The mortality from appendicitis is still far from negligible (969 deaths in 1954 in England and Wales) although it is falling. Allowing for changes in the age structure of the population, the mortality of the males is 27% of what it was in 1938 (Registrar-General, 1955b).

Age, sex, social class, and place of residence probably affect the incidence of the disease, and these and other factors certainly affect the incidence of appendicectomy and the death rate from appendicitis. The distinction between (a) the distribution of the disease, (b) the distribution of the operation, and (c) the mortality rate is necessary at the present time, as nothing is known about possible variations in the minor forms of the condition. The variety of factors that influence the operation and death rates, and interact in a complex way, seems to rule out the possibility of there being a single cause for the disease. At the present time we are almost entirely ignorant of what these causes may be. Fuller knowledge, while valuable for its own sake, might well lead to better treatment or rational prophylaxis. Thus the use of purgatives is still very common among young people—a problem to which Reid (1956) has recently drawn attention.

What is the geographical and social distribution of the use of these drugs? Is appendicitis related to their routine or sporadic use? The operation rate is very high in young women, while the death rate is very low. What proportion of these appendixes removed from young women show good evidence of inflammation? Is the severe disease commoner here, or do these young women have an excess of the minor forms of the disease? If they do, why is this so? Children and young people in certain areas seem unduly exposed to the disease. Is the disease process different from that found in old people, when the social distribution may be quite different? These and many other problems of the disease could be approached by epidemiological methods.

Summary

Young males are more likely to be operated on for appendicitis and to die of the disease in the Glasgow area than they are in London. This is an unexpected finding, in view of the association between appendicitis and high economic and social status. The existence of a further factor in the causation of the disease is postulated.

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INFLUENCE OF VITAMINS UPON SOME TERATOGENIC EFFECTS OF RADIATION

AN EXPERIMENTAL STUDY

BY

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Developmental malformations may readily be produced in the embryo by exposure of the dam to ionizing radiation during pregnancy (Hicks, 1953). Extensive investigations have been carried out upon chemical agents which either increase or diminish the radio-sensitivity of the tissues, but little attention has been paid as yet to the possibility that the teratogenic effects of radiation may be modified in a similar fashion. Wolff and Kirmann (1954), however, have shown that certain substances, such as cystamine, protect the developing tissues to some extent from the effects of x-radiation, and thus reduce the incidence of malformations in the offspring of dams exposed to x-radiation during pregnancy.

A large body of evidence has now accumulated which indicates that the induction of a maternal hypovitaminosis or hypervitaminosis is an effective method of producing a wide range of deformities in the embryo. The literature has recently been reviewed by Woollam and Millen (1956). Alteration of the maternal vitamin intake produces deformities in the young remarkably similar to those which occur when the dam is exposed to ionizing radiation during pregnancy. Defects of the eye and hydrocephalus which are readily produced by radiation (Hicks, 1953) also occur when the dam is subjected to the effects of hypovitaminosis or hypervitaminosis A (Giroud, 1955). The question naturally arises whether alteration of the vitamin intake of the dam during pregnancy might not have some effect in increasing or reducing the sensitivity of the young to the teratogenic action of radiation. The present communication deals with a group of experiments in which the effects of a combination of vitamins on the radiosensitivity of the foetus were studied.

Material and Methods

Preliminary Investigations.—It was considered necessary to concentrate on a single deformity, the presence or absence of which could be demonstrated unequivocally. Anophthalmia fulfilled this criterion satisfactorily. Preliminary experiments were therefore conducted to establish the time of administration and level of dosage of x-radiation which would produce a suitable standard incidence of anophthalmia.

Experimental Details.—Virgin female white rats of the Wistar strain were divided into four groups of 12 each as follows: Group 1 received radiation and vitamins; group 2 received radiation only; group 3 received vitamins only; and group 4 (controls) received neither radiation nor vitamins. Pregnancy was dated by vaginal smears taken daily at 9 a.m.; the day on which sperm was found in the smear was taken as Day 1. Animals in groups 1 and 3 received the following vitamins by parenteral injection at 2 p.m. on Day 1: vitamin A, 10,000 i.u.; vitamin D₂, 50,000 i.u.; α -tocopherol acetate, 60 mg.; aneurine hydrochloride B.P., 70 mg.; nicotinamide, B.P., 45 mg.; riboflavin B.P.,

1 mg.; pyridoxine hydrochloride *B.P.C.*, 15 mg.; calcium pantothenate, 1.5 mg.; benzyl alcohol *B.P.*, 40 mg.; and ascorbic acid *B.P.* as sodium ascorbate, 150 mg.

The animals of groups 1 and 2 received x-radiation on Day 2 at 9 a.m. The details of the radiation are as follows. Each animal received a single dose of x-radiation. The animal was placed in a lead tube which had an aperture $1\frac{1}{2}$ by $1\frac{1}{4}$ in. (3.8 by 4.4 cm.) situated over the anterior abdominal wall so as to expose both cornua of the uterus to the rays. A beam of x rays was used at a potential of 85 kV.P., filtered through 1 mm. of aluminium at a tube current of 8 mA and exposure of 2 minutes; the skin dose, as measured with a Baldwin-Farmer substandard dosimeter at focal skin distance of 10 cm., was 258 r. The animals were killed on Day 20. The young were removed and weighed. The heads were preserved in Bouin's solution. Celloidin sections of heads were later prepared and the presence and dimensions of each eye accurately ascertained.

