366 luminizers employed during the war, and having had no exposure for periods of one to five years, have been followed up and examined both clinically and haematologically. The comparison of their present blood picture with that observed during their employment may be summarized as follows: (1) Abnormal cells are absent in all cases except one, a girl who suffers from an endocrine dysfunction, with amenorrhoea, adiposity, and hypertrichosis. (2) Relative lymphocytosis is present in only a few cases and is of slight degree. (3) White cell counts are generally rather lower—5,000 to 7,000 per c.mm. as compared with 7,500 to 8,500 during employment. (4) Red cell counts and haemoglobin values show a fall—in those cases in which they formerly reached 5,000,000 per c.mm. and 100% they fell to 4,000,000–4,500,000 and 80–90% respectively.

Extent of Exposure of Luminizers to Radioactive Substance

The potential exposure consisted of (1) external irradiation by alpha particles and beta and gamma rays, (2) inhalation of radon, emanating from the luminous compound, (3) ingestion of luminous compound from contamination of the hands, and (4) inhalation of radioactive dust.

With regard to *external irradiation* the hazard was obviously small, partly because the actual amount of radium in use at each workplace was very small, not more than 1 g. of compound being mixed in the paint container at a time, and partly because the distance factor of safety was utilized by placing a glass screen between the luminizer and her work. *Inhalation of radon* was reduced to a minimum by the provision of mechanical exhaust draught so arranged as to produce a current of air in a direction from the worker towards the work.

The danger of *ingestion* was much less than in the New Jersey cases, where it was known that the luminizers were

in the habit of pointing with their lips the brushes used for applying the luminous paint; by the Luminizing Order of 1941 the use of brushes was prohibited, pens or solid applicators being used instead. Ingestion from contamination of the hands was obviated by special requirements for frequent washing.

There remained the hazard of *inhalation of radioactive dust*, and, though this was reduced to a minimum by the enforced daily washing of benches and floors and prohibition of extraneous articles in the luminizing room, the fact that small splashes of paint on benches and floors were occasionally allowed to dry and become converted into fine powder was not seldom revealed by the illumination of an ultra-violet lamp. It is chiefly to this small amount of what might be called "internal" exposure, as contrasted with the "external" exposure of alpha, beta, and gamma radiation, that I am inclined to attribute the changes, which I consider characteristic, in the blood picture of luminizers, to be described below. That the amount of radium so inhaled was not sufficient in the great majority of cases to lead to a measurable deposition in the tissues has been proved by the fact that repeated tests of luminizers in whom such deposition might have been suspected have shown the presence of less than 0.2 μg . except in one case, a woman who had luminized, to a large extent in unregulated conditions, for 25 years; she showed a radium content of the tissues amounting to 0.7 μg . These tests, carried out by the National Physical Laboratory, Teddington, consisted of direct gamma-ray estimation by means of a Geiger counter and estimation of the radon content of the expired air. Thus it would seem that any effect reflected in the blood picture would be slight and temporary, and the results of blood examinations of luminizers after an interval of non-exposure bear out this view.

Blood Picture in Severe Exposure to Radium

It is well known that the most frequent consequence of overexposure to the gamma rays of radium is a depressive effect on the bone marrow, leading to a severe, often fatal, aplastic anaemia. This may occur as a direct result of a single very severe exposure; during the course of long-continued less severe exposure; or after exposure has ceased, either from irreparable damage to the bone marrow due to external irradiation or to internal irradiation from the deposition in the tissues of radium derived from ingested or inhaled radioactive substance. Such a depressive effect is reflected in the blood picture as an eventual diminution of all the formed elements of the blood—the development of aplastic anaemia.

In the early stages the one consistent sign of overexposure is an absolute and progressive leucopenia, with a relative lymphocytosis causing an associated neutropenia or in some cases with a lymphopenia. *This sign has been conspicuously absent in the luminizers examined between 1940 and 1947.* The deviations in their blood picture suggest on the contrary a hyperstimulative effect, which appears to be produced by a mode of action entirely different from the depressive effect on the bone marrow of external gamma radiation.

Discussion

The Normal Monocyte and the Reticulo-endothelial System.—In 1937 Schilling suggested that the monocyte was derived chiefly from the reticulo-endothelial system and to a less extent from the bone marrow and the lymph glands. This theory is strongly upheld by the French school of haematologists, especially Tzanck, Dreyfus, and Bessis (1944) and Frühling and Roger (1948). The latter authors have described in great detail the reasons on which they base their opinion. These consist chiefly in examinations,

by the peroxidase-staining method of Sato, of portions of human lymph glands, bone marrow, adult and embryonic liver, and spleen. They state that they have been able to follow by this method the actual process of monocytogenesis from a special functional portion of the reticulum—that portion which possesses the function of granulocytophagia.