Findings

There were no significant variations in the weights of the young in the four groups. The incidence of anophthalmia, microphthalmia, and hydrocephalus in the four groups is given in Table I.

In Table II the incidence of anophthalmia and microphthalmia in the hydrocephalic young of groups 1 and 2 is shown.

TABLE I.—Incidence of Anophthalmia, Microphthalmia, and Hydrocephalus in the Four Groups

Group No.	No. of Dams	No. of Young	Anophthalmia, No. of Absent Eyes	Microphthalmia, No. of Eyes Less than 1.5 mm. in Diameter	No. of Hydrocephalic Young
1	12	88	47	36	8
2	12	81	15	30	3
3	12	100	0	0	0
4	12	88	0	0	0

TABLE II.—Incidence of Anophthalmia and Microphthalmia in the Hydrocephalic Foetuses of Groups 1 and 2

No. of Hydrocephalic Young in Groups 1 and 2	Anophthalmia, No. of Absent Eyes	Microphthalmia, No. of Eyes Less than 1.5 mm. in Diameter
11	13	8

A litter of 5-weeks-old rats; the dam was exposed to 258 r on Day 11 of pregnancy.

Nature of the Deformity.—Only the neuro-ectodermal elements of the eye were affected, the muscles and lacrimal apparatus being present and well differentiated. Anophthalmia was more commonly bilateral than unilateral. In the preliminary experiments, in which the young were allowed to survive for one month after birth, bilateral anophthalmia was more rarely encountered (see Fig.), suggesting that some anophthalmic foetuses were either born dead or destroyed at birth by the mother. Hydrocephalus was invariably associated with stenosis of the cerebral aqueduct.

Discussion

The findings of this investigation indicate that the administration of vitamins A, B, C, D, and E to the pregnant rat increases to a marked extent the incidence in the young of anophthalmia induced by x-radiation. The incidence of anophthalmia in group 2 (10.8%) contrasts markedly with that in group 1 (37.4%). The absence of anophthalmic young from the control group (group 4) suggests that genetic factors are not in any way involved. Moreover, since there were also no anophthalmic young in the group which received vitamins alone (group 3), the possibility can be ruled out that the increased incidence of anophthalmia in group 1 over group 2 represents an additional teratogenic effect of excess of one of the vitamins.

It seems, therefore, that the action of the vitamins in the combination administered is to sensitize the cells of the developing eye to the destructive action of radiation. It is tempting to associate this effect with the part played by the vitamins in the metabolism of the cell, and to contrast the findings of this experiment with the observation of Wolff and Kirmann (1954) that the protective action of cystamine applied equally to the developing foetus as to the adult.

The finding that the development of the lacrimal apparatus and other structures associated with the eye are not affected by radiation administered on Day 11 confirmed the report of Hicks (1953). Hicks also noted hydrocephalus in the young of dams irradiated on this day, and attributed its occurrence to stenosis of the cerebral aqueduct. Although the present investigation confirms the association between hydrocephalus and stenosis of the aqueduct, it is far from certain that stenosis of the aqueduct invariably bears a simple causal relationship to hydrocephalus when both are present (Millen, Woollam, and Lamming, 1954). It was particularly interesting to find that, whilst deformity or absence of the eye occurred frequently in association with apparently normally developed brains, hydrocephalus when present was almost invariably associated with absence or severe retardation of development of the eye. It is important to note, however, that in the case of hydrocephalus due to maternal hypovitaminosis-A the appearance of hydrocephalus may be delayed for some weeks after birth (Millen and Woollam, 1956). It is possible that the association between hydrocephalus and anophthalmia would have been as constant as that which occurs in the young of female rats subjected to experimental vitamin-B₁₂ deficiency (Ransdell, 1956) if the anophthalmic young had been allowed to survive for some weeks after birth.

It would be most satisfactory if subsequent investigation were to disclose that a single vitamin was responsible for the effects described in this paper. There is, however, much evidence of interaction between the vitamins in the development of the foetus. Lefebvres-Boisselot (1951), for example, has shown that the teratogenic effects of a maternal deficiency of pantothenic acid are greatly enhanced if the diet is supplemented with an excess of nicotinic acid. It therefore appears that the effects of the administration of a wide range of vitamins do not represent a simple summation of the individual actions of the vitamins but result from a complex interaction in which the relative amounts of each vitamin given may be of considerable significance. In following up the present study, therefore, and in attempting to find an explanation for the phenomenon described in this paper, the effects of combinations of the various vitamins in various proportions as well as the influence of individual vitamins on the teratogenic effects of radiation will require investigation.

Summary

The effect of the combined administration to pregnant rats of vitamins A, B, C, D, and E upon the incidence of anophthalmia produced in the embryo by subsequent x-radiation has been studied.