The Primitive Monocyte.—The normal monocyte (Figs. 1 and 2) therefore, according to the results of Frühling and Roger's investigations, differs from the polymorphonuclear leucocyte and the lymphocyte in being derived from a matrix tissue and not from a primitive blast cell; there is no such cell as a monoblast. There seem to be different grades of the young monocytes or, as Hittmair calls them, "promonocytes," the youngest of all resembling in some respects the myeloblast (Hittmair, 1942), the later ones being difficult to distinguish from large lymphocytes (Duvalon, 1947).

Radium and the Reticulo-endothelial System.—When radium is taken into the body by ingestion, by inhalation of radioactive dust, or by inhalation of radon, which during disintegration is reconverted to radium, a certain amount is excreted by the urine and faeces and by the lungs in the form of radon. With small dosage and interrupted exposure it is highly improbable that the amount deposited in the tissues will exceed the "tolerance dose," estimated in America as 0.1 μg . With larger doses and long-continued exposure the results of heavy deposition in the bones are unfortunately well known—the development of malignant growths in the bones or of severe injury to the bone marrow leading to aplastic anaemia.

Whether the reticulo-endothelial system is involved in the potential deposition in or the passage through the tissues before excretion has not been investigated in human beings, but some unpublished observations by Dr. Mather Cordiner (personal communication), though not entirely relevant to the conditions under discussion, suggest that this is the case. In investigating the possible deleterious effects of a radioactive substance introduced as a contrast material for x-ray diagnosis, Dr. Cordiner, in conjunction with Dr. Hamilton Fairley, administered thorotrast by mouth to rats over a period of two years. At the end of this time the radioactive material was found deposited in the reticulo-endothelial system of the liver and spleen, where it produced areas of necrosis in these organs and to some extent remained as a potential source of radioactivity in the body.

Conclusions

It would not seem unreasonable, taking the above facts into consideration, to formulate the following hypothesis to explain the haematological findings in luminizers: That the actual effects are of the nature of a hyperstimulation rather than depression of the haemopoietic system; that this hyperstimulation is related to the reticulo-endothelial system rather than to the bone marrow; that it is caused by inhalation of small amounts of radioactive dust; and that it is transient only, and in the working conditions of luminizers is not likely to be accompanied by a permanent deposition of radium in the tissues. Each of these points is discussed in detail.

Hyperstimulation.—The hyperstimulative effect is suggested by the "high normal" total white count, the relative lymphocytosis, and the presence of abnormal cells, which consist chiefly of what seem to be young forms of the large monocyte. That these deviations are practically non-existent in ex-luminizers who have had no exposure to radioactive substance for some years, and that red cell and haemoglobin values which were rather higher than would be expected in some girls of this age group and social environment show a fall when exposure has ceased, are

facts which also point to the occurrence of a hyperstimulative effect during employment.

Relation to the Reticulo-endothelial System.—The character of the abnormal cells observed—young forms of the monocyte—suggests that these are being produced by the reticulo-endothelial system under the influence of hyperstimulation. The hyperstimulation would account also for the increased output of lymphocytes from the reticulo-endothelial cells of the lymph glands.

Inhalation of Radioactive Dust.—While it is possible, taking into account the human factor, and in spite of the facilities provided and prohibitions enforced, that careless luminizers may have ingested small amounts of luminous compound or that they may have inhaled a certain amount of radon, it seems more probable, from a study of their working conditions and from estimations of the radon content of the air in luminizing departments, that the inhalation of dust contaminated with dried luminous compound was the chief source of any radioactive material being introduced in small amounts into the body.

Transient Effect.—Both the haematological findings in ex-luminizers without any signs of hyperstimulation and the estimations for radium deposited in the tissues carried out on a number of luminizers employed for long periods suggest that no permanent effect has been produced by the introduction into the body of any small amount of radioactive material.

Whether an actual hyperplasia of the reticulo-endothelial system occurs during the period of exposure it is impossible to judge. As Hittmair (1942) remarks: "When can one assume a hyperplasia of the reticulo-endothelial system in the sense of a leucosis, and when is blood formation in this system to be judged superfluous? We know that we cannot expect any striking histological findings of myelosis or lymphadenosis, since the reticulo-endothelial system is not a closed system but scattered cell groups." On the evidence here presented I can only say that, if such hyperplasia does occur, it must be of a transitory nature, subsiding when the causal agent is removed.

Summary

The results of blood examinations of a number of luminizers over a period of five years have shown no evidence of a depressive effect on the bone marrow, but rather of a slight hyperstimulation, which is tentatively ascribed to an effect on the reticulo-endothelial system.

Blood examinations of the same girls after a period of one to four years following cessation of exposure show a complete disappearance of this hyperstimulative effect.

The characteristic abnormalities of the blood picture of luminizers are described, and the reasons for attributing them to hyperstimulation of the reticulo-endothelial system are discussed.

The transient nature of these changes is supported by the results of direct gamma-ray estimation of the tissues and of estimation of radon in the exhaled air.