The incidence of anophthalmia in the group receiving radiation and vitamins (37.4%) is in strong contrast with that in the group receiving radiation alone (10.8%).

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HYPERTENSION AND TUBERCULOUS RENAL LESIONS

BY

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Since the first demonstration of hypertension resulting from clamping of renal vessels by Goldblatt *et al.* (1934) and the subsequent report of a case of renal hypertension treated with nephrectomy by Butler (1937), great interest has been shown and large numbers of papers have been written on the subject. Reviews of the literature have been given by Abeshouse (1941), Langley and Platt (1947), Pickering and Heptinstall (1953), and others. The literature on tuberculous renal lesions and hypertension, however, is surprisingly small, and it is intended to review the published cases in the literature and to report two further cases.

Literature

The first reference I can find to renal tuberculosis as a possible cause of hypertension is Leadbetter, who is quoted by Mulholland (1940) as having performed nephrectomy on two cases of unilateral renal tuberculosis with initial blood pressures of 160/100 and 180/100; in one of these patients the blood pressure returned to normal after operation.

Braasch *et al.* (1940) referred to a series of 158 patients operated on for renal tuberculosis of whom 12 were hypertensive. He also reports a group of 37 patients with "auto-nephrectomy" due to tuberculous renal lesions of whom five were hypertensive. In discussing the reasons for this low incidence of hypertension in patients with extensively damaged kidneys he points out that these patients tend to be from a lower age group and also that "vascular sclerosis is uncommon in the presence of the renal pathological changes which occur with tuberculosis." He also noted that there was no greater incidence of hypertension in bilateral disease. Of the 11 cases which were traced, only two showed no fall in blood pressure post-operatively, and seven maintained a normal blood pressure on follow-up.

Abeshouse (1941) reviewed the literature concerning renal tuberculosis and hypertension and quoted details concerning five cases of tuberculosis of the kidney and hypertension which were operated on with successful cure of their hypertension. He adds three cases of his own, two of which are not quoted here, for although they had a fall in blood pressure the initial diastolic pressures were at no time above 96 mm. Hg.

Goidsenhoven (1947), in a review of 92 cases of renal tuberculosis, found six with hypertension, of which two only had a nephrectomy, both with subsequent fall in blood pressure. Barker (1951), in reporting a series of 100 patients with hypertension and unilateral renal disease, quoted nine cases of renal tuberculosis (some of which had been pre-

viously reported by Braasch), five of which were reported as successful two years post-operatively, two fair, and two unsuccessful.

In the accompanying Table are shown the cases reported in the literature. Seventeen of these are from series of five or more cases, and therefore give an indication of the actual success rate.

Cases of Hypertension and Tuberculous Renal Lesions from the Literature

Source	No. of Cases	Suc-cesses	Doubt-ful	Unsuc-cessful	Length of Follow-up
*Braasch <i>et al.</i> (1940) ..	11	7	2	2	2-5 years
*Crabtree and Chaset (1940) ..	1	1	—	—	14 months
Ostry (1948) ..	1	1	—	—	1 year
*Goidsenhoven (1947) ..	2	2	—	—	
*Barker (1951) ..	2	—	—	2	2-5 years
Leadbetter and Burkland (1938) ..	2	1	—	1	
Everett (1940) ..	1	1	—	—	
Abeshouse (1941) ..	1	1	—	—	2 years
*Pickering and Heptinstall (1953) ..	1	—	—	1	
Nesbit and Ratliff (1940) ..	1	1	—	—	
Total ..	23	15	2	6	

* From series of five or more cases.

Case 1

The patient, a boy of 17, was admitted to hospital on May 4, 1955. His story was that he had had a tuberculous thoracic spine at the age of 4 and for the year prior to admission he had complained of frequency, haematuria, and right-sided renal pain. Three months before admission he had been found to have a lesion in the right retina which was diagnosed as being a tuberculoma.

On examination he was seen to be small for his age. He had an angular kyphosis of the thoracic spine. His blood pressure was 210/180, but there were no other abnormal cardiovascular signs.

Investigations.—Blood urea, 36 mg. per 100 ml.; haemoglobin, 78%; leucocytes, 13,500 (polymorphs 78%). Urine culture showed the presence of tubercle bacilli in two out of three specimens examined. An intravenous pyelogram showed a non-functioning kidney on the right side.

As a result of these findings cytoscopy was carried out on May 11, when a diffusely inflamed bladder was seen and both ureteric orifices were partially occluded. It was impossible to pass catheters up either of the ureters because of the inflammation.

Following this investigation he began to develop severe headaches, blurring of vision, and slight but definite papilloedema. Furthermore, his blood urea rose from 36 to 59 mg. per 100 ml. and it appeared that his hypertension had entered the malignant phase. In view of this, a right nephrectomy was performed on May 28, when a kidney extensively damaged by tuberculosis was removed.

Following this his blood pressure came down from 210/180 to 136/90 and has remained at this level for the seven months that he has been at this hospital (see Chart). During this time he has received antituberculosis therapy, but while on this he developed a cold abscess on the sternum.

Blood-pressure chart of Case 1.