My thanks are due to the Senior Medical Inspector of Factories for permission to publish the above results; to the National Physical Laboratory for their helpful co-operation in estimating tissue radium; to Dr. Mather Cordiner for permission to publish his results on ingestion of radioactive material by animals; and to Mr. K. Goodall, H.M. Inspector of Factories (Engineering and Chemical Branch), for producing the photomicrographs of abnormal blood cells.

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ACUTE IDIOPATHIC PULMONARY HAEMOSIDEROSIS

BY

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[WITH PHOTOGRAVURE PLATE]

Non-occupational pulmonary haemosiderosis has often been described in Continental medical literature, but has only recently aroused any interest in this country. It has been reported as a rare complication of mitral stenosis and also as an idiopathic phenomenon. Wyllie, Sheldon, and others (1948) have reviewed the relevant literature, summarized the reported cases of idiopathic haemosiderosis, and presented several cases encountered during recent years at the Hospital for Sick Children, Great Ormond Street, London. All these previously reported cases, with one exception, have pursued a chronic remittent course. The exception is a case described by Ceelen in 1931, in which a period of one month encompassed the onset of symptoms and necropsy confirmation of the diagnosis.

A further rapidly progressive case, in a previously healthy child, is here presented, in which only five weeks separated the initial symptoms and a fatal issue. Clinically the diagnostic problem and general course of the disease, apart from its rapid course, strongly resembled the clinical picture given by Wyllie, Sheldon, and others (1948), but the post-mortem findings did not correlate in the finer details with all those described by them. They do, however, resemble those outlined by Scheidegger and Dreyfus (1945).

Case Record

A small deathly-pale girl aged 2½ was admitted from an outlying village to the Sheffield Royal Hospital, with a month's history of increasing pallor, lassitude, and general debility. Previously she had been a very active, healthy, and intelligent child, and neither the mother nor the family doctor could recall any previous illness. She was a full-term, breast-fed child, and had developed normally. No family history of consanguinity, allergy, or blood disorder was elicited. No cough, haemorrhage, or petechial phenomena had been noted, and there had been no recognized exposure to noxious agents. No drugs had been administered. In view of a remote family history of tuberculosis a radiograph of the chest, which was reported as normal, was taken at a local tuberculosis clinic.

On admission the child lay inert and uninterested in her surroundings, with no cyanosis or dyspnoea. She was well nourished and of good physique, but her skin showed a translucent waxen pallor unmarred by petechiae or bruises. The pulse was rapid and regular, and there were no signs of cardiac failure or of valvular disease. Respiration was normal, and no abnormal signs were found in the chest. The liver edge was just felt, but the spleen was not palpable. No neurological abnormalities were noted; the ears, fauces, and fundi were normal; and the only other recorded physical sign was a generalized slight adenopathy. The temperature was normal.

Clinically, acute leukaemia or aplastic anaemia appeared highly probable, but the blood picture revealed a severe hypochromic anaemia with leucopenia and the bone marrow showed no gross changes: haemoglobin, 22% (3.2 g.%); red cells, 1,640,000 per c.mm.; colour index, 0.6; white cells, 3,600 per c.mm. (polymorphs 50%, lymphocytes 50%); one late normoblast was seen; slight anisocytosis and poikilocytosis; Group A (II) Rh-positive; no abnormal haemolysins detected; bleeding time, 4 minutes; clotting time, 8 minutes (normal for methods used). Van den Bergh reaction was faint direct positive; serum bilirubin, 1 unit; icteric index, 4. The urine contained excess urobilin and urobilinogen.

One pint (570 ml.) of appropriately selected packed cells was given with suitable precautions, and dramatic improvement ensued. The child became bright and lively, and played with

LESLIE NANCEKIEVILL: ACUTE IDIOPATHIC PULMONARY HAEMOSIDEROSIS

FIG. 1.—Slight mottling of both lungs in early phase.

FIG. 2.—Diffuse gross reticulation in late phase.

FIG. 3.—Iron-containing cells in alveoli. Prussian blue. (× 100.)

ETHEL BROWNING: BLOOD CHANGES IN LUMINIZERS

H. M. LAWSON: DISSEMINATED OSSIFICATION OF THE LUNGS

FIG. 1.—Normal monocyte of diameter 13.5μ. (× 2270.)

FIG. 2.—Normal monocyte of about 15μ diameter. (× 2270.)

FIG. 3.—Lymphoidcytic monocyte of diameter 11.5μ. (× 2270.)

FIG. 4.—Abnormal (intermediate type) lymphoidcytic monocyte, 13.5 by 11μ.

FIG. 1.—Miliary shadowing of both lungs. The heart contour is typical of mitral stenosis.

FIG. 5.—Abnormal large monocyte (18.5μ) resulting from initial stimulation of reticulo-endothelial system by ingested radioactive material. Some granularity in cytoplasm. (× 2270.)

FIG. 2.—Section of lung showing irregular nodule of bone with laminations and included osteoblasts. (× 100.